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REVIEW ARTICLE

Cellular Stress and General Pathological Processes

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Abstract: From the viewpoint of the general pathology, most of the human diseases are associated with a limited number of pathogenic processes such as inflammation, tumor growth, thrombosis, necrosis, fibrosis, atrophy, pathological hypertrophy, dysplasia and metaplasia. The phenomenon of chronic low-grade inflammation could be attributed to non-classical forms of inflammation, which include many neurodegenerative processes, pathological variants of insulin resistance, atherosclerosis, and other manifestations of the endothelial dysfunction. Individual and universal manifestations of cellular stress could be considered as a basic element of all these pathologies, which has both physiological and pathophysiological significance.

The review examines the causes, main phenomena, developmental directions and outcomes of cellular stress using a phylogenetically conservative set of genes and their activation pathways, as well as tissue stress and its role in inflammatory and para-inflammatory processes.

The main ways towards the realization of cellular stress and its functional blocks were outlined. The main stages of tissue stress and the classification of its typical manifestations, as well as its participation in the development of the classical and non-classical variants of the inflammatory process, were also described.

The mechanisms of cellular and tissue stress are structured into the complex systems, which include networks that enable the exchange of information with multidirectional signaling pathways which together make these systems internally contradictory, and the result of their effects is often unpredictable. However, the possible solutions require new theoretical and methodological approaches, one of which includes the transition to integral criteria, which plausibly reflect the holistic image of these processes.

Keywords: Cellular stress, tissue stress, systemic inflammation, low-grade inflammation, oxidative stress, mitochondrial stress, DNA-damage response, autophagy.

1. INTRODUCTION

The use of the clinical practice of personalized approach is only possible with the verification of most common manifestations of various human diseases. In the international classification of diseases, ICD-10 recorded more than 10 thousand nosologies, which are grouped into 21 different classes of known human diseases.

From the viewpoint of general pathology, most diseases share various general pathological processes, two of which being tumor growth and classical (canonical) inflammation. The more common typical pathological processes and conditions include thrombosis, necrosis, atherosclerosis, typical manifestations of neurodegenerative diseases, fibrosis, atrophy, pathological hypertrophy, dysplasia and metaplasia, ischemia, shock states, and some others.

Generally, pathological processes could be integrated into blocks based on the pathogenesis pattern of mechanisms, a well-known complex of pathological changes is the phenomenon termed "Chronic low-grade inflammation" [1-3]. This phenomenon integrates the various processes associated with aging and the pro-inflammatory mechanisms, such as; atherosclerosis, obesity-associated insulin resistance, activation of stromal macrophages in the liver and adipose tissue, and moderate manifestations of the systemic inflammatory response, at the tissue and organ level.

The big question remains on the existence of a single elementary component that could integrate numerous diseases and general pathological processes. This component should reflect the cellular level of the organization of living matter, and integrate the typical changes into the cellular genome, transcriptome, proteome and metabolome. As a basic element of various pathologies, one can consider cellular stress, which has both physiological and pathophysiological significance as such component [4]. Noteworthy, cellular stress can characterize a pathological process if it occurs as an elementary functional component of tissue stress. These two phenomena in relation to human pathology should be considered in a single context.

Cellular stress represents the typical reaction of cells to any form of macromolecular damage, with the aim at restoring cellular and tissue homeostasis [5]. This stress involves universal mechanisms that employ a phylogenetically conserved set of genes and their activation, as well as specific mechanisms inherent in specific biological species and individual types of cells within a single multicellular organism [6].

Cell stress programs are initiated by sensory structures that recognize signs of a real or potential (probabilistic) damage to macromolecules, followed by the involvement of transcription factors, and the formation of a stress proteome and metabolome in the cellular response [5]. The factors of the stress proteome are combined into functional systems to achieve a specific beneficial goal for the cell and organism, on accomplishing this task, the functional systems disintegrate. The theory of the functional systems was first used to explain the processes involved in higher nervous activity [7]. In physiological condition, the development of tissue and cellular stress is limited in terms of intensity, time, and space; and balanced with other processes that ensure the safety of homeostasis. In adverse condition, the mechanisms of cellular stress may themselves play the role of damaging factors and contribute to the development of pathological processes [8]. Authors emphasized on the role of the formation of dysfunctional systems in the mecha-

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nisms of cellular stress, and their possible involvement in the pathogenetic cycle of various diseases manifestation [9]. The purpose of this review is to understand relevant findings on the description of cellular stress as an elementary functional link of various variants of tissue stress, occurring in inflammation and other typical pathological processes.

2. GENERAL CHARACTERISTICS OF CELLULAR STRESS

2.1. Definition of Cellular Stress, Connection with Tissue Stress, Adaptation and Maladaptation, Physiological and Pathological Processes

The section includes a description of the most universal patterns of cellular stress, as well as answers to potential questions that may arise to the authors of the article on this problem, as a necessary condition for the systematization of the subsequent material.

2.1.1. Definition of Cellular and Tissue Stress

Cellular stress is a typical way of active adaptation of cells to the action of damaging factors, aimed at ensuring cell survival and preserving or restoring cell and organism homeostasis under extreme condition, such as evolutionary conservative mechanisms of cell defense, the formation of cell receptor and secretory phenotype, providing intercellular communication during development tissue stress.

Tissue stress is the implementation of qualitatively more complex tissue and organism-level programs aimed at preserving homeostasis and the function of individual organs and the organism as a whole, under the conditions of a systemic (supracellular) action of actual or potential internal or external damaging factors.

Genetically determined tissue stress programs are not homogeneous, these form the basis for the implementation of processes that are different in their functional purpose. Additionally, these processes are based on a large number of common signaling pathways at the cell level and phlogogenic (pro-inflammatory) mechanisms at the cell and tissue levels. The main task of classical inflammation remains the localization and elimination of the damaging factor even by possible irreversible damage to one's own cells in the inflammatory focus [10]. In systemic processes, the primary aim of pro-inflammatory mechanisms is aimed at preserving or restoring the function of vital organs. Similarly to other biological mechanisms, the cellular processes and tissue stress could be found to be disrupted, dysfunctional and pathological. At the same time, functional and dysfunctional phenomena of cellular and tissue stress are the pathogenetic core of a large number of diseases.

2.1.2. Relationship of Cell Stress with Cell Proliferation, Differentiation, Cell Dysfunction Processes

The underlying components of cellular stress can occur in different forms in all cells of the human body, and at any stage of the cell cycle or cell differentiation, aging, or any other states of cells. At the same time, cellular stress is not identical to these cellular states but share functional component, depending on the force of action of the factors damaging the cell and the consequences of these effects. Generally, in the physiological state of a cell, the activation of cellular stress mechanisms is relatively moderate (as a rule) and situational (reaction to latent injuries). During cell dysfunction which usually manifests as detrimental changes to vital activity or homeostasis, the development of cellular stress remains inevitable and must precede the restoration of a normal physiological state or aggravated outcomes on the cell. Furthermore, the value of cellular stress during cellular dysfunction may be ambiguous in association with the cell itself or the needs of the tissue.

2.1.3. The Relationship Between Cell and Tissue Stress, the Main Directions of their Outcomes

Cellular stress is an elemental functional component of tissue stress. Concurrently, the programs of survival of a higher (supracellular) level are also priorities at the cellular level, such as programs of cellular suicide, and the violation of these priorities is the main condition for tumor growth. Proapoptotic and antipathic signaling pathways are universal manifestations of cellular stress, and apoptosis or programmed necrosis is preferable to be considered as the outcomes of cellular stress. Apoptosis of individual cells is an unfavorable outcome of stress for their existence but could be actualized within the framework of physiological cell turnover at the tissue level. However, if the regeneration processes do not compensate for cell loss, this can lead to tissue atrophy (maybe pathological and physiological) or sclerosis - replacement of parenchymal cells with more stress-resistant elements of connective tissue.

The most optimal outcome during cellular and tissue stress is the self-destruction by a negative feedback mechanism when cells return to a normal physiological state from a state of temporarily altered homeostasis (allostasis) [11]. However, in the process of cell aging and the accumulation of damages of the genome, proteome, and metabolome, the preservation of allostasis occurs and its further deviation from the original homeostasis.

An alternative outcome of cellular stress is tumor transformation, and when this occurs, the mechanisms of cellular stress are reoriented towards ensuring the survival of abnormal cells. Thus, these or other cellular stress mechanisms manifest themselves both in pathology and in various physiological states.

2.1.4. Cellular Plasticity and Cell Differentiation

Cellular stress includes both conservative, relatively universal components, and mechanisms that determine its plasticity, with the latter primarily concern to the cells of the immune system, their secretory and receptor phenotype. Particularly, this plasticity determines the alternative differentiation of inflammatory macrophages (M) and T-helper cells (Th) towards different functional poles, respectively, M1 and Th1, and M2 and Th2 on the other [12].

Cellular stress of immunocompetent cells could be controlled through the production of cytokines and other mediators by tumor cells or through various pathogenicity factors microbial cells. Tumor-associated macrophages (TAM) has been reported to block anti-tumor immune processes and contribute to the survival of parasitic cellular systems [13-15].

Cellular stress is a complex system of “checks and balances” - it is an internally contradictory process, and this ensures its self-regulation and external regulation, and determines the mosaic pattern of its manifestations and outcomes in the development of tissue stress, even in cells of the same type.

2.1.5. Physiological and Pathological Manifestations of Cellular Stress are not Synonymous with the Concepts of Physiology and Cell Pathology

Cellular stress is actively involved in physiological and pathological processes. This stress state is not involved in the activation of any cell function, but improving certain cell survival programs under extreme conditions. It remains obvious that cells are tasked to survive even under physiological conditions such as in the secretory cells, the proteome may be disturbed with the subsequent development of endoplasmic reticulum stress (ER-stress) [16, 17]. This type of stress includes the production of inducible heat shock proteins (HSP), oxidative stress and a number of other mechanisms. Furthermore, this stress may lead to a short-term restriction of the secretory function, but with its subsequent recovery within the framework of the physiological state of the cell. In the case of advanced significant damage, stress can lead to the apoptosis of cells. Moderate manifestations of cellular stress in an almost normal state of the cell can be characterized as a kind of stressful tone. In some cases, this stressful tone may acquire a pro-inflammatory character (the formation of a pro-inflammatory cell phenotype), such as in the implementation of conventional cell selection processes in primary lymphoid organs [18], or the maintenance of the physiological state of the intestinal epithelium constantly in contact

with an aggressive microbial environment [19]. When performing individual extreme physiological functions, these processes go beyond the usual limits of their "tone" and lead to the development of the systemic inflammatory response phenomenon (SIR); an example of such manifestation could be presented as the expression of a relatively wide range of cytokines (IL-1β, IL-6, IL-8, IL-10, IL-15, TNF-α, MCP-1, LIF, and TGF-β) when the work performed by skeletal muscle tissue is enhanced [20, 21]. The blood levels of IL-6 were reported to increase up to 100 times into the development of the SIR [22]. Furthermore, in this case of SIR, cellular stress mechanisms provide the contractile function of skeletal muscles and protect the muscles from more severe (pathological) damage [23, 24]. However, cell stress can not characterize all the functions of muscle tissue in isolation from the other processes neither can it characterize all pathological states and cell reactions, such as a large number of tissue-specific processes. Relatively, tissue stress reflects the function of the cells of the immune system - the "professional" cells of the inflammatory focus, since most of these functions are directly determined by the mechanisms of cellular stress.

2.1.6. Classical Inflammation as One of the Manifestations of Pro-inflammatory Tissue Stress

Canonical inflammation is an independent form of the general pathological process which is characterized by the presence of a focus of inflammation which includes the phenomenon of inflammatory microcirculation and the formation of leukocyte infiltration. The presence of an inflammation focus determines the manifestations of the five classic signs of inflammation, such as heat, redness, swelling, dolor (pain), and loss of function [10]. Additionally, inflammation may include the systemic component - SIR. Systemic inflammatory reaction includes an increase in the blood levels of proinflammatory mediators, an acute phase response of the liver, a stress response of the neuroendocrine system, activation of metabolic cycles and transition to endogenous nutrition, and a number of other processes that facilitates inflammation while limiting the transition of the phlogogenic mechanisms of the center of inflammation, primarily proinflammatory microvessel reactions to the systemic level. At the system level, this phenomenon is associated with the development of shock states - clinical manifestations of systemic inflammation, which could be considered as an independent type of general pathological process that is not in the category of classical inflammation [25]. A feature of systemic inflammation is the systemic effect of damaging factors that are comparable in intensity with the action of these factors in the focus of classical inflammation.

Pro-inflammatory tissue stress is not a sign limited to classical and systemic inflammation, at the system and local level, it forms an integral part of most other typical pathological processes (Fig. **1**). It was reported that some signs of pro-inflammatory tissue stress are also detected in tumor tissue, including the presence in its structure of TAM with the M1 and M2 phenotype [26]. Chronic low-grade inflammation includes a number of independent forms of typical pathological processes that underlie the pathogenesis of a large number of somatic diseases [1-3]. A unique characteristic feature of the chronic low-grade inflammation is the development of para-inflammation (non-classical inflammation) at moderate SIR manifestations. The qualitative differences between the various manifestations of tissue stress lie with its intensity and prevalence increase in the body (Fig. **2**, Table **1**). This qualitative differences determines the dominant type of cells involved in the development of these processes, namely: leukocytes and macrophages in the focus of classical inflammation; microvascular cells in cooperation with the intravascular reaction of the hemostatic system and complement in systemic inflammation; stromal macrophages, with the participation of other cells of the connective tissue and parenchymal cells of internal organs in various variants of chronic low-grade inflammation; TAM and the tumor cells themselves during tumor growth.

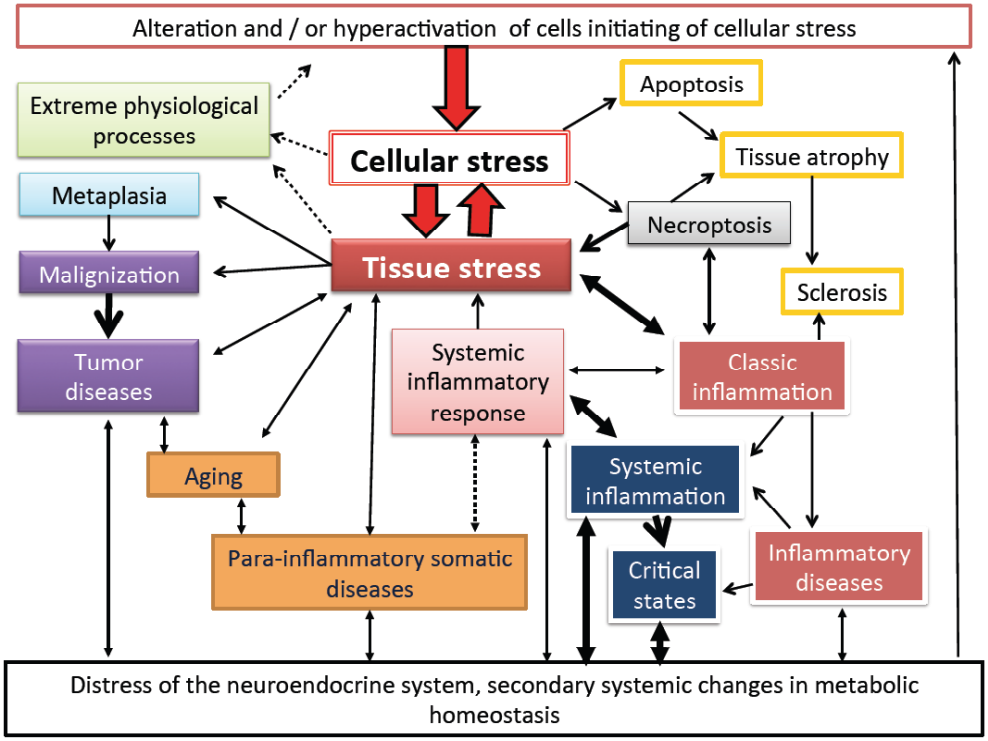

Fig. (1). Causes and outcomes of cellular stress in the development of general pathological processes and the main classes of diseases in humans.
The systemic inflammatory response manifest from the accumulation of acute phase proteins, mediators of inflammation and other products of cellular stress in the bloodstream. The dotted arrow shows a less significant influence, while the bold line signifies predominant influence. Necroptosis was classified as all types of programmed necrosis in cells, including necroptosis, netosis, pyroptosis and other variants.

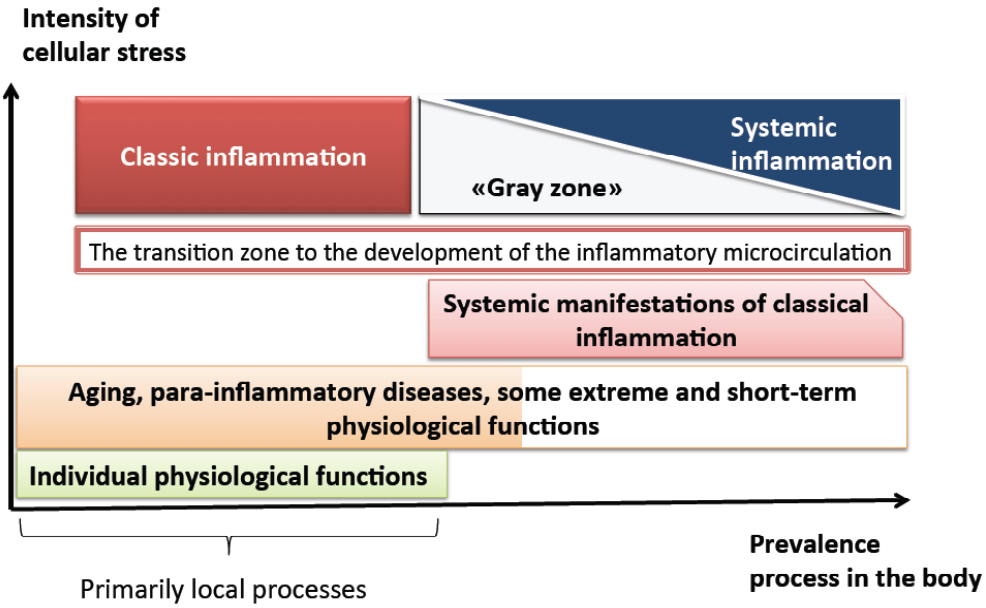

Fig. (2). The importance of proinflammatory intensity and prevalence of cellular stress in the development of various diseases and pathological processes. The gray zone signifies the transition state from classical to systemic inflammation, owing to the fact the phenomenon of systemic "inflammatory microcirculation" inflammation is not a discrete process.

Table 1. The principal differences and similarities of the two variants of tissue stress: para-inflammation and classical inflammation.

Signs	Para-inflammation	Classical Inflammation
Localization and distribution	Occurs at the levels of organ, tissue or whole organism; the border of this process remains unclear.	Based on specific mechanisms in inflammatory focus
Stress and distress of neuroendocrine system	Yes	Yes
Association with acute phase response, leukocytosis, cytokinemia	No or not expressed	No or not expressed
External signs of inflammation	No	Yes, sometimes not expressed
Damaging factor effect	Low intensity but widespread	High intensity but localized action
Main inducers (factors and processes)	Aging of cells and whole organism, slow viral infections, metabolic and endocrine dysfunctions, impaired oxygen transport not reaching the stage of tissue necrosis, other factors with low damage	Various infections, necrosis, injuries, autoimmune and allergic processes that cause the reaction of microvessels, hemostasis systems, complement, kallikrein-kinin system, other mechanisms that are characteristic of the inflammatory focus
Main mechanisms of induction	Different mechanisms of cellular stress development in response to intracellular damage of the genome, proteome, and recognition of relative low concentrations of PAMP and DAMP, aberrant metabolites by cells using different PRRs, with special role of scavenger receptors	Critical changes in various parameters of homeostasis, which are capable of initiating exudative-vascular reaction. Recognized high concentrations of PAMP and DAMP using classic PRRs. Recognition of antigens by the mechanisms of adaptive immunity in infections and autoimmune diseases.
Association with physiological functions	Short-term adaptive tissue stress in physiological state. Chronization and further development of tissue stress is associated with pathologies.	Inflammation is the programmed response of the body to localized high-intensity damage, before the sign of pathology.
Association with diseases and typical pathological processes	Processes associated with insulin resistance, endotheliosis, age neurodegeneration, atherosclerosis, essential hypertension, factor of metafibrosis and tissue atrophy development	General pathological process, the basis of pathogenesis for numerous classic inflammatory diseases, tissue atrophy and sclerosis, risk factor for tumor growth and metaplasia
Organ functions	May occur in tissue stress progression	Different degree of manifestation

Noteworthy to state that the term "inflammation" generally covers a large number of para-inflammatory processes that are not in the category of classical inflammation. However, it is necessary to classify these processes from the standpoint of tissue stress or to clarify the nature of these inflammatory (para-inflammatory) processes from the standpoint of general pathology.

2.1.7. Inconsistent Unity of Adaptation and Maladaptation Mechanisms of Cellular Stress in Pathology

By their nature, genetically determined programs of cellular and tissue stress are the mechanisms of active adaptation to the action of the damaging factors of individual cells and the organism as a whole. It was reported that when the action of the damaging factors exceeds the adaptive capacity of stress, pathogenetically perverse cycles of mutual stimulation of changes in homeostasis and stress at the cellular and tissue levels can form [27]; such variants of tissue stress development underlie the pathogenesis of many chronic somatic diseases. However, if tissue stress manifests without any adaptive properties, the pathological process would take a chain character and quickly lead the body to death. It is obvious that cellular and tissue stress is a complex system, including both adaptation and disadaptation processes that are difficult to distinguish from each other.

2.1.8. Blurred Manifestations of Cellular and Tissue Stress, the Problem of "Gray Areas" and Transition States

The concepts of cell and tissue stress are abstractions that reflect the general patterns of active adaptation and artificially separate them from more particular processes that do not have a direct relationship to these patterns. These abstractions only truthfully reflect reality, but they are necessary to form a holistic picture of the pathogenesis of various diseases. Similarly, during the transition from the general to the particular pathologies, one encounters the vagueness of the “dividing lines”, the presence of numerous “gray zones”, the abnormality and the nonlinearity of the distribution of specific indicators. This fuzziness is associated with the presence of transitional states between normal and pathological conditions, between local manifestations of para-inflammation and classical inflammation, between systemic manifestations of classical inflammation and systemic inflammation (Fig. **2**). There are also a large number of intermediate variants of differentiation of macrophages in the M1-M2 range (see below).

The real picture of the pathological process lies in the combination of several general pathological processes, which determines the need to isolate the main link, such as, when defining pathogenetic therapy schemes. Furthermore, this also predetermines the use of methodological approaches based not only on the principles of formal but also on multiple (probabilistic) logic [28], the use of various methods of mathematical analysis, the need to specify the general provisions in their practical use. Currently, it can be noted that there are more than 100 definitions of health (a fuzzy concept), but there is no single, generally accepted definition of it. However, this circumstance does not prevent researchers from separating conditionally healthy and sick patients in each particular case. Moreover, it is inappropriate to assume that cellular stress develops from any adverse changes or even damage rather it develops only on stimuli that perceive its sensory mechanisms. In addition, some of these mechanisms may be blocked with drugs or microbial toxins, or they may be genetically defective. Meanwhile, the perfection and redundancy of these mechanisms make cellular stress an effective tool for recognition and response to real or potential threats.

2.1.9. Three Stages of Tissue Stress

Selection of the general patterns of developmental dynamics is one of the key characteristics of any pathological process. The main stages of classical inflammation development are currently canonized in the system of general pathology. The dynamics of systemic inflammation as one of the variants of non-classical inflammation has its own characteristics and will be discussed below. In this case, let us focus on the most common patterns of development of tissue stress associated with pathological and some physiological processes belonging to the category of para-inflammation. These general patterns to a certain extent reflect the dynamics of cellular stress underlying these processes.

In the most simplified form, the dynamics of tissue stress can be reflected in the form of three main stages.

Stage 1 is characterized by active cell proliferation, the predominance of anabolic processes with increased tissue tolerance to the action of damaging factors. Cellular stress at this stage allows the genome to remain stable under the conditions of the cell cycle, and to involve abnormal cells in the process of apoptosis [29]. The secretory phenotype of cells is substantially associated with the production of various growth factors. The pro-inflammatory activity of the cells (such as the production of pro-inflammatory cytokines and oxidative stress) is at a relatively low level. Particularly, the pro-inflammatory activity is related to DNA vulnerability in the process of cell cycle realization, including from the part of phlogogenic factors of cellular stress.

Stage 2 is characterized by increased catabolic processes, insulin resistance in insulin-dependent tissues, an increase in the intensity of oxidative stress, more pronounced manifestations of the pro-inflammatory cell phenotype, and in pathology - the formation of a relatively stable allostasis.

Stage 3 or stage functional decompensation is characterized by morphofunctional changes and chronic dysfunction of the corresponding organs. At this stage, there is a steady formation of a vicious pathogenetic circle linking the mechanisms of cellular stress with increasing changes in homeostasis - the formation of unstable allostasis.

While only the third stage of tissue stress can definitely be attributed to the pathology, other stages (mostly the first stage) can manifest themselves both in pathology and in the implementation of physiological processes. The first stage may also be involved in pathological processes, such as, tumor growth and lymphoproliferative diseases.

The problem of insulin resistance can have both physiological (for example, during fasting) and pathological significance. An increased level of insulin resistance is characteristic for many cell types in insulin-dependent (optional glycosytic) tissues at 2-3 stages of tissue stress. The insulin signaling pathways at the cellular level are controlled by many metabolic and endocrine factors, mainly changes in the level of glucose in the blood. At the same time, insulin signaling pathways are interconnected with cellular stress signaling pathways. Functional inhibition of insulin signaling pathways primarily affects the function of organs involved in the implementation of metabolic cycles. These cycles largely ensure the preservation of metabolic homeostasis, prominently, the level of glucose in the blood. The main metabolic cycles that perform these tasks are the glucose-lactate or Corey cycle, the glucose-amino acid or alanine cycle, and the glucose-fatty acid or Rendela cycle [30]. The main organs responsible for the implementation of these cycles are: Adipose tissue, skeletal muscle, liver, and endocrine apparatus of the pancreas. In obesity, insulin resistance increases due to the metabolic and endocrine regulatory mechanisms of negative feedback. With the spread of para-inflammation in the areas indicated above, many pro-inflammatory factors support the increased insulin resistance by the mechanism of the vicious pathogenetic circle [31]. Insulin resistance and other changes lead to the development of metabolic syndrome and then type 2 diabetes, the totality of these changes that is the core of the pathogenesis of pathologies, combined under the concept of chronic low-grade inflammation.

The development of cellular stress will greatly depend on the type and condition of the cell (proliferation, differentiation, postmitotic state), the characteristics of the cellular microenvironment and the action of damaging factors, and other reasons. The array of

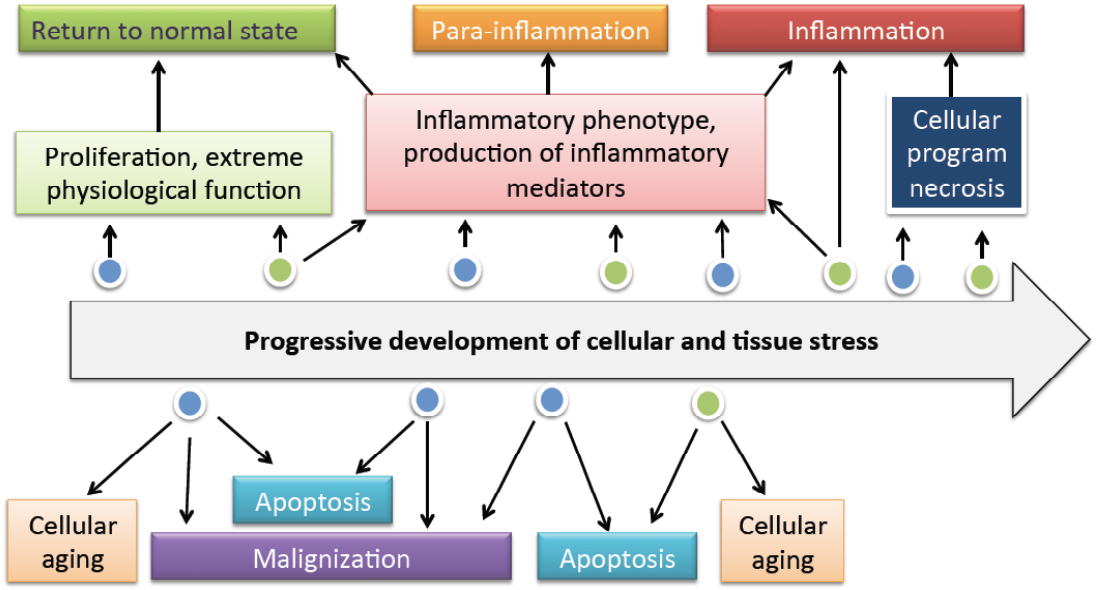

Fig. (3). Simplified scheme of probabilistic outcomes of cellular and tissue stress as it progresses (increased expression of phlogogenic factors). The blue circle shows proliferating cells, while the green circle signifies the differentiated cells with a stop of the cell cycle. (*The color version of the figure is available in the electronic copy of the article*).

factors implicated in the development of cellular stress prevent the use of universal approaches in assessing the dynamics of cellular stress. However, it is possible to fix different degrees of development of pro-inflammatory mechanisms on the conditional vector (Fig. **3**). These mechanisms include a certain repertoire and the degree of expression of signaling pathways of stress, the expression of pro-inflammatory cytokines, their receptors, other phlogogenic factors, and the severity of oxidative stress. In general, a relatively low degree of pro-inflammatory activity is characteristic of proliferating cells and more pronounced in specialized cells of the immune system in the focus of inflammation. As the pro-inflammatory activity of the cells increases, the likelihood of their programmed necrosis similarly increases. On the contrary, the development of apoptosis does not have a linear dependence on the severity of the pro-inflammatory activity of the cells as activation and anti-apoptotic mechanisms are also involved in this process [27, 29, 32].

2.2. The Main Directions of Development and Outcomes of Cellular Stress

To characterize any important process with respect to the development and outcome of cellular stress, it is critical to evaluate the final consequences of the main and alternative ways of the process development, and the ability of the organism to influence their implementation under specific conditions. With respect to this, the following listed general patterns can be attributed to typical results of the development of cellular and tissue stress:

2.2.1. Adaptation of Tissue

Adaptation of the tissue to the action of the damaging factor remains the main focus of cellular and tissue stress.

Cells can acquire resistance from the cellular stress reaction. However, if the effect of damaging factors exceeds the adaptive potentials of the cellular and tissue stress reaction, these processes themselves become factors in the pathogenesis of various diseases [33].

2.2.2. Apoptosis

This state arises as a result of the genetic program of cellular suicide implementation. This process is normally accompanied by the rounding up of cells, retraction of pseudopods, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), few or no ultrastructural modifications of cytoplasmic organelles, and plasma membrane blebbing. The cell integrity is maintained until the final stages of the apoptotic process [34]. Various ways involved in the development of cellular stress could lead to apoptosis, hence, it is crucial both in physiological and pathological conditions to ensure a certain intensity for the development and survival of organs, tissues and the organism as a whole in any cellular stress process. Cellular stress remains an indispensable component of various processes, which include: normal cell turnover, the proper development and functioning of the immune system, hormone-dependent atrophy of unwanted tissues, embryonic development and death of damaged or malignant cells without the development of a pro-inflammatory reaction [35]. The path leading to cell death has both morphological and biochemical features [35]. Apoptosis interrupts the cell malignization process, but can likewise contribute to tissue atrophy and resulting in subsequent sclerosis of the internal organs parenchyma [36, 37]. Apoptosis is associated with many signaling pathways that can be divided based on caspases into external and internal pathways [38, 39]. Caspases are a family of cysteine proteinases that act in cascades to actualize cellular suicide. They exist as inactive proenzymes but undergoes proteolytic treatment to form two subunits; large and small, which dimerize to form an active enzyme.

External proapoptotic signals are linked to the transmembrane receptors of the cytolemma, especially the tumor necrosis factor (TNF) family cytokines receptors (such as the FAS (CD95), TNFR1, TRAILR1,2) [40, 41]. The cytoplasmic regions of these receptors contain the domain DED (death domain), which participates in the activation of caspase-8, that triggers effector caspases of apoptosis (caspase-3 and 7). The internal (mitochondrial) path leading to apoptosis development is regarded as the pivot mechanism in all mammalian cells, the increased mitochondrial permeability coupled with the release of proapoptotic molecules (primarily cytochrome C) into the cytoplasm, leading to a mitochondrial path of apoptosis development [42]. In addition, the mitochondrial response is triggered and controlled by pro-apoptotic (Bax, Bak, Bad, Bmf, Hrk, Noxa, Bcl2A1, Bim, Bid, Puma) and anti-apoptotic (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, A1 / Bfl-1) Bcl-2 family proteins, and many other factors that are influenced by the responses to diverse fluctuations in intracellular homeostasis [42-44]. The cytochrome C released from the mitochondria, binds to the Apoptotic

protease activating factor 1 (Apaf-1), forming a more complex protein with caspase-9, this complex is activated in the apoptosome, and subsequently, leads to the activation of the other caspases, which eventually lead to cell death [42, 44].

Generally, most of the ways implicated in apoptosis development are associated with cellular stress; either with cell pathological activation or damage to various cellular structures [45, 46]. Fragmented dead cells formed during apoptosis, are rapidly absorbed by stromal macrophages for terminal degradation. Caspases that participate in apoptosis are largely divided into initiator caspases (caspases 2, 8, 9, 10, and 12), and effector caspases (caspases 3, 6, and 7) [35]. The apoptosis development is also controlled by complex systems of anti-apoptotic factors [46], prominently, the inhibitors of apoptosis (IAP) and Bcl-2 families can simultaneously suppress different signaling pathways of apoptosis [47, 48].

The complexity of the apoptotic regulatory mechanisms determines whether this process can manifest itself in the development of various variants of cellular stress and stages of tissue stress.

2.2.3. Program Necrosis of Cells (Necrosis, Pyroptosis, Netosis, Parthanatos, Autophagic Cell Death, Oxytosis, Ferroptosis, Secondary Necrosis, etc.)

This is one of the outcomes of cellular stress, usually associated with inflammation [49]. Studies have shown that numerous actions of this process reflect the differences in signaling pathways, features of the biochemical and morphological characteristics [50]. Active mechanisms, such as aggravated accumulation of Ca2+ in the cytoplasm, increased permeability of the mitochondrial membrane, enhanced formation of reactive oxygen species, external signals from death receptors, and activation of specific necrosis caspases are all implicated in the programmed necrosis of cells.

Pyroptosis is a variant of the programmed necrosis, which predominantly develops in the innate immunity cells, epithelial tissues of the integumentary system, and some other cells. This process mostly occurs during the pathological activation of cells by pathogenic bacterial antigens, especially lipopolysaccharide of gram-negative microbes (LPS). Pyroptosis is associated with the formation of pro-inflammatory protein complexes in the cells, inflammasomes (pyroptosoms), which are crucial for the activation of caspase-1, pyrogenic interleukin-1β (IL-1β), and IL-18 (another representative of the cytokine IL-1 family) [51, 52]. In addition, the formation of inflammasomes and the existence of additional activation effects (for example, the action of LPS in the intracellular environment) lead to the activation of caspase-4 and 5 in humans or caspase-11 in mouse, which is directly linked to pyroptosis development [53]. This sort of program necrosis is associated with the destruction of the cell membrane and the release of products of cellular decay into the extracellular environment, which drastically increases the pro-inflammatory response of the surviving cells.

Hitherto, NETosis (from necrotic or neutrophil extracellular traps) was originally associated with neutrophils [54] but was later revealed in other types of professional phagocytes [55, 56]. The development of NETosis is connected to the phenomenon of unfinished phagocytosis and cellular stress, particularly, severe oxidative stress is critically needed for NETosis development [57]. NETosis is characterized by the release of extracellular DNA traps from the necrotic phagocytes such as the enlarged nuclear DNA, mitochondrial DNA (on occasion); in combination with cationic proteins, hydrolases, and specific oxidases. These traps are capable of binding and damaging various pathogens, as well as indigenous tissues, especially in the face of purulent inflammation [58-60]. The process of NETosis was suggested to exert both a protective, and negative influence in the development of many diseases, a typical example could be seen in the development of intravascular environment in sepsis or systemic autoimmune diseases, which gives rise to severe complications associated with endothelial damage and intravascular blood coagulation [61, 62]. Authors also suggested that such complications could be amended by serum DNase [62]. Active release of NETosis products by neutrophils in diabetes have shown to slow the healing process of wounds [63], while in the case of sepsis, they provoke the formation of inflammasomes in macrophages and the development of pyroptosis, thereby promoting the inflammatory response in infected tissue [64]. In addition, neutrophils NETosis products in the intravascular medium and the brain parenchyma disrupt the blood-brain barrier, damage the nerve cells, thereby exacerbating the course of Alzheimer's disease [65].

"Cornification" is the generation of the stratum corneum in the epidermis, hair and nails; and this has shown to be associated with the programmed death of epithelial cells by apoptosis or necrosis, depending on the intensity of the damaging factors and the severity of cellular stress [66]. Caspases may participate in this process.

The term "autophagic cell death" (ACD) is widely used to refer to cases of cell death accompanied by massive cytoplasmic vacuolization [50]. This process occurs in the absence of chromatin condensation, but it is accompanied by large-scale sequestration of parts of the cytoplasm in autophagosomes, resulting to a vacuolized appearance of the cell [1]. In most known cases, autophagy is a cytoprotective response activated by dying cells when trying to cope with stress, and its inhibition has been reported to accelerate cell death rather than the opposite [1, 67].

Necroptosis, alongside pyroptosis and NETosis, is one of the main ways of program necrosis. It is usually associated with the activation of receptor-interacting protein kinase 1 and 3 (RIPK1 and RIPK3), and the formation of an intracellular protein complex known as necrosome [68]. Necrosome formation can be initiated by various intracellular and extracellular stimuli, which include the typical microbial antigens (pathogen patterns), interferons type I and II, TNF-α cytokine and its TNFR1 receptor. However, necroptosis acts as a competitor to apoptosis, it was found that the proapoptotic caspase-8 inhibits necrosome formation [69, 70]. The process of necroptosis is normally affiliated with cellular response to severe damage, or with the weakening of restrictive control, over the development of this response. In particular, necrosis of neurons is observed in the development of inflammatory reaction, and tissue destruction caused by ischemic brain lesion [71]. Specific depletion of caspase-8 in the intestinal epithelium, or the Fas-associated protein with death domain (FAAD) signaling factor involved in the activation of apoptotic caspases (8 & 10), can lead to the development of spontaneous necroptosis of epithelial cells and present pathologies that are morphologically similar to those in inflammatory intestines diseases, especially Crohn's disease [72]. Thus, necroptosis is a variant of cell death rivaling apoptosis and is more pronounced in inflammation and tissue destruction.

Secondary necrosis. When apoptotic cells are not cleared up in a timely manner, this could progress to a phenomenon referred to as "late apoptosis". Late apoptosis is characterized by partial destruction of the cell membrane, vacuoles formation, which are atypical of the classical apoptosis; this autolysis process is known as secondary necrosis [73]. It may be associated with the insufficient activity of stromal macrophages in tissues as a result of a large number of apoptotic cells [74, 75], or deficiency of the scavenger receptor function [76]. and it is involved in the pathogenesis of many diseases, which include systemic lupus erythematosus and Alzheimer's disease [77].

Some authors use the term "mitotic catastrophe" to refer to the death of cells in mitosis, it was used to reference to cases of cell death arising from aberrant mitosis [78, 79]. Mitotic catastrophe is one of the tumor suppressive manifestations of the cellular stress outcome, besides cellular aging and apoptosis [80, 81].

A common characteristic of all variants of program necrosis is the formation of cellular decay products, which act as secondary inducers of cellular stress and inflammation [77, 82]. It was shown that NETosis, pyroptosis and necroptosis processes, increased the

development of inflammation in response to infection [83]. However, in autoimmune diseases, program necrosis process is a theoretical link of dysfunctional systems [84]. Both program necrosis and apoptosis require a complex signaling information system to overcome processes of cellular stress self-regulation, for the purpose of the survival of cells.

2.2.4. Malignant Cells

The formation of a malignant tumor is closely associated with multiple damage and modification of the cell's genome (*e.g.*, viruses or chemical carcinogens). These changes cause the cells to react to the DNA damage, with an aim to interrupt the malignancy process (reaction such as apoptosis), but on the contrary, these reactions invariably contribute to the survival of the tumor cells [85]. Tumor growth is often associated with inflammation and is one of the most apparent negative outcome of cellular stress in living organisms [85]. Looking at gastritis, various oxidation products damage cellular DNA, RNA and proteins; and these effects lead to an increased in the mutations key proteins, and the disruption of their functions in the precancerous tissues of the stomach, contributing to the multistage carcinogenesis process [86]. In addition, tumor cells acquire resistance to hypoxia, immune system factors and antitumor therapy following stress response [33, 87]. Simultaneously, the bioaggressive factors of inflammation and immune response can promote necrosis and apoptosis of tumor cells, disrupt the blood supply of tumor tissue, and facilitate its localization. Thus, inflammation and other variants of tissue stress can promote or inhibit the tumor development depending on the types of tumors, specific pathogens, the stage of process development, and the effector molecules. The complex role of inflammatory diseases in tumor growth creates new opportunities and challenges for the manipulation of inflammatory pathways in cancer treatment [88].

2.2.5. Cell Aging

This arises from the stochastic accumulation of lesions in important biomolecules, which are vital for the proper cellular function. These changes induce cellular stress, Sequentially, cellular stress has an ambiguous effect on the dynamics of cellular and tissue aging. In general, cellular stress is an essential and attribute functional component of aging cells, which largely determines their phenotype, lifespan, and the degree of dysfunctionality [89, 90]. Cell aging is characterized by morphological transformations, a high level of expression of β-galactosidase (SA-β-gal), accumulation of inhibitor of cyclin-dependent kinase (CDK) p16INK4a and aging-related secretory phenotype (SASP), generation of heterochromatin foci (SAHF), build-up of protein aggregates in cells, telomere shortening, and cell response to increasing DNA damage [91, 92]. Stimuli form the basis of the maturation and development of organs and tissues, as well as a number intracellular and extracellular stressors. On the completion of the developmental growth of the living organism, the effect of these stressors, in addition with other aging factors could contribute to the cellular stress emergence and dysregulation, leading to either the normal or premature cell aging.

Authors reported that cell aging is characterized by the development of oxidative stress associated with mitochondrial dysfunction and damaging effects on various cellular structures by free radicals [93], the progressive accumulation of uncoordinated and aggregated proteins, and other damage to the cellular genome and proteome in the cell [94].

Cell aging acts as an alternate route to the cellular stress malignant process, in this case, the continuous accumulation of sublethal damage ultimately results in some variant of cell death or persistent dysfunction [95].

Cell aging is also linked to a prolonged blockade of the cell cycle, relative resistance to apoptosis, gradual progression of cellular stress pathways, such as the pro-inflammatory signaling mechanisms of intercellular communications [96]. This process could also span to stem cells, which gradually lose the ability of self-regeneration and differentiation, and eventually become dysfunctional [97, 98]. On normal conditions, aging of the organism gradually leads to chronicization of cellular and tissue stress, its systemic nature, secondary atrophic and sclerotic changes, a decrease in the functional potential of organs and systemic metabolic dysfunctions.

2.2.6. Tissue Metaplasia

This phenomenon is often connected to the change in cell differentiation occurring in a specific type of tissue, such as the replacing of single-layered epithelium by multilayered. In some cases of metaplasia, endometriosis morpho-functional changes in cells are pronounced, but cells still preserve their original tissue predisposition. Metaplasia is associated with the development of cellular and tissue stress (including oxidative stress and the production of pro-inflammatory cytokines), such association can be seen in metaplasia of the respiratory tract epithelium [99], endometrium [100, 101], and the connective tissues [102]. Metaplasia of the stomach epithelium occurs under inflammatory and atrophic changes of the gastric mucosa, prominently, in stomach glands [103]. As a rule, the process of metaplasia is progressive, and it is a product of the malignization of the tissue [103, 104].

2.2.7. Sclerosis of the Internal Organs

Sclerosis of the parenchyma of internal organs is the outcome of other general pathological processes, such as classical inflammation, and various variants of para-inflammation [10]. Sclerosis is associated with tissue stress, especially the 2nd and 3rd stage of para-inflammation or chronification of the classic inflammation. The process is characterized that the tissue cannot for various reasons to compensate for a decrease in parenchymatous cells that occurs as a result of apoptosis and programmed necrosis. In contrast to tissue atrophy, a decrease in parenchymatous cells is compensated with connective tissue as a rule of diffuse nature.

The most typical forms of sclerosis can be observed in a state such as, arteriosclerosis of the vessels, and fibrosis of internal organs, usually not reaching the stage of collagenosis. Manifestation such as the neurodegenerative processes, in which neurons are replaced by macroglial cells (primarily astrocytes), and stromal macrophages of microglia are equally examples of sclerosis which occurs as result of the hypertrophy and metaplasia of astrocytes (astroglyosis). These neurodegenerative conditions can be either diffuse or be accompanied by the formation of compact astrocytic scars that limit the focus of infection and/or tissue damage [105]. Findings have shown from the pathology of the neurodegenerative diseases, astrogliosis can disrupt the growth and regeneration of axons and dendrites [105, 106]. In sclerosis, more sensitive damaged parenchymal tissues are replaced by cell elements, and in fibrosis, they are replaced by extracellular matrix, connective tissue [107].

2.2.8. Classical Inflammation

Classical inflammation is the most well-formalized variant of manifestation of cellular stress at the tissue and organism level [10]. From the viewpoint of general pathology, classical inflammation can be defined as “a defensive process that a living body initiates against local tissue damage. It takes the form of a complex reaction of blood vessels, certain plasma components and blood cells, and cellular and structural components of connective tissue». This formulation sheds more light on the main objectives of classical inflammation, the focus of inflammation is an attribute of this process. The development of SIR characterizes only some of its variants. The concept of SIR covers various changes, such as signs of the stress response of the neuroendocrine system, changes in the levels of various metabolites and leukocytes in the blood in addition to the accumulation of markers of tissue stress in the blood.

The presence of these changes reflects the four criteria of SIR syndrome namely, specific values of tachycardia, tachypnea, fever

and multidirectional changes in the number of neutrophils in the blood [108].

2.2.9. Systemic Inflammation

For systemic inflammation to play the central link in the pathogenesis of shock and many other critical states, it has to be characterized as an independent form of the general pathological process associated with a certain quality of systemic tissue stress [25].

2.3. Biological Role of Cellular Stress, Functional Subsystems of Cellular Stress and their Pathogenetic Significance

To perform useful functions, the cell must maintain the integrity of its structures under normal and extreme conditions. Cellular stress is a protective-adaptive response of the cell to its macromolecules damage, critical changes in homeostasis or signs of potential damage (preventive response). This protective mechanism represents a genetically conserved process in the cell, owing to the fact the earliest organisms were faced with the challenge of constant changing unfavorable environmental conditions. At the time being, representatives of all biological kingdoms have highly conservative common sets of homologous stress proteins (products of orthologous genes), such as some chaperones, cell cycle regulators, proteasome regulators and proteins involved in the regeneration and repair of damaged nuclear and mitochondrial DNA [6].

The development of cellular stress is usually accompanied by pathological changes in the body; authors reported that cells can realize an adaptive stress response that nonspecifically increases the resistance of tissues to various stress factors, which include the intercellular exchange of stress signals during short-term changes in homeostasis under physiological conditions [32].

In view of the foregoing, the development of cellular stress can be distinguished into the following classes:

1) Adaptive response of individual cells and tissue to short-term and local changes in homeostasis under physiological conditions;
2) Prevention of damage to macromolecules, primarily the genome and proteome in the presence of threatening damage signals (preventive response);
3) Restoration or disposal of damaged macromolecules and organelles;
4) Preservation or restoration of physiological functions under action of damaging factors;
5) Self-destruction of cells with irreversible violations of their functions, through apoptosis or program necrosis;
6) Prevention of malignancy of cells (tumor growth) or other forms of their pathological functioning;
7) Inflammation and immune response.

The cellular stress development has its own distinctive features depending on the type of cell and the effect of factors, but also has universal manifestations presented in the form of relatively independent components of interrelated processes. These components are closely interconnected with each other, resulting in a holistic process of the cellular stress response. Most review articles have equally focused on the characterization of individual components of cellular stress: such as the oxidative stress [109-116], DNA-damage response [117-119], stress of endoplasmic reticulum (ER-stress) [120-122], reaction of heat shock proteins (HSPs) [123-125], formation of inflammasomes [126-128], enhancement of autophagy [129-131], typical outcomes of cellular stress *e.g*. apoptosis [8, 29, 132, 133], program necrosis [8, 134], and the association of cellular stress and inflammation with cell malignancy [135].

Recent studies have highlighted the pathogenetic significance of cellular and tissue stress in conditions such as aging [90, 136], various somatic diseases (*e.g*. atherosclerosis) [137, 138], diabetes mellitus type 1 and 2 [139, 140], hypertension [141, 142], nonalcoholic fatty liver disease [143], osteoporosis [144, 145], neurodegenerative diseases, multiple sclerosis [146] , Alzheimer's disease [147] and Parkinson's disease [148]. In addition, the likelihood of developing oxidative stress in the nervous tissue in response to psychogenic trauma [149, 150] and sleep deprivation has equally been revealed [151]. In most cases of classic infectious, allergic and autoimmune inflammatory diseases, strokes, heart attack, and other types of necrosis, the pathogenetic role of cellular stress is pronounced, and as such the stress is linked with the development of canonical inflammation.

2.4. The Main Typical Causes of the Development of Cellular Stress

In order to perform a protective function, cells must have an array of sensory structures that are sensitive to macromolecular damage and changes in other parameters of homeostasis. As a protective feature, cells directly involved in the development of inflammation and the immune response (leukocytes, macrophages, mastocytes, endotheliocytes, certain epithelial cells, platelets) can remotely sense alarm signals emanating from pathogens and damaged tissues through pattern-recognition receptors (PRRs) [152]. These receptors ligands are the conservative structures of microorganisms - pathogen-associated molecular patterns (PAMPs), some membrane stress-molecules of indigenous cells and soluble endogenous DAMPs (molecularly damaged patterns). On receiving a signal through the PAMPs and DAMPs, the cells can quickly take up a stress state, and this could contribute to their anti-inflammatory and immunocompetent functions until total damage of the cells.

Typical PAMPs are fragments of viral and bacterial DNA, evolutionarily conserved proteins, lipids and sugars of the cell wall of microorganisms [153]. One of the most powerful triggers of cellular stress is LPS. DAMPs are products of the decomposition of the cells, and structures of the intercellular substance of the connective tissue or some stress molecules that are purposefully secreted by pathologically activated cells, or some metabolites. The DAMPs nomenclature includes nuclear protein HMGB1, beta-defensins, some calcium-binding proteins of the S100 family, individual HSPs, uric acid and extracellular ATP [85, 154]. The general properties of DAMPs are their isolation from necrotic cells of various types; in some cases, inducible secretion by intact cells of the immune system; active participation in the development of inflammation and immune response [155, 156]. In the emergence of the phenomenon of purulent inflammation, DAMPs and direct damage factors such as hydrolases, free radicals, various cationic proteins (including defensins) are released upon activation, especially, neutrophil necrosis with the greatest intensity [157].

The well-known families of PRRs are the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), RIG-1 like receptors (RLRs), and AIM2-like receptors (ALRs) [158]. TLRs and NLRs recognize PAMPs and DAMPs within the cell or located on the cell surface. Signal pathways from these receptors cause a strong pro-inflammatory response in the cell and the production of cytokines [158]. Typical ligands of TLRs are evolutionarily conserved fragments of pathogenic bacteria, such as the lipid A (an LPS component) and other PAMPs. The principle of cross-regulation follows a tight rule where PAMPs and DAMPs of the same type can simultaneously use several PRRs to actualize this phenomenon [159]. The response to signaling information from PRRs (in particular, TLRs) requires both specific and the universal ways of triggering cellular stress, which range from the activation of transcription factors activator protein 1 (AP-1), Nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) [160-162]. The consequence of this response includes the rapid inducible synthesis and secretion of pro-inflammatory cytokines by cells, the overexpression of pro-inflammatory receptors on the outer membrane, and the formation of a cytokine network for intercellular interaction. Multi-

ple signaling pathways play a role in the formation and regulation of the cytokine network, this includes those from different types of PRRs. The ccompetition and synergy between TLRs allow the innate immune system to organize immediate local and systemic responses to various types of infectious agents [161]. The immediate local and systemic responses range from the self-regulation to cross-regulation mechanisms, that prevents inappropriate cell activation, and make cytokine response depending on the nature of the damaging effect [153, 162].

Many factors of the innate and adaptive immunity initiate cellular stress [163]. Individual cytokines at high concentrations, especially from the families of the TNF and IL-1 have been shown to activate cells like PAMPs and DAMPs [12]; the IL-1 receptor (IL-1R) contains a TIR (Toll-interleukin-1 receptor) common to TLRs signaling domain [164].

Scavenger receptors (SRs) play a crucial role in the development of cellular and tissue stress [165, 166]. Numerous cell types express SRs, but they are more pronounced in stromal macrophages [165, 167]. These receptors are responsible for filtering the blood and other tissues of damaged and apoptotic cells and aberrant metabolites, PAMPs and DAMPs, and perform a number of other homeostatic functions.

Studies have reported that information from SRs is capable of activating the universal intracellular signaling pathways of cellular stress associated with NF-κB and MAPKs [167]. However, the use of SRs, in contrast to classical PRRs, does not always lead to pronounced cell activation. Furthermore, a vast number of SRs are able to form receptor complexes with TLRs and some other PRRs and regulate their function in different directions.

This attribute shows the great relevance of SRs in maintaining homeostasis of cells in physiological conditions [165]. A new standardization system for SRs was adopted in 2017 [166], SRs were divided into 11 classes (A-L). The uniqueness and array of the functionality of the SRs were reported by authors, they are capable of binding to several ligands, cooperate with receptors of other families (*e.g*., TLRs), and form receptor complexes on the cell membrane [165].

These receptors may be involved in the development of cellular stress and the pathogenesis of various chronic diseases, including atherosclerosis [168, 169], neurodegeneration [170-172], hypertension [173], diabetes mellitus [170, 171, 174], and tumor growth [167, 175]. In view of the foregoing, the development of cellular stress can be distinguished into the following classes:

1) Non-lethal, but critical to the preservation of cell physiological functions and damage to the genome, cell membranes, and any structures of cellular proteins;
2) Critical changes in homeostasis, *e.g*. that of the ones associated with hyperthermia [176], hypoxia [177], changes in osmotic pressure [178], shifts to the left AMP / ADP / ATP ratio [179], impaired dynamic characteristics of blood flow [180];
3) Effects on cells, predominantly the innate and acquired immunity, PAMPs and DAMPs, or other molecules carrying information about real or probabilistic damage to tissue structures [181, 182];
4) Effects on cells involved in the development of inflammation and immune response, the activation factors of the complement system, hemostasis, immune complexes, inducible receptors of contact interaction, and inflammatory mediators [12];
5) Changes in the physiological interactions between cells that disrupt their normal functions [183, 184], such as the constitutive receptors of cadherins families providing contact interactions between adjacent cells [185, 186], and integrins providing contacts between cells [50];
6) Effect of antigens on lymphocytes antigen-specific receptors, in order to perform their immune functions, lymphocytes are tasked to receive additional activation signals via PRRs, cytokine receptors and contact-interaction receptors [187];
7) Various cases leading to a critical accumulation of Ca2+ or a decrease in the cytoplasmic K+ concentration levels [188-191].

Cellular stress can be caused by the action of a single but powerful inductor, or a combination of a large number of relatively weak inductors. The manifestations and functional significance of cellular stress reactions depend on both the nature of the inducing changes, and the type, and the initial state of the cell itself.

The presence of indicator molecules of cell damage (indicator transaminases), inducible pro-inflammatory cytokines, and DAMP, in the blood of healthy people even at trace amount [192], indicate latent, preclinical lesions in the body. These changes are eliminated by the adaptation mechanisms of cellular and tissue stress in physiological conditions. However, an increase in these changes can become pathological.

3. BASIC TYPICAL PHENOMENA OF CELLULAR STRESS

Hitherto, it was difficult describing a holistic picture of the cellular stress processes, even in the most simplified form, it became necessary to subdivide these processes into relatively independent subsystems. Currently, the molecular mechanisms of the typical components of cellular stress have been extensively studied, and thus, could be characterized in a simplified form listed below.

3.1. Oxidative Stress

Oxidative stress is the most renowned component of cellular stress and plays a key role in the pathogenesis of various diseases. This fact is evident considering the various listed reasons:

1. Both prokaryotes and eukaryotes are prone to developing oxidative stress;
2. Oxidative stress is classified as a component of various types of pro-inflammatory and inflammatory reactions at the cellular, tissue and organism level [193];
3. Most neurodegenerative diseases such as Alzheimer's disease [194], Parkinson's disease [195]; prion diseases [196]; glaucomatous neurodegeneration [197]; some other neurodegenerative diseases [198], and also those associated with post-traumatic stress disorder syndrome (PTSD) [199], are connected with typical morphofunctional changes and death of cells caused by oxidative stress;
4. Oxidative stress is an important link in the pathogenesis of many socially significant diseases, *e.g*. atherosclerosis, obesity, diabetes, hypertension, renal and cardiovascular insufficiency, pulmonary fibrosis, various arthrosis and arthritis, endothelial dysfunction and aging [109, 114-116, 200-202];
5. Oxidative stress has been implicated as a risk factor for tumor development [111, 115];
6. At the cellular level, the action of oxidants results in an array of responses, such as proliferation, differentiation, apoptosis, immune and pro-inflammatory responses [109, 203]. Hyperproduction of reactive oxygen species (ROS) and nitrogen (RNS) has been associated with many physiological processes, as these reactive species can act as signaling molecules, and help to maintain physiological functions, such as the effect observed in skeletal muscles function [204, 205].
7. At present, a wide range of methods is available for the assessment of oxidative stress, as well as methods of antioxidant therapy [112, 113, 116].

The over-consumption of O2 in the formation of ROS under hypoxia conditions indicates the dual role of free radical oxidation either in the protective or pathological process in the organism [206]. One of the sensors of O2 deficiency identified in different

cells is the transcription factor hypoxia-inducible factor 1 (HIF-1), this sensor plays a key role in the inducible biosynthesis of more than 60 stress proteins. HIF-1 expression is tightly regulated by the concentrations of ROS and NO [207].

The formation of pro-oxidants can occur spontaneously as a result of external factors acting on the cell, and specifically as a result of enzymatic reactions [113, 116].

The pro-oxidants-antioxidants or reduction-oxidation reaction (redox) balance is one of the crucial parameters of homeostasis [109, 115]. The redox status of the cell is supported by a redox buffer with the participation of glutathione (G-SH), and a number of other non-enzymatic and enzymatic antioxidants [115, 208]. The capacity of this buffer is robust, requiring a large amount of oxidant to upset the G-SH / GS-SG ratio for the development of oxidative stress. Oxidative stress in the cell develops when the accumulation of pro-oxidants interrupts the redox equilibrium, causing an imbalance between oxidants and antioxidants in favor of oxidants [115, 208]. Both excessive and insufficient oxidative stress response could trigger a wide range of human diseases and their progressive development.

The mitochondria are the main site of ROS formation; cytochrome C released from the mitochondria during oxidative stress, coupled with NADPH oxidase of microsomal oxidation, 5-lipoxygenase, xanthine oxidase, and cytochrome P-450, have all be highlighted in the generation of ROS / RNS in the cytoplasm [115]. Microsomal oxidation, a process that occurs in most tissues under normal condition, with the exception of the skeletal muscles, are stimulated by external and intracellular stress signals acting through various signaling pathways, in particular, those associated with mitogen-activated protein kinases (MARK) and transcription factors of the AP-1 and NF-κB [201, 202, 205, 208, 209, 210]. Under physiological conditions, microsomal oxidation influences the synthesis of various substances and is involved in the detoxification of many endogenous toxins and xenobiotics [211, 212].

Under oxidative stress, molecular modifications of various signaling molecules caused by ROS / RNS, play a key role in the initiation and development of all other components of cellular stress [203, 213]. Aldehydes and ketones formed during the oxidation of polyunsaturated fatty acids further modify proteins, and also promote the activation of some stressor kinases (such as the ASK1-SEK1-JNK signaling pathway) that binds oxidative stress to inflammation [214]. Under extreme condition ROS / RNS directly or indirectly activates numerous transcription factors associated with the development of cellular stress, such as the NF-κB, HIF-1, AP-1, Sp1, p53, c-Jun, c-Fos, early growth response factor-1 (EGR-1), heat shock transcription factor 1 (HSF-1), protein kinase MAPK, protein kinase C (PKC), small G-proteins Ras, various growth factor receptors and other molecules involved in signaling pathways that regulate cell growth and death, apoptosis processes, program necrosis, stress resistance of cells and their pro-inflammatory functions [109-112, 115, 116, 215]. The action of prooxidants on proteins has been shown to be dose-dependent, which predicts the ambiguity of their effects at various stages of the development of cellular stress. A typical example of this dose-dependent action can be seen on the action of prooxidants on MAPK family which includes a large number of serine-threonine protein kinases involved in the regulation of a wide range of cellular processes, such as proliferation, differentiation, adaptation to stress, and apoptosis [109, 209, 216]. Similarly, the MAPK subfamilies, ERK (extracellular-regulated kinases), JNK (c-Jun N-terminal kinase), and p38 are activated in response to the action of various concentrations of the oxidant; although they are activated independently of each other, they share partial overlapping signaling cascades. The ERK pathway is more often associated with the regulation of cell proliferation and their subsequent differentiation, whereas the JNK and p38 pathways are more involved in the processes of cell differentiation and enhancing the pro-inflammatory orientation of cellular stress [209, 217, 218]. The signaling pathways of JNK and p38 are also connected with the production of cytokines, and other phlogogenic factors with more pronounced oxidative effects [217]; JNK and p38 are often grouped together into complementary functional systems, and often referred to as stress-activated protein kinases (SAPK) [209]. ERK promotes cell survival, but can also exhibit an apoptotic effect; JNK and p38 can also show both pro-apoptotic and anti-apoptotic effects in response to oxidative stress, depending on the circumstances and the specific signaling pathways into which they will enter [209, 219, 220].

The p53 protein regulates the repair of DNA damaged during the cell cycle, in conditions of irreversible cell damage, these proteins exhibit a pro-apoptotic effect through increasing the formation of ROS; this is made possible by the activation of the redox enzyme p66 that oxidizes cytochrome C, resulting in the formation of the necessary amount of H_2O_2 for apoptosis [221]. Authors have highlighted that p53 and NF-κB inhibits the expression of each other, while p53 is associated with more moderate manifestations of oxidative stress, survival or apoptosis of proliferating cells, NF-κB, on the other hand, is linked with a pro-inflammatory stress orientation, usually in more differentiated cells with limited proliferative opportunities [222, 223]. P53-mediated DNA repair occurs at a moderate level of oxidative stress, in a situation where this process becomes ineffective, cells die by apoptosis. Further increase in the oxidative stress levels, activates NF-κB and inhibits p53-induced apoptosis of cells [224]. Relatively small concentrations of ROS are involved in activation of signaling pathways of growth factors and increase in cell resistance to damage, however, high concentrations of oxidants contribute to damage of macromolecules of the genome and proteome [203], and interruption of the cell cycle [225, 226]. Many stressor signaling pathways play a role in the development of oxidative stress. The oxidizing interface is a phenomenon used by some authors to describe the combined action of the ROS / RNS to directly activate signaling molecules that trigger many ways of developing cellular stress [110].

While the processes of free radical oxidation take place mainly outside the nucleus of the cell, their accumulation in the nucleus promotes DNA damage, mostly during cell replication, this effect helps to maintain a relatively stable redox equilibrium in the nucleus even under cellular stress [227]. As a regulatory mechanism of the negative feedback during cellular stress, oxidants activate the transcriptional factor Nrf2 (signal pathway Keap1 / Nrf2), triggering the biosynthesis of glutathione, thioredoxin, some other antioxidants and xenobiotic detoxifying enzymes [115, 228]. This regulatory pathway inhibits the activation of NF-κB, reducing the severity of acute inflammatory reactions and enhanced the resolution process of cells to physiological state [229]. The expression of Nrf2 is controlled by a complex transcriptional and post-translational network, on the principle of negative feedback, particularly, are activated mainly in proliferating cells by the transcription factors NF-κB, AP-1 *via* Jun and Myc [228]. Drugs that potentially activate Nrf2 are currently considered as promising antioxidant therapy in the treatment of diabetes mellitus and some other somatic diseases [230].

Oxidants, primarily NO and hydrogen peroxide, can participate in intercellular signal communications under normal conditions, and in tissue stress, such as inflammation [215, 231, 232]. The main part of oxidative stress is purulent inflammation and the main cellular element of which are the neutrophils. Free radicals released from phagocytes not only damage tissue structures but also inactivate antiproteinases, paving a way for tissue destruction processes [233].

At certain stages of the development of cellular stress, oxidative stress acts like a shield to cells, but when cellular stress is amplified and get chronic, it promotes cell aging, apoptosis and program necrosis.

3.2. Mitochondrial Stress

Mitochondria are the main donors of ATP and ROS, a site for the end point of catabolism and the starting point for the anabolism of lipids, glucose, interchangeable amino acids, nucleotides and a number of other biologically active molecules; these organelles act as suppliers of energy and key metabolites, such as the metabolites of the Krebs cycle, they are involved in the regulation of calcium homeostasis, and they facilitate the synthesis of urea in hepatocytes [206, 234, 235].

In the mitochondria of humans, there are approximately 1500 proteins, 13 of which are encoded in mitochondrial DNA (mtDNA), these mtDNA are the most important proteins of respiratory complexes [235, 236]. The remaining proteins found in the mitochondria are encoded in nuclear DNA, synthesized in the cytoplasm, and then enter the mitochondria. The formation of the mitochondrial proteome also depends on many mechanisms of post-translational modification of proteins, for example, their phosphorylation [206, 234]. The composition and activity of many mitochondrial proteins will change with cellular stress, and these changes, in turn, largely determine the response of cellular stress in general [227, 237]. The energy and other metabolic functions of the mitochondria depend on the type of cell. Therefore, the mitochondrial proteome corresponds to the specific needs of tissue, to the functional state of its cell and depends on the effect of the activation and damaging factors on the mitochondria itself [234, 237].

Like cellular stress, mitochondrial stress develops in response to various damages, including excess accumulation of fatty acids, and some other toxic metabolites [238], and effects of cellular stress agents to mitochondria as well [206, 234]. In turn, mitochondria are involved in the reaction of cellular stress and oxidative stress.

Complex mitochondrial stress includes several components, which include the increase in mitochondria division, the development of oxidative stress, the interaction of mitochondrial processes with processes of cellular stress, the regulation of activated cells metabolism. In the mitochondria, mitochondrial ribosomal proteins, respiratory chain and ROS production decreases with the restoration of disturbed mitochondrial homeostasis. Restoration of disturbed mitochondrial homeostasis occurs by the integrated mitochondrial-nuclear signaling pathway called the mitochondrial unfolded protein response (UPRmt) [239, 240].

Irreversibly damaged mitochondria are identified and utilized by the lysosomes in a process known as mitophagy (autophagy of mitochondria). Mitophagy requires PINK1 kinase (PTEN-induced kinase 1), which is imported into healthy mitochondria and eventually degrades, just like the ATFS-1. However, when the import of this kinase into damaged mitochondria is disturbed, PINK1 is stabilized and activated on the outer mitochondrial membrane, leading to the phosphorylation of a number of proteins that trigger the process of mitophagy [236]. Mitophagy is a natural process of recycling old mitochondria in a cell, but with the development of cellular and mitochondrial stress this process can be activated and have both positive and negative value for the cell depending on various circumstances and its balance with other processes of cellular stress [236].

The development of UPRmt causes various damage to the proteome and mtDNA, such as the accumulation of uncoordinated proteins in the mitochondria [241].In this process, there is a multidirectional change in the biosynthesis of various mitochondrial proteins (reduction of potentially toxic proteins), and the increase in production and transport to mitochondria of chaperones capable of remediating damaged mitochondrial proteins, increase in antioxidants, proteases, some transport proteins, with activating the ubiquitin-proteasome pathway for the utilization of irreversibly altered proteins.

In mammals, UPRmt is closely related to other factors of cellular stress by direct and inverse interactions [236]. This also applies to mitochondrial stress in general, for example, the release of mitochondria from cytochrome C promotes oxidative stress, and mtDNA appears in the cytoplasm and in the intercellular environment as a mitochondrial DAMP (mtDAMP) [241]. The integrative response of mitochondrial stress is associated with the activation of the mechanistic target of rapamycin complex 1 (mTORC1), mTORC1 is a kinase that stimulates cell growth in response to adequate cellular nutrition, the accumulation of ATP, and the effect of growth factors [242]. This kinase can inhibit the processes of autophagy and mitophagy [243]. The regulation of mitophagy with mitochondrial stress remains controversial, on one hand, the removal of nonviable mitochondria is required, and on the other hand, it is necessary to preserve mitochondria and to repair it. Another manifestation of the integrative response is the enhancement of some metabolic cytokines expression in the cells, which include the fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) [244]; these factors contribute to the regeneration of tissue, increase in the insulin sensitivity of cells, and the survival of cells in conditions of moderate effect of damaging factors.

It is now evident that the aging process is associated with cellular stress in general and mitochondrial stress [90]. Activation as a result of moderate and short-term cellular stress of sirtuins, mammalian target of rapamycin (mTOR), AMP-activated kinases (AMPK), is aimed at restoring damaged structures, limiting aggressive pro-inflammatory mechanisms of cellular stress, counteracting insulin resistance and promoting cell tolerance for moderate damage [245, 246]. It was also reported that the activation of UPRmt correlates with the longevity of both worm C. elegans and mice [247]. However, these factors in the conditions of increasing cell damage and further development of cellular and tissue stress can contribute to the preservation of aging, cells dysfunction, and promote the longevity of malignant cells. Authors reported on the negative role of UPRmt in tissue aging and tumor growth [248].

The accumulation of mtDNA mutations leads to the aging of mitochondria and to an increased risk of malignancy of cells in mammals [249, 250]. Lipotoxicity is another factor contributing to damage and dysfunction of mitochondria with aging [251-253]. The discrepancy of the damaging effect of lipotoxicity arises from the difference between the quantity of fatty acids (especially saturated ones) entering the cell and its energy need. First of all, this mechanism of mitochondrial dysfunction affects facultatively glycosylating tissues such as liver, myocardium, red (slow) muscle fibers, adipocytes and macrophages of adipose tissue [254-258], with the exemption of the brain.

Under normal aging, these processes proceed slowly and are more associated with a decrease in the functional reserves of the mitochondria, however, in several diseases, mitochondrial dysfunction and inadequate mitochondrial stress lead to severe complications. Some examples of such severe complication can be seen in the development of myopathy and cardiomyopathy in type 2 diabetes mellitus (high level of lipotoxicity against insulin resistance) [259, 260] and genetic pathologies of the group of diseases FAOD (Fatty Acid Oxidation Disorders) with violation of the catabolism of fatty acids [261]. In experimental type 1 diabetic mice with the development of diabetic cardiomyopathy, mitochondrial proteome remodeling is observed, while mitochondrial functions in the kidneys, brain and liver are retained, but not in the heart [262].

In pancreatic β-cells, mitochondria are involved in glucose-stimulated insulin secretion by generating metabolic signals, including the formation of intermediate compounds of the tricarboxylic acid cycle. However, mitochondrial dysfunction caused by lipotoxicity disrupts these processes and contributes to death of β-cells [263]. Strengthening the oxidation of fatty acids, lipotoxicity against oxidative stress and the dysfunction of the mitochondrial respiratory chain may contribute to the development of cellular necrosis and fibrosis in non-alcoholic fatty liver disease [264, 265].

In experimental hypertension model, mitochondrial dysfunction and oxidative stress associated with mitochondria were reported in the brain, blood vessels and myocardium [266]. Mitochondrial dysfunction is a characteristic feature of various neurodegenerative diseases [267]; authors reported that in response to high doses of glucocorticoids in the skeletal muscles of chickens, the dysfunction of the first complex of the respiratory chain was observed [268].

Thus, mitochondrial stress is directed toward the elimination of mitochondrial damage and dysfunction. However, under certain conditions, it may be incompletely effective or even contribute to maladaptation. In the latter case, individual mechanisms of mitochondrial stress can become participants in the dysfunctional systems of the formation of a vicious pathogenetic circle, which is associated with the development of many diseases. However, this also applies to all other functional components of cellular stress.

3.3. The Stress of the Endoplasmic Reticulum (ER-stress)

The endoplasmic reticulum (ER) consists of continuous membranes that include the nuclear envelope and the peripheral ER, consisting of flat sheets and branched tubules [269]. ER of cells that synthesize many secreted proteins, largely consists of sheets, and ER of cells participating in lipids synthesis, transmission of calcium signals and contacting with other organelles consists mainly of tubules. Thus, ER is the place for synthesis, bending (packing), maturation and transportation of secretory and many membrane proteins, as well as a place for lipid synthesis, and the main place of deposition of Ca^{2+} [270]. Most cellular proteins fit into the cytosol with the help of chaperones immediately after translation, while membrane and secreted proteins are folded and matured in ER. Correctly folded proteins are moved away from the ER to the intracellular organelles and the extracellular medium, while the uncoordinated proteins either persist within the ER, or are degraded by cytoplasmic proteasomes [17].

Violation of the integrity of the ER or the accumulation in the cellular compartments of inappropriate proteins initiate ER-stress, primarily in the form of unfolded protein response (UPRER) [16]. The UPRER process is aimed at restoring the altered ER homeostasis, while solving the following main tasks: 1) suspension of the synthesis and secretion of secretory proteins from the cell; 2) facilitates an increase in the transcription of chaperones and other proteins involved in the bending and maturation of proteins; 3) inducing degradation of uncoordinated proteins through an ER-associated degradation complex (ERAD) [271].

Many causes such as the elevated levels of glycated proteins, protein modifications by oxidant, calcium metabolism disorders, viral infection, hypoxia and other cell homeostasis disorders lead to the accumulation of unfoldable proteins in the ER, resulting in an evolutionarily conservative response in the form of UPRER [272].

Specific mechanisms of UPRER help the cell cope with the accumulation of damaged proteome in ER, these mechanisms include the stages of damaged structures detection, transduction of the voltage signal into the nucleus, the initiation of protection programs and the restoration of cellular homeostasis. Proteom quality control involves the detection of damaged proteins using damage sensors which could be certain chaperones and folded enzymes [273]. UPRER is mediated by three major transmembrane sensors: 1) the inositol-requiring enzyme 1 (IRE1), 2) the PERK protein kinase and 3) the activating transcription factor 6 (ATF6), which are all kept inactive, mainly by the BiP / GRP78 chaperone [264]. The sensors are released, activated and cause the following basic UPRER responses:

PERK phosphorylates and thereby inhibits the factor Eukaryotic Initiation Factor 2 alfa (eIF2α), preventin additional protein synthesis,and blocking the synthesis and secretion of secretory proteins from the cell.

The PERK / eIF2α pathway stimulates the translation of several specific mRNAs involved in the development of cellular (in particular mitochondrial) stress [273].

The ATF6 factor is modified as a result of partial proteolysis, after which it is transported to the nucleus, where it is a transcriptional activator of genes involved in ERAD, lipid biosynthesis, protein folding (ER chaperones) and ER membrane biosynthesis.

IRE1 activates the transcription factor X-box-binding protein 1 (XBP1), which in turn, activates the nuclear DNA genes involved in the production of ER chaperones, ERAD complex proteins and the synthesis of membrane phospholipids [273-275].

All these pathways contribute to the survival of the cells under ER-stress conditions. Accumulating in ER, damage sensors of the proteome and the BiP / GRP78 chaperone free from contact with uncoordinated proteins block the UPRER sensors; this serves as the main mechanism of negative feedback of the development of ER-stress.

Prolonged intensity of the UPRER induces apoptosis through several pathways [276, 277]. Apoptosis is also promoted by the excessive output of Ca^{2+} into the cytoplasm from the ER [272]. Since anti-apoptotic pathways (anti-apoptotic proteins of the Bcl-2 family, and other mechanisms) could simultaneously induce the ER-stress [278], apoptosis becomes the extreme and far from the only outcome of ER-stress.

ER stress leads to the activation of two ways of protein degradation, namely: 1) ubiquitin-proteasome, through ERAD and 2) lysosomal mediated protein degradation by the autophagy process [279]. ERAD includes the translocation of deployed ER proteins to the cytosol, where they covalently bind to ubiquitin (ubiquitination of the protein), and then are utilized in proteasomes. When the number of uncoordinated proteins exceeds the capabilities of ERAD, autophagy as an additional pathway for the utilization of damaged proteins and especially their aggregates can be effectively activated by ER stress [279].

Chronic ER-stress and deficiencies in the transmission of UPRER signals are pathogenetic factors of many human diseases, including diabetes, neurodegeneration and cancer [280, 281]. ER-stress can also be activated in the development of metabolic syndrome in many organs, including hypothalamus, liver, adipose tissue, muscle and pancreatic β-cells [282]; this activation could lead to an increase in insulin resistance in the liver, β-cells, adipose and muscle tissue. High expression of products of UPRER has been revealed in visceral fat for severe obesity, type 2 diabetes, especially in hypoxia-complicated adipose tissue [283]. Saturated fatty acids cause ER-stress in the muscles, and prolonged ER-stress disrupts the synthesis of insulin and promotes apoptosis of the pancreatic β-cells [273]. However, ER-stress in mice inhibits transcription of resistin in adipocytes [284], and resistin is a pro-inflammatory factor promoting insulin resistance. The inhibitory effect on resistin suggests that any mechanism of cellular stress cannot be considered unilaterally, since all mechanisms of cellular stress can exhibit both adaptive and maladaptive value, depending on the situation. Cellular stress of cardiomyocytes, including ER stress, can be mediated by the accumulation of saturated fatty acids and other factors of lipotoxicity in these cells [285]. ER-stress develops in the atherosclerotic focus in the macrophages, endotheliocytes and vascular myocytes, in response to systemic and local metabolic dysfunction [277]; authors reported that ER-stress promoted the survival of tumor cells in the hypoxic environment [278].

Thus, ER-stress is a genetically programmed response of the cell to various lesions and a relatively independent component of cellular stress. UPRER anomalies can explain early events in the pathogenesis of a wide range of somatic diseases [286].

3.4. Heat Shock Proteins

Heat shock proteins (HSPs) consist a significant proportion (approximately 5-10%) of cellular proteins in a steady state, and under cellular stress, their amount substantially increases due to inducible forms [287]. The HSP reaction is an evolutionary, highly conserved molecular response of the cell to the disturbances of its protein homeostasis (proteostasis) [288]. In humans, HSPs are the main types of molecular chaperones in all cells [289], the protective functions of these proteins were originally identified in the development of heat shock, but later became evident in other variants of cellular and tissue stress [290]. The main biological functions of HSPs as chaperones are:

1) Participation in folding (packing) of the spatial structure of proteins in the post-translational period of their biosynthesis, and realization of other functions characteristic of chaperons in different tissues [125, 223, 291-294];
2) Regulation of cellular stress signaling pathways, including pro-apoptotic and anti-apoptotic pathways [295-298];
3) Direct participation in the UPRER and UPRmt processes;
4) Participation in the formation and transport of steroid hormone receptors (the HSP90 family) [125] and in the immune interactions [123, 287, 299].

In addition, HSPs are actively involved in the processes of the cell cycle, cell differentiation, regulation of secretory and endocytic function, inflammation, and survival of tumor cells [125, 288, 295]. They are also important pathogenetic factors in various neurodegenerative diseases, diabetes, and many other human pathologies [124, 294, 300-303].

Initiation of HSP-response can be realized from external and intracellular signals [304]. The synthesis of inducible HSPs triggers signaling pathways associated with protein kinases - MAPK (JNK, p38, ERK) and with calmodulin-dependent protein kinase II (CaMKII) [301]. Furthermore, these kinases ultimately activate several transcription factors, among which is the transcription factors of the HSF family (, mostly the HSF-1 [289, 304]. HSF-1 promotes longevity, prevents the instability of the proteome during aging, stress and development (cell proliferation and differentiation); simultaneously, the HSF-1 also promotes the survival of tumor cells, this has been observed from the ability of many HSPs: HSP90, HSP70 and HSP40 (DNAJB1) to inhibit HSF-1 function by negative feedback [305].

The triggering of the signaling pathways for the biosynthesis of inducible forms of HSPs, is specifically aimed at various damage to the proteome, such as the exposure to hyperthermia, oxidative stress, accumulation of prion cells or other amyloid proteins. Indicator chaperones bind to damaged proteins, exerting a suppressor effect by the release of a number of protein kinases and transcription factors that initiates the synthesis of HSPs. In conditions where HSPs are synthesized excessively, their products are inhibited, as well as many other mechanisms of cellular stress, according to the principle of negative feedback [288, 304]. The biosynthesis of inducible HSPs participating in UPRER and UPRmt is regulated by standard mechanisms of UPR self-regulation.

3.5. Strengthening the Processes of Autophagy (Lysosomal Stress)

Autophagy is a term that summarizes all processes of intracellular material degradation with the participation of lysosomes, and the processes in which macromolecular components are recycled through their biosynthesis and subsequent decay [306]. Autophagy is an evolutionarily conserved process in all eukaryotes and proceeds in all human cells, it is chiefly a catabolic process involving the lysosomal stage [307]. This process is a part of many physiological or pathological processes, with its severity reported to be increased during fasting and cellular stress, in these cases, it usually contributes to cells survival [308-310]. Autophagy facilitates the hydrolysis and utilization of damaged and dysfunctional individual proteins, protein aggregates or organelles, in a cell in need of essential amino acids. Owing to the fact that autophagy is involved in cell growth (negative), survival and death, its levels should be strictly regulated; dysregulation of autophagy is a companion to many human diseases, such as cancer, myopathy, neurodegeneration, cardiovascular pathology, liver and gastrointestinal tract and metabolic diseases [311, 312].

Autophagy acts as a mechanism for the disposal of irreversibly damaged proteins, however, they are not the only mechanism involved in this disposal; most cellular damaged and short-lived proteins are degraded after they are labeled with ubiquitin, through the proteasome pathway [313]. In cellular stress, the ubiquitin-proteasome pathway becomes more pronounced, which could act as an additional mechanism for the activation of autophagy [314]. In addition, many aged proteins, large protein aggregates, and individual organelles can be utilized only in the process of autophagy with the participation of lysosomes and numerous auxiliary protein factors [314]. Thus, autophagy largely determines the balance between protein biosynthesis, the biogenesis of organelles and their decay. In particular, mitophagy is the only physiological autophagy degradation mechanism of mitochondria. Furthermore, autophagy can also be crucial in the prevention of apoptosis or necrosis of the cell by removing damaged and pathologically activated mitochondria, as well as protein complexes associated with the development of cellular stress. The process of autophagy is associated with apoptosis, while the anti-apoptotic proteins of the Bcl-2 family are negative regulators of macroautophagy, and the proapoptotic members of this family stimulate macroautophagy [306].

Autophagy is divided into three main types, namely, the macroautophagy, microautophagy, and chaperone-mediated autophagy [312]. The macroautophagy includes the formation of vesicles (autophagosomes), which are formed by a double membrane surrounding the object of autophagy, with the participation of more than 30 autophagy proteins involved in the recognition of the object of autophagy, and the establishment of the contact between the autophagosome and the lysosome; an autophagolysome is formed after the establishment of contact, in which the object of autophagy is cleaved by acidic lysosomal hydrolases, especially cathepsins. Microautophagy arises when the lysosome directly captures a relatively small object of autophagy with the help of membrane involution. The chaperone-mediated autophagy is observed when the chaperone complex+ damaged protein (especially those containing the KFERQ pentapeptide) binds to the lysosome-associated membrane protein 2A (LAMP-2A), and translocated inwards to the lysosomes for degradation [310].

The regulation of autophagy has been shown to occur on several levels [307, 310], namely:

1) Activation or inhibition of autophagy factors acting before the formation of autophagosomes, the key inhibitor of this stage is the mTOR factor;
2) Modulation of autophagy-related genes (ATG) expression [315], and the regulation of the expression of their products, such as the Atg proteins that are directly involved in the formation of autophagosomes;
3) Regulation of the maturation process of autophagosomes and their fusion with lysosomes, including the final cleavage of autophagy products by lysosomal enzymes.

Several key molecular components participate in the regulation of autophagy when activated by growth factors and excess amino acids; mTORC1 has activated, that leads to the inactivation of the ULK1 / 2 complex (ULK1/2+Atg13+Atg101+FIP200) important for the initiation of autophagy. In contrast, inducers of autophagy, such as glucose deficiency, ATP (through activation of AMPK), amino acids, DNA damage (in particular, through the p53 / AMPK /

mTORC1 pathway), hypoxia, and ROS abolish the inhibitory effect of mTOR on the complex ULK1 / 2 + Atg13 + Atg101 + FIP200 [314, 316]. This latter effect leads to the activation of alternate routes of inducing autophagy, such as the PI3K (inositol-3-phosphate kinase, Phosphoinositide 3-kinases) pathway [310, 316]. It is known that PI3Ks of Class I (the product of this reaction is phosphatidylinositol-3,4,5-trisphosphate) are involved in the signaling pathway of mTOR activation and inhibition of autophagy, whereas, PI3Ks of class II and III catalyze the formation of phosphatidylinositol-3-phosphate, and activate macroautophagy [317]. Inhibitory macroautophagy signaling pathway class I PI3K / Akt / mTOR triggers insulin, many growth factors and metabolic cytokines [318], this pathway also promotes the proliferation, growth and survival of cells, but in some cases, can also facilitate their tumor transformation [319].

Fasting primarily activates the first two stages of autophagy, due to the lack of an activating effect of amino acids, glucose and ATP on mTORC1 [320]. In conditions of an excess of amino acids, cell growth factors, and binding-free uncoordinated proteins, the chaperones activate the mTOR protein and block the initial stages of autophagy, and many cell stress factors, which include ROS and RNS, with the exception NO (act in the opposite direction) inhibit mTOR and, subsequently, activate autophagy [310, 312, 321]. The action of prooxidants in cellular stress on one side contributes to the damage of cellular structures, and on the other hand, promotes the utilization of damaged proteins and whole organelles. However, this process is not always balanced. In Alzheimer's disease, toxic proteins accumulate and develop mitochondrial and oxidative stress [322], with this pathology, the final (third) stage of autophagy is broken, which leads to the dysfunction of the process and accumulation of amyloid proteins in neurons [323]. The artificial deficiency of mTORC1 in adipocytes of experimental mice has been shown to promote pro-inflammatory changes in adipose tissue, increased insulin resistance and hepatic steatosis [324].

As cells age, the regulation and realization of autophagy may not be balanced. In normal aging and neurodegenerative diseases, a balance can be maintained or disturbed, a typical example can be seen between the number of mitochondria (depending on the intensity of mitophagy) and the degree of their dysfunction (also depends on mitophagy, but in the opposite way) [325]. Under the conditions of the blockade of apoptosis, intensification of the autophagy processes can lead to autophagic cell death, and an increase in the severity of tissue stress, which does not necessarily facilitate the adaptation of cells to the changes in tissue homeostasis in most cases [326]. The mechanisms of autophagy are also involved in the destruction of extracellular (in phagocytosis) and intracellular pathogens and in the development of anti-infective adaptive immunity, which includes the presentation process of antigens to T cells [327, 328]. In infection and tissue damage, the signal information from various TLR activates different protective mechanisms of innate immunity cells, such as the phagosome maturation, and also stimulates autophagy processes [329]; however, in response to this, many pathogens acquired the ability to disrupt various stages of autophagy, thereby preventing phagocytosis and the development of an immune response [307].

Thus, activation of the processes of autophagy and proteasome proteolysis is a typical manifestation of a vast number of variants of cellular stress with a more pronounced pro-inflammatory orientation. However, with increased tissue regeneration processes (stage 1 of tissue stress), autophagy activity becomes limited.

This protective mechanism is aimed at the utilization of damaged proteins and organelles, byproducts of metabolism, and the activation of regulatory factors to fulfill these protective functions. In addition, the splitting of short-lived proteins is a mechanism for controlling and regulating many physiological functions and the development of cellular stress.

Ambiguous changes in autophagy and proteasome pathway are observed with aging and tumor cell transformations. On the contrary, the activity of autophagy usually increases at a certain stage of intensifying oxidative and mitochondrial stress, increasing damage to the proteome, phagocytosis and other pro-inflammatory cell reactions. Autophagy appears as a mechanism of negative feedback in the regulation of pro-inflammatory cellular stress, by removing damaged and pathologically activated structures. Autophagy also contributes to the removal of damaged mitochondria, inflammasomes and other stress protein complexes, while limiting the development of mitochondrial and oxidant stress, the production of pro-inflammatory cytokines, such as the IL-1β and a number of other pro-inflammatory mechanisms [330-332]. It is worthy to mention that, the processes of autophagy must be considered with other manifestations of cellular and tissue stress, as well as with causative factors that initiate them; the dysfunction of autophagy and ubiquitin-proteasome pathway could act as a pathogenetic mechanism for the disruption of the physiological state of the cell and the development of many human diseases.

3.6. Inflammasome Formation

The inflammasome is a multimeric cytosolic protein complex that has sensory molecules in the form of intracellular PRRs of two families, namely the NLRs (the prominent receptors) or the Absent in melanoma 2 like receptors (ALRs) [333]. These receptors bind when assembling the protein complex with procaspase-1, in most cases through an additional protein (apoptosis-associated speck-like protein), which contain the caspase activation and the recruitment domain CARD (ASC), afterwards, the procaspase-1 is activated and converted to caspase- 1 [334-339].

The main function of all inflammasomes is the activation of caspase-1, which induces the processing of IL-1β and IL-18, and the development of pyroptosis with the participation of caspase-4 and 5 (in humans) [53, 340]. Several additional conditions are necessary for the formation of an inflammasome, such as the activation of pro-inflammatory signaling pathways associated with the transcription factor NF-κB, the development of oxidative stress, and a decrease in K+ concentration in the cytoplasm [191, 341-343].

Currently, the role of AIM2, IFI16 (including the ALR family receptors), NLRP1, NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4 (NLR family receptors) inflammasome in the induction of pro-inflammatory signals have been extensively established.

As earlier stated, caspase-1 is activated during the assembly process of inflammasomes, which initiates a whole spectrum of pro-inflammatory processes, *e.g.*, that of the formation of IL-1β and IL-18 (cytokines from the IL-1 family), fibroblast growth factor 2 (unconventional pathway) and activation of pyroptosis factors (caspase - 1 is activated, then caspases - 4, 5). A direct consequence of the inflammasomes formation can be observed in the hypersecretion of IL-1β by cells, which in turn, triggers a wide range of pro-inflammatory processes in cells, including the secondary production of pro-inflammatory cytokines and coagulation factors. The IL-1 receptor contains a signal domain common to TLR, therefore, the regulatory effects of IL-1 family cytokines exert similar effects as the PAMP and endogenous DAMP on cells.

A significant amount of DAMP and other damage factors enter the extracellular environment in the process of inflammasomes-induced pyroptosis, placing the formation of inflammasomes as an attribute of cells associated with inflammation and the development of an immune response [333, 334].

The inflammasome assembly is unique in its induction by various exogenous and endogenous signals, individual inflammasomes perceive specific activation signals, but signals can also overlap among all inflammasomes Typical examples of the specific activation of inflammasomes can be shown from the following examples; AIM2 is activated by double-stranded DNA in the cytoplasm of the

cell, IFI16 is activated by a viral DNA sensor in the nucleus and perinuclear region of the cell, NLRP1 is activated by lethal toxin, Bacillus anthracis, Toxoplasma gondii antigens, some viral proteins, muramyl dipeptide, β-amyloid and depletion of intracellular ATP; NLRC4 is activated by complexes of flagellin, some other bacterial proteins with autogenic NAIP proteins [344-347]. Furthermore, inflammasomes NLRP6 and NLRP12 are activated by uninstalled PAMPs and DAMPs. The inflammasomes NLRP12 are involved in the migration of neutrophils and dendritic cells [348], while inflammasome NLRP7 are involved in the activation of caspase-1 in monocytes and macrophages in response to the action of bacterial lipoproteins in the cytoplasm of these cells [349].

The assembly of NLRP3 is activated by various PAMP and DAMP, ROS (via the formation of free thioredoxin), lysosomal proteinases (with the formation of phagolysosomes and autophagolysomes), cholesterol crystals (such as the formation of foamy cells in atherosclerotic plaques). Equally, the assembly of NLRP3 can also be activated by β-amyloid, uric acid, calcium phosphates, many exogenous irritants (for example, asbestos and silicon), the export of mtDNA to the cytoplasm, additional recognition of internal and external signals mediated by intra – and extracellular PRRs [242, 341-343]. Many activation factors can induce formation of NLRP3 inflammasome through common collector mechanisms, including accumulation of RSO in the medium, a decrease in the concentration of potassium cations in the cell, and the release of lysosomal proteinases. The formation of these inflammasomes requires an intensive action on a cell of damaging factors and several additional activation effects on the transcription factor NF-κB. The assembly, function, and utilization of inflammasomes are dependent on oxidative stress [341, 342], mitochondrial stress and lysosomal breaks [350, 351], contacts with actin microfilaments of the cytoskeleton [352], autophagy of inflammasomes [353], and the regulatory effects of heat shock proteins [354].

Biological and pathogenetic role of inflammasomes is very different, they participate in a large number of immune processes [355-361]. Inflammasomes can also enhance the tolerance of organism to certain types of tumor growth, studies have shown that mice that are deficient in the formation of inflammasomes, such as NLRP3, NLRP1, NLRP6, NLRC4 or caspase-1, are highly susceptible to colitis-associated colon cancer, and increased number of colon polyps [362-364].Contrast studies reported that inflammasomes and IL-1 play a crucial role in the development of tumor growth and metastases in breast cancer [365]. The formation of inflammasomes NLRP3 in the endotheliocytes and activation of caspase-1 have been characterized as the driving factor for endothelial dysfunction [366-368]. In conditions such as myocardial ischemia, NLRP3 and caspase-1 levels increases within 3 hours of exposure to hypoxia and persist for the next 24 hours [369]. Experimental alcohol poisoning in the cerebellum revealed signs of tissue and cellular stress, including increased expression of NLRP1, NLRP3, ASC, caspase-1 and cytokines: IL-1β, TNF-α and MCP-1 [370]. Some authors suggested that inflammasomes NLRP3 is a key player in the pathogenesis of neurological disorders in neuroinfection, acute craniocerebral trauma and neurodegenerative diseases [371]. Findings in the experimental model of Alzheimer's disease showed that inflammasome NLRP1 activates caspase-1 and pyroptosis in cultured cortical neurons in response to β-amyloid [372]. The production of ROS in dysfunctional mitochondria and increased NF-κB signaling, coupled with aging can also potentiate the priming of NLRP3 inflammasomes in microglia and astrocytes of the brain [373]. Authors reported that the AIM2 inflammasomes regulated the growth of axons (strengthen) and dendrites (decrease), and reduced anxiety level in mouse neurons, through the production of IL-1β [374] that, NLRP3, ASC and caspase-1 are found in macrophages, and sometimes in the smooth vascular myocytes in atherosclerotic plaques [375].

It is noteworthy to state that the mechanisms of cellular and tissue stress and formation of NLRP3 in cells do not only promote the development of atherosclerosis, NLRP3 together with the ASK-1 / JNK-1 signaling pathway, can equally induce apoptosis of altered macrophages and thereby contributing to the reduction of atherosclerotic damage to the vascular wall [376].

Non-alcoholic fatty liver disease (NAFLD) has been reported to be associated with the activation of the transcription factor NF-kB, NLRP3, caspase-1 in hepatocytes, hepatic macrophages, and the formation of IL-1β [377]. Activation of the NLRP3 assembly process in the hepatocytes has been linked to pyroptosis, hepatic inflammation and fibrosis [378]. Meanwhile, the activation of inflammasomes NLRC4 in hepatocytes mediated by carbon tetrachloride and partial hepatectomy, can induce proliferation of hepatocytes and prevent the development of hepatic fibrosis [379].

Activation of inflammasomes NLRP3 in macrophages of the pancreatic islets in experimental type 2 diabetes is associated with the partial loss of beta cells [380]. Caspase-1 is activated during adipocyte differentiation, and it modifies the adipocytes into a phenotypic insulin-resistance form [381]. The activity of caspase-1 and IL-1β in adipose tissue is increased both in dietary and in genetically induced obese animal models, studies showed that mice deficient in caspase-1 maintained a high sensitivity to insulin as compared to wild-type animals [381]. Caspase-1 and inflammasome NLRP3 was reported to mediate fibrosis and differentiation of myofibroblasts in systemic sclerosis [382]. Inflammasomes NLRP3 in fibroblasts of synovial membranes promote sclerotic changes in the joints [383], and the formation of NLRP3 in the keratinocytes coupled with the production of IL-1β is a characteristic feature of many dermatitis [384, 385]. Inflammasomes NLRP3 are associated with the pathogenesis of gout and many autoimmune diseases [386, 387]. The formation of NLRP3 in the epithelium and cells of innate immunity of the lung tissue is a distinctive feature of the destructive acute and chronic lung diseases, such as bronchial asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome [336, 388, 389]. Inflammasomes NLRP1 in critical conditions contributes to the development of lung fibrosis in chronic diseases and acute respiratory distress syndrome [347].

Diabetic nephropathy is associated with protein glycation, oxidative stress, and mitochondrial dysfunction in endotheliocytes and podocytes of renal glomerular microvessels. The expression of inflammasomes NLRP3 under dystrophic and sclerotic changes in the cortical substance of the kidneys has been reported [390]. In infectious and aseptic renal damage, NLRP3 can be generated in the renal epithelium, macrophages, and the dendritic cells, and this promotes the development of an inflammatory response, such as in autoimmune diseases [391].

Inflammasomes do not only promote the development of proinflammatory cellular stress, but also regulate it at the level of the cell and tissue through their negative feedback mechanism, as shown by the modulation of the production of hormones in tissues. A typical example of such dual attribute of inflammasomes could be seen from the generation of NLRP3 and IL-1β in the macrophages, which influenced the production of stanniocalcin-1 (stanniocalcin-1) in mesenchymal stem cells, and exerted both anti-apoptotic and anti-inflammatory properties [392].

Inflammasomes formation in cells cannot only signify an inflammatory process, as this can also occur under physiological conditions, for instance, in epitheliocytes of the large intestine that come in contact with microbial antigens, but inflammasomes NLRP1, NLRP3, NLRP6 and NLRP12 are also detected. Inflammasomes do not only contribute to the inflammatory process in pathology but also to physiological functions, they can also promote the survival, proliferation and differentiation of epithelial cells, and the release of mucus by goblet cells [393-396]. Mice deficient of NLRP6 in epithelial cells of the intestine are character-

ized by reduced baseline IL-18 levels, changes in the fecal microbiota, spontaneous intestinal hyperplasia, and frequent exacerbations of colitis [397]. NLRP6 supports inflammation when the inflammatory response is vital. Studies showed that NLRP6 is able to weaken the TLR-induced pathways when the inflammatory response is unreasonable and its activity is harmful [398].

Inflammasomes can act as a powerful pro-inflammatory defense mechanism against infection. Controversially, some infectious diseases have employed the inflammasomes for their own purposes, such as the production of several toxins and other pathogenicity factors. A typical example of the negative influence of the inflammasomes can be seen from the secretion of a lethal toxin of virulence (LeTx) by Bacillus anthrax, which activates NLRP1, and with the help of a program of caspase-1-dependent pyroptosis, destroys the fibroblasts, macrophages and dendritic cells thereby promoting the development of the infectious process [399]. The role of NLRP6 in intestinal infections caused by intracellular pathogens Listeria monocytogenes and Salmonella typhimurium are also known the negative influence of inflammasomes in disease pathogenesis [400].

Genetic anomalies in the formation of inflammasomes could be implicated in inherited auto-inflammatory diseases associated with uncontrolled spontaneous activation of innate immunity cells. Thus, diseases of the CAPS group, such as the familial cold autoinflammatory syndrome, MacLay-Wells syndrome, and chronic infant neurologic skin-articular syndrome are associated with mutations in the NLRP3 gene (CIAS1 gene) [401].

Thus, the formation of inflammasomes could be a sign of pro-inflammatory cellular stress and is closely related to its other components. This pro-inflammatory cellular stress process develops mainly in cells of integumentary tissues and "professional" cells of inflammation, and in many parenchymal cells of internal organs, and its biological role enhances the damaging signal in the development of inflammation and immune response, through pyroptosis, production of IL-1β, and other phlogogenic factors. However, the violation of these processes can cause serious acute and chronic complications.

3.7. DNA-damage Response

The variability of DNA allows biological systems to adapt to changes in the external environment, and this is the driving force of the evolutionary process. The accumulation of DNA damage in the cell leads to a number of alternative outcomes, including, temporary or chronic cell cycle arrest, aging, malignancy or apoptosis. Despite the accumulation of permanent and stochastic damages of the genetic matrix, the DNA repair mechanisms remediate these functional damages in each living cell [402, 403].

Damage to DNA includes various changes in the chemical structure, such as the single-stranded or double-stranded pentose phosphate backbone, loss or chemical changes of nitrogenous bases, covalent cross-linking of DNA chains, cross-linking of DNA-protein, introduction of viral DNA into the DNA host structure, and changes in tertiary DNA structure that conform resistance to normal packing of DNA in the chromosome [402]. A study has shown that in each human cell, about 104- 105 different lesions of the genome occur daily, most of which are corrected in a normally functioning cell [404]. The DNA-damage response (DDR) mechanisms are permanently functioning in the cell, and can further be strengthened by the development of cellular stress where the amount of DNA damage exceeds a certain threshold for a particular cell type or when cell receives signals about damaging factor (threat of damage). The most serious DNA lesions are double-stranded DNA breaks, and the S-phase of the cell cycle is the most sensitive to DNA damage [405]. Damage to DNA can occur as a result of spontaneous errors in replication, side effects of hydrolases, oxidoreductases, other enzymes involved in the process of non-enzymatic methylation and glycation, exposure to ionizing radiation, heavy metals, environmental mutagens, viruses, and oxidative stress factors [402, 403].

In human cells, more than 1,000 proteins are directly or indirectly involved in the DDR process. More than 30 syndromes and diseases have been associated with mutations in DDR genes, which include neuronal degeneration, immune dysregulation, progeria (accelerated aging), cancer and other critical diseases [406]. Molecular mechanisms of DDR are represented by a network of dynamically interacting proteins and protein complexes that are capable of recognizing DNA damage, signaling the necessity for the termination of the cell cycle, eliminating damage or genetically unstable cells by inducing cell death programs [407]. Most DNA damage can be corrected during DDR, however, this repair mechanism is not always effective, in some cases, the elimination of DNA damage leads to errors, which could possibly lead to mutations. Furthermore, the repair process of double-stranded DNA ruptures can lead to epigenetic changes, which can occur in the form of methylation, and consequently, block the expression of the corresponding genes [408]. However, some DNA damage cannot be restored, instead, get engulfed by DNA polymerase with less stringent base pairing requirements than replicative polymerases [409]. A direct negative consequence of DNA damage that is fully an effective development of DNA, is the prolonged blockade of the cell cycle in proliferating cells [410]. In addition, DNA damage in the post-mitotic brain cells and other tissues can cause dysfunction and aging [411-413], same damage can lead to tissue metaplasia or malignancy [414], or trigger the program mechanisms of apoptosis [415] or necrosis [416], and the violation of tissue function and structure.

DDR includes several processes [417-421], namely:

Non-homologous end joining (NHEJ) which restores double-stranded DNA breaks;

Homologous recombination (HR) which repairs double-stranded DNA breaks;

Single-strand break repair (SSBR) which restores single-stranded DNA damage;

DNA mismatch repair (MMR) which eliminates deletions and incorrect insertions of bases during replication;

Base excision repair (BER) which restores modified (deaminated, oxidized, alkylated and methylated) bases with DNA glycosylases;

Nucleotide excision repair (NER) which eliminates DNA damage caused by ultraviolet radiation.

The signaling cascade generated by DDR include sensory, mediator and effector proteins and is regulated by the post-translational modifications of proteins, primarily by their phosphorylation, acetylation and SUMOylation [422-425]. The biosynthesis and the activity of nuclear chaperones (primarily ubiquitin, nucleophosmin and SUMO protein), nuclear protein kinases (primarily, ATM, ATR, DNA-PKcs and Chk1 / 2), various nuclease, polymerase, ligase and DNA glycosylases, regulatory histones, increases with the development of DDR stress, and are thus, involved in the DDR process [426-431].

The development of DDR is associated with two signal pathways of cellular stress:

Signal pathway (1st class); PI3K/Akt (protein kinase B) / mTORC1/2 [432-436]. This is one of the universal signaling pathways that are typical of most human cells; they are responsible for proliferation, repair of DNA, cell growth, increased anabolic processes, inhibition of autophagy. Signal pathway Ras/MEK/ERK [437]. This pathway can be initiated by extracellular molecular signals, such as various cell growth factors and chemokines, which are recognized by the receptors associated with tyrosine kinases and /or G proteins [434].

The Ras-ERK pathway is activated with DDR, and the ERK activation is upregulated by DNA damage, which eventually promotes the activation of key protein kinases DDR; the ATM and ATR [437]. Ras-ERK signaling ultimately leads to cell survival and proliferation, DNA retention at various stages of the cell cycle and cell migration, and the cross-reactivation of the PI3K / mTORC1 signaling [434].

Both aforementioned signaling pathways, provide relative DNA stability and cell growth, which is only possible in conditions of mild cellular stress and its individual manifestations, such as the oxidative and mitochondrial stress, intensity of autophagy and mitophagy, and the pro-inflammatory activity of cells. Both signaling pathways ensure a tightly controlled relationship between the DNA repair and DDR mechanisms, with the metabolic support for the normal functioning of the cell cycle; alteration of this relationship turns cells into more extreme variants of DDR development and cellular stress.

Kinase ATM (ataxia telangiectasia mutated) is recruited and activated by double-stranded DNA breaks, and it is one of the main proteins involved in maintaining genetic stability through the initiation of NHEJ and HR processes, in telomere length control, cell cycle arrest, DNA repair or apoptosis [438, 439]. Some of the proteins phosphorylated by ATM are tumor suppressors and these include the transcription factors of the p53 family, protein kinase Chk2 and regulatory histone H2AX. In the normal physiological state, p53 is blocked by the mouse double minute chromosome amplified oncogene (Mdm2) protein; in conditions of increased activity of ROS or ATM, and some other factors associated with cellular stress, the Mdm2 protein is suppressed, and the p53 becomes activated [440]. In cells that undergo significant DNA damage, p53 can promote apoptosis, while in cells that are less damaged, p53 promotes the expression of many genes involved in DNA repair, cell survival, cell growth, or, conversely, cell cycle delay, this depends on the type and level of damage to the cells [440]. However, like any other mechanism of cellular stress, p53 can equally aid the development of pathological processes in various diseases.

ATM activities have also shown to be stimulated by some cytokines (TGF-β, IL-6 and thrombopoietin) [441]. Furthermore, ATM is involved in the development of mitophagy, and in the removal of old and dysfunctional mitochondria, which may contribute positively to the reduction of mitochondrial and oxidant stress under certain conditions [442].

Kinase ATR (ataxia-telangiectasia and Rad3-related protein) is a serine/threonine protein kinase that tracks DNA damage, and when detected, activates the stopping of the cell cycle at the control point [443]. ATR is activated in the presence of single-stranded DNA that is formed during single-stranded DNA breaks or as an intermediate product for some reparations of damaged DNA [443, 444]. Additionally, ATR can be activated at a certain stage of the repair to a double-stranded DNA rupture, and they function cooperatively with the ATM [445].

The protein kinases ATM and ATR decrease the activity of several cyclin-dependent kinases (CDK), which slow down or stops the cell cycle (at the phases of G1, S, G2, M), this, in turn, extends the time required for DNA repair [446].

The blockade of the ATR / Chk1 pathway leads to a deficiency of Chk1, which manifest as premature onset of mitosis, a mitotic catastrophe due to abnormal activation of cyclin B-Cdc2 and the associated release of cytochrome C from mitochondria, and the activation of caspases 3 and 9. Similarly, to the ATM/Chk2, the ATR/Chk1 pathway involves the transcription factor p53 in the development of DDR, which also contributes to the survival of proliferating cells, and with more pronounced DNA damage, they can lead to apoptosis [447]. Authors reported that ATM and ATR transcriptionally or post-transcriptively induce many DDR proteins directly, or indirectly influence other enzymes via the modulating of their phosphorylation, acetylation, killing or SUMOylation [446].

Furthermore, the DDR mechanisms have been associated with normal growth processes, which include neurogenesis and immune system development [448]. Controversially, various carcinogens cause multiple mutations, such as the defects in DDR genes that allow tumor cells to overcome apoptosis and maintain proliferative activity despite multiple genome damages [402, 449]. A finding has suggested that DDR in tumor cells could contribute to their resistance to radiation and chemotherapy [450]. Genomic rearrangements involving DDR factors, occur during the development of the immune system, this has implicated the DDR defects to B- and T-cell immune deficits [448], as well as the formation of leukemias associated with a disruption in the recombination of V (D) J segments in genes antigen-recognition structures [402]. Some DDR defects could also cause infertility [402, 451]. Patients with hereditary DDR defects often show signs of premature aging, caused mainly by an accelerated telomere shortening [452, 453]. As organism age, various DNA lesions accumulate in the nucleus and mitochondrial genome [454, 455]. There is evidence that atherosclerosis and other age-related human pathologies are characterized by increased DNA damage (which include double-strand breaks), which leads to the aging of smooth muscle cells of the vessels, and the death of other cells in the zone of atherosclerotic lesions [456, 457]. Cell aging is an alternative tumor growth variant of cellular stress [457]. The ineffectiveness of DDR and the accumulation of DNA damage in neurons are associated with neurodegenerative pathologies, such as the ataxia, Alzheimer's, Huntington's and Parkinson's diseases [448, 458, 459]. Authors found that the activation of DDR processes due to the accumulation of single-stranded DNA ruptures in post-mitotic cardiomyocytes of experimental mice promotes the development of heart failure [460].

DDR for various pathologies cannot be considered separately from other components of cellular stress as they are could be involved in typical variants of cellular stress outcomes, pathogenesis of the same diseases, and general pathological processes of tissue and organism level. The development of DDR is specific to processes such as the chaperones, protein kinases, other regulatory and effector enzymes, many nuclear proteins, such as the regulatory histones, and various mechanisms associated with the activation of the transcription factor p53. The signal pathways of cellular stress are significantly associated with the processes of anabolism, energy storage, cell growth, and damage to DNA; the response to these damages occur in any given cells. The DDR predominately proliferate cells that are most sensitive to genome damage, they equally halt the cell cycle to implement DNA repair and cell survival, and in such case, the process of apoptosis becomes an extreme variant of the DDR development, with an aim at preventing malignancy and transmission of genetic abnormalities to the daughter cells. The functions of the DDR mechanisms still persist despite an increased action of damaging factors and the progression of cellular stress. The DDR processes have been associated with the mobilization of cellular resources, development of insulin resistance, increased autophagy, oxidative and mitochondrial stress, unfolded protein response, and the pro-inflammatory orientation of cellular stress.

3.8. Reaction of microRNA

The human genome includes 2.85 billion nucleotides in nuclear DNA molecules [461]. Protein-encoding genes constitute only 1.5-2% of the human genome (approximately 20-25 thousand active genes) [461, 462]. Some non-coding DNA regions are responsible for the transcription of RNAs involved in regulatory functions [463]. Among these RNAs are the microRNA that occupies a special place, they are small, non-coding RNA proteins with a length of 18-25 nucleotides that participate in transcriptional and posttranscriptional regulation of gene expression by RNA interference

[464]. It has been shown that these molecules regulate various physiological functions, which include development, growth, metabolism and cellular homeostasis. There are about 2 thousand microRNAs in human [465]. According to the generally accepted rules of the nomenclature, microRNA are assigned a code in the order of their opening: miR-digit-letter, sometimes an additional digit (if there are isoforms), for example, miR-34a [466].

Different cells and tissues can synthesize different sets of microRNA on the basis of nuclear DNA. According to various estimates, about 50% of human genes encoding proteins are targets of microRNAs [467]. It has been reported that an extracellular microRNA included in vacuoles circulates in the blood can participate in the intercellular exchange of information [468]. In humans, microRNAs recognize mRNA at 6-8 nucleotides at its 5'-end [569]. Authors also observed that microRNA may have several mRNAs, and mRNA can equally have several microRNAs [470]. It has been established that each vertebrate microRNA has an average of about 200 target transcripts [471]. From the nucleus, pre-microRNA is transferred via the exportin5 protein to the cytoplasm where it undergoes processing involving the Dicer protein [472, 473] Dicer protein is a ribonuclease that cuts pre-microRNA molecules into microRNA, then the mature microRNA forms a regulatory complex with the AGO protein. The AGO protein maintains contact with a new microRNA after the dissolution of the previous complex, and the new complex is designated as RISC (RNA-induced silencing complex) [474], The RISC complex interacts with mRNA due to the recognition of its specific site [475]. This interaction promotes the degradation of mRNA or prevents its translation [475, 476].

The microRNAs system is involved in embryogenesis and regulation of various organ-specific physiological functions. Recently, more information has been gathered about the involvement of microRNAs in the regulation of various processes of cellular stress in many diseases. The participation of microRNA in the development of cell malignancy and tumor growth [477, 478], diabetes mellitus [479], cardiovascular diseases [480, 481], neurodegeneration [462, 482], atherosclerosis and endothelial dysfunction [483] normal and pathological aging [484, 485], have also been implicated. Different miR-34 isotypes (a, b, c) have been highlighted for their involvement in the regulation of aging and age-related brain disease; however, their expression decreases in neurons in Parkinson's disease [486]. Several microRNAs namely: miR-106b, miR-125b, miR-126, miR-146a, miR-21, miR-22, miR-29, miR-210, miR-34a, miR-449a, miR-494, miR- 17-92 and the microRNA-200 family are differentially expressed in aging cells [484]. Exosomal microRNAs, which include the miR-126, miR-130a, miR-142, miR-21 and miR-93, miR-211-5p, miR-374a, miR-340, miR-376c, have been detected in the blood serum [587, 488]. Increased expression of miR-217 induced a premature phenotype like aging, impaired angiogenesis and endothelial cell dysfunction [489].

Overexpression of miR-335 and miR-34a caused premature aging of the young mesangial cells by suppressing antioxidant enzymes, thereby promoting the production of ROS [490]; the overexpression of miR-125a-5p in endothelial cells also increased the production of nitric oxide, reduced the production of ROS, and improved the function of endothelial cells [491]. However, ox-LDL, a risk factor for vascular diseases, suppresses the expression of miR-125a-5p in the endothelial cells of the microvessel of the human brain, inducing pro-inflammatory and proatherogenic responses; in turn, miR-125a-5p limits the negative effects of ox-LDL by regulating the ERK / p38 MAPK and PI3K/Akt signaling pathways [491].

Dysregulation of these processes has been implicated in the chronicization of cellular stress and the development of various diseases, including cancer [477]. The signal pathways of cellular stress and the mechanism involved in the biosynthesis of microRNAs are interrelated at different levels, microRNAs appear as critical regulators of a stress response, and the dysregulation of microRNA activity makes the cell more prone to stress and damage [492]. Generally, various microRNAs exhibit ambiguous effects in the development of cellular stress, various diseases and aging; the involvement mechanisms of the microRNAs in these processes are diverse. Studies have highlighted on the relationship between decreased dicer protein expression and the development of cellular stress, it was found that the loss of function of the dicer protein reduces stress tolerance, whereas their overexpression is associated with stress resistance [492, 493]. Numerous stress molecules (such as the interferon type I and ROS) act as inhibitors of the dicer protein expression [Mori 2012]; lowering the dicer level reduces stress tolerance, while and increase stress level inhibits the dicer activity [Mori 2012, 494]. A vicious circle is formed in aging in which the activity of dicer gradually decreases, and the severity of cellular stress gradually increases in various organs and tissues [492]. The loss of dicer in the adult brain has been associated with a neurodegenerative phenotype [495, 496]. Hypoxya inhibits the RISC function and microRNAs formation [492].

Many microRNAs contribute to the regulation of various processes of cellular stress, and the regulation of UPRER; miR-214 and miR-30c have shown to regulate the expression of ATF4 and XBP1 [497, 498]. Authors have reported on the influence of the UPRER on microRNAs, examples of such include the inhibitory effect of the IRE1 on the expression of several microRNAs [499], and the multidirectional regulatory effects of ATF4, ATF6 and XBP1 on the expression of several microRNAs [500, 501]. It was found that miRNAs fine-tune the expression of the UPR signaling cascade components and modulate cellular adaptation to stress. [492, 500, 502]. MicroRNAs can suppress the UPR signal through negative feedback, mechanism or can promote the activation of cellular stress by inhibiting negative regulators or act as direct positive-link activators capable of regulating the sensitivity threshold for the development of cellular stress and its phase transitions. The dna-damage response is controlled by microRNAs, the p53 transcription factor is normally inhibited by miR-125b under normal conditions; however, the miR-125b expression decreases after DNA damage and p53 is activated, leading to the activation of miR-34 transcription, and the translation of other miRs involved in the development of DDR [503, 504]. Activation of the miR-34a increases the transcription activity of p53 [505] and activates p53 by suppressing Mdm4 [506]. Ectopic expression of miR-34a results in cell cycle arrest, apoptosis or aging, and the simulation of p53 activation [507].

In the transfection of the renal cells, miR-184 and miR-150 suppressed the expression of autophagy-associated Rab1a and Rab31 proteins, decreased autophagy activity, increased the manifestations of oxidative stress, which result in cellular aging [508]. A study showed that in the macrophages, NF-κB activates the transcription of miR-9, miR-155 miR-146, and other cellular stress genes [509]. The miR-9, miR-155 and miR-146 miRNA targets that regulate these microRNAs could also act as pro-inflammatory signaling molecules (eg, NF-κB). The effects of miR-9, miR-155 and miR-146 can be multidirectional, and might not be the same from the onset of induction [510]. Such time-controlled expression allows macrophages to cause a strong attack on pathogenic microorganisms while minimizing the duration of undesirable damage to the host due to the mechanisms of cellular stress [510].

4. THE ROLE OF CELL SIGNALING PATHWAYS IN THE DEVELOPMENT OF TISSUE DYSFUNCTION

Maintaining the physiological status of the tissue depends on a coordinated regulation, anabolism and catabolism, proliferation and apoptosis, rest and tension at the level of organization within the organism. Homeostasis imbalance leads to metabolic disorders, and if left uncompensated by the TS mechanism, pathological processes manifest. The essence of this processes is to steadily distort the information field of tissues and individual cells representing the

interaction of many signaling pathways directed to the genome of the cell and its complex response in the opposite direction. These interactions are extremely large-scale; they form a complex information network that isare very complex for integral assessment. Taking this complexity into account, this article rather focuses on the basic only on the basic typical patterns of the relationship between signaling pathways of stress and changes in metabolic processes that determine the development of insulin resistance and dysfunction of para-inflammation in insulin-dependent organs.

At the cellular level, signal and effector proteins situationally change their functions due to conformational changes and enzymatic post-translational modifications (PTM).

Stress signals in the cell cause multiple cascading PTM of a large number of regulatory proteins, which lead to the formation of signaling pathways such as the transcription factors. Concurrently, it was reported that different cell signaling pathways form horizontal links and network systems, where individual trunk paths compete, duplicate (the redundancy principle) or complement each other resulting to integrated responses [511]. Activated transcription factors regulate the transcription of many genes and microRNAs that are involved in the post-transcriptional regulation of the information and function of mRNA (section 2.8). The regulatory network of the cell includes the formation of loops of positive communication and a negative feedback connection aimed at the development and resolution of cellular reactions. In addition, the transduction of stress signals causes modulation of the proteome that is aimed at ensuring the survival of cells in extreme conditions by changing their normal functions and the formation of specific functions of cell voltage.

Different combinations of PTM histones and transcription factors form peculiar codes in severe conditions usually when a limited set of elements could be needed to produce a large set of combinations that initiate specific biological responses [512]. Authors reported that over 1 million proteins, protein isoforms and modifications with specific functions could arise from the alternative splicing of mRNA and PTM [513]. Presently, more than 200 different types of PTM have been identified [514], the most commonly studied are the phosphorylation, glycosylation, acetylation, methylation, hydroxylation, nitrosylation, ubiquitination, and activation by limited proteolysis [514]. Each type of modification is carried out by specific enzymes, more than 500 of which catalyze protein kinases phosphorylation of about 2000 proteins in over 6000 sites [512]. Different signals can activate both general protein kinases of the collector type, such as the MARK, Akt, PI3K, PKC, ATM, ATR, AMPK, PKA, and more specific pathways that act competitively or synergistically. The protein kinases can play roles in different signaling pathways depending on the level of activation, the presence of appropriate substrates, and the parallel effect of co-stimulating and inhibitory signals that change their PTM and functional orientation. Under cellular stress conditions, opposite processes are activated through the action of various enzymatic antioxidants, phosphatases, sirtuins (NAD-dependent deacetylases), the ubiquitin-proteasome splitting of inducible stress proteins, and other mechanisms of recovery to normal stress PTM and expression of inducible genes.

Depending on the stage of the TS, signaling pathways could be influenced by various effects on cellular metabolism. At the stage of cell growth and relative predominance of anabolic processes, the insulin-dependent pathway will be activated: class I PI3K / Akt2 / mTOR (Section 2.5). Authors reported on the involvement of the glucose transporter type 4 (GLUT-4) and the transcription factor forkhead box protein O1 (FOXO1) in the metabolic effects of insulin in optional glycolizing tissues [515, 516]. ATP deficiency triggers AMPK activation that is associated with cellular stress, leading to the activation of lipolysis, proteolysis, autophagy, and the subsequent increase in glucose transport to cells using GLUT-4 [516]. The metabolic effects of AMPK in cells are vital for the implementation of various stages of TS, owing to the fact that they play a pivot role in the maintenance of energy balance. Under conditions of nutrient deficiency, AMPK acts as a metabolic control point that interferes with cell growth through the inhibition of mTORC1 [517].

When the effect of damaging factors on cells is enhanced, the development of mitochondrial and ER-stress occurs, and the activation of UPRmt (section 2.2 and 2.4), UPRER (sections 2.3, 2.4), and the outcomes of DDR (section 2.7) are shifted towards cell cycle arrest, aging of cells or apoptosis, the pro-inflammatory orientation of the secretory phenotype of cells also increases.

Eukaryotic Initiation Factor 2 kinase (eIF2) plays a key role in the assembly of the translational complex (ribosome, tRNA, mRNA) [518], and its action can be inhibited by kinases of the signaling pathways of cellular stress. Four protein kinases regulate the function of eIF2 during the development of TS:

1) Activation of one of the three main UPRER pathways through PERK, which leads to the phosphorylation and inhibition of eIF2α (section 2.3) [519].
2) The influence of PKR kinase (double-stranded RNA-activated protein kinase) on UPRER and DDR which results in the activation of NF-kB, JNK and p38, and subsequently inhibits eIF2 [520]. PKR kinase is located at the center of the cellular response to various stress signals, such as pathogens, nutritional deficiencies, cytokines, radiation, double-stranded DNA breaks, and mechanical stress [520].
3) GCN2 kinase (general control non-derepressible kinase 2) is activated by the deficiency of amino acids, as well as ATF4 (the key factor UPRmt and UPRER in mammals), DNA damage. This enzyme restricts protein biosynthesis through the inhibition of eIF2 and lipids, thereby delaying the entry of cells into the S - phase of the cell cycle [521].
4) HRI kinase (heme-regulated inhibitor kinase) or EIF2AK1 (Eukaryotic translation initiation factor 2-alpha kinase 1) inhibits the eIF2 synthesis at the level of translation in response to various stress states such as oxidative stress, heme deficiency, osmotic and heat shock, linked to UPRmt and UPRER [522].

The action of these 4 kinases may contribute to compensatory or abnormal insulin resistance, mostly in the optional glycolizing tissues (liver, adipose tissue, muscle). In addition, during cellular and tissue stress, the function of eIF2 is regulated in all cells by numerous microRNAs within the RISC complex which selectively recognize their mRNA targets in the process of translation (section 2.8).

Stress-activated protein kinases JNKs and p38 may respond to metabolic stress or possible induce metabolic stress when cells are exposed to pro-inflammatory cytokine action (*e.g.* TNF-α and IL-1), infection (PAMP) and other strong stimuli [476]. This attribute distinguishes the MAPK Stress-activated protein kinases pathways from the MAPK-ERK pathways, with the latter closely related to the receptors of mitogens and growth factors. Activated MAPK transforms external stimuli into cellular reactions by phosphorylating downstream substrates, such as the transcription factors, cytoskeleton proteins, translational proteins, and other protein kinases that ensure the specificity, diversity, and amplification of the MAPK cascade [523]. It was found that the isoforms of JNK (JNK1, JNK2 and JNK3) and p38 (p38α, p38β, p38γ and p38δ) have their own specific tissue localization and functioning [524]. Studies reported on the key role of JNK1 and the partial role of JNK2 as regulators in obesity and insulin resistance-induced metabolic disorders [525]. The JNK pathway is strongly activated in the liver, adipose tissue and muscles during dietary and genetically induced obesity; additionally, this pathway also restricts cellular insulin signaling [526]. The metabolic cytokine FGF21 enhances hepatocyte insulin sensitivity, it was reported that elevated concen-

trations of free fatty acids (FFA) in the blood activate JNK1 / 2 in the liver, which leads to the inhibition of FGF21 signaling pathway and contributes to systemic insulin resistance [527]. Furthermore, the JNK1 pathway has shown to slow insulin clearance in the liver, thereby preventing liver steatosis [527]. The MAPK p38 has been found to increase insulin resistance by activating gluconeogenesis in hepatocytes [522].

The key pro-inflammatory transcription factor NF-κB (a family of 5 proteins and 15 combinations of dimers with its functional features) can be expressed during stress in most cell types, but plays a special role in activated cells of the immune system. Authors reported that NF-κB contributes to the polarization of macrophages towards the direction of M1 with a more pronounced pro-inflammatory phenotype over the morphofunctional pole of M2 [528]. In the focus of inflammation, the polarization of macrophages by NF-κB is associated with monocytes migrating to the focus, and beyond its borders mainly with tissue-specific stromal macrophages. A characteristic feature of pathological obesity, metabolic syndrome, and type 2 diabetes lies in the activation and increase in the number of stromal macrophages in adipose tissue and their transformation towards M1 associated with the activation of NF-κB [529].

It was reported that only macrophages are the cells involved in maintaining TS in adipose tissue [530]. A contrary study reported that the T-lymphocytes may also take part in the maintenance of TS in adipose tissue [531]. However, the relationship between macrophages (secrete pro-inflammatory cytokines that increase insulin resistance in adipocytes) and adipocytes (effect on macrophages through FFA and other lipotoxicity factors) play the key role in the maintenance of TS in adipose tissue [528, 529]. In this case, the activation pathway of NF-κB also plays roles in the adipocytes [532]. The increased expression of NF-κB in liver cells (including Kupffer cells) is one of the molecular mechanisms implicated in the development of type 2 diabetes. In hepatocytes, NF-κB enhances insulin resistance by inhibiting the synthesis of phosphodiesterase 3b, which leads to the inactivation of cyclic AMP [533]. A contradictory finding in experimental mice models with increased expression NF-κB in the liver and myeloid cells reported otherwise on the role of NF-κB in the induction of diet-related obesity or leptin deficiency [534]. It is evident that for the formation of pathological obesity, a complex combination of causal factors that are capable of overcoming the adaptation mechanisms of cellular and tissue stress is required.

The accumulation of damage of the genome and proteome of cells during aging leads to cell stress and a steady change in the cellular secretory phenotype, this accumulation has shown to result to an imbalance between the processes of regeneration and apoptosis, tissue atrophy, latent fibrosis or meta-fibrosis at the organ-tissue level [535]. These changes at the organ level have shown to change the metabolic status and the response of the neuroendocrine system, resulting in the formation of allostasis at the level of the organism [11]. The effects of the accumulation of many aberrant metabolites as factors of systemic damage and inductors of the systemic TS contribute to the formation of a loop of a vicious pathogenetic circle that changes the information field of various organs and tissues. It is worthy to note that the mechanisms of TS are adaptive reactions that are aimed at ensuring the survival of cells, and fully or partial preserve the function of organs under extreme conditions. The mechanisms of cellular and tissue stress are of the great importance in many physiological processes, and in pathological cases they form difficult complexes of functional and dysfunctional systems, making it impossible to distinguish between the protective and negative role of these mechanisms in many cases.

5. TISSUE STRESS AND GENERAL PATHOLOGICAL PROCESSES

5.1. Existing Tissue Stress Concepts

There are different theories and concepts of cellular stress, one of such is the theory of Selye in 1950 that characterized two types of tissue stress: the general adaptation syndrome, which is mainly associated with reaction of the hypothalamic-pituitary-adrenal system and secondary changes in other organ systems; and the local adaptation syndrome which is associated with focus inflammation processes [536].

The discoveries of the middle 20th century further shielded light on the mechanisms of TS, it was reported that these mechanisms in addition to classical inflammation, were also linked to various formally non-inflammatory diseases (*e.g*. tumor growth) [537]. It has been shown that cytokines and other inflammatory mediators can mediate changes at the level of the whole organism [538]. These inflammatory mediators enter the bloodstream from the focus of inflammation or could be systemically produced by various tissues during aging [539]. Some authors had termed the pro-inflammatory secretory phenotype of cells during aging as "inflamm-aging", and has associated them with neurodegeneration, sarcopenia, the development of metabolic syndrome, cardiovascular and many other diseases [540].

The concept of low-grade inflammation, as noted by authors, reflects the relationship between pro-inflammatory status and the development of insulin resistance [31], and the observed changes have a strong correlation with age. A relationship between the degree of obesity and blood concentrations of some pro-inflammatory (*e.g*. IL-6, IL-18), and anti-inflammatory (IL-10) cytokines was observed in children and adolescents [541]. Furthermore, these changes depend on a large number of genetic, lifestyle, developmental and environmental factors. Studies in humans supported the role of pro-inflammatory cytokines in the pathogenesis of obesity, the feedback between the blood level of C-reactive protein and abdominal obesity was equally reported [542]. The theory of *physical tissue stress* binds the TS development with the dysfunction of the musculoskeletal system under physical stress [543, 544]. Changes in the level of physical stress result in a predictable adaptive response in all biological tissues; however, there are different thresholds for the development of stress response in an individual type of tissue. Some authors have distinguished 5 qualitative tissue responses to physical stress such as, the reduced tolerance to stress (*e.g*. atrophy), maintenance of normal functioning state, increased tolerance to stress (*e.g*. hypertrophy), injury, and death [544].

Elbakidze G.M. and his coworkers formulated the concept of TS as an adaptive response of tissue (tissue-specific mechanisms) to various nature of injuries [545]. These mechanisms are aimed at replacing damaged and dying cells with new cells that are more resistant to stress. According to the concept, the inhibition of specialized functions of cells can contribute to the self-protection of intensive functioning cells, which could be vital for the survival of the organism under organ functional insufficiency. TS mechanisms controlling cell mass can affect both the mitotic and proapoptotic activity of cells.

Milisav *et al*. reported on the crucial role of humoral factors such as the growth transforming factors, adenosine, adrenomedullin, metabolic cytokines, and contact factors of TS in cell survival and apoptosis - the realization of both apoptotic and anti-apoptotic signaling pathways [27, 29, 32]. It was found that most of the humoral and contact factors or TS are agonists of individual members of the G protein-coupled receptor (GPCRs) superfamily [546-548], which reduced the level of insulin resistance of cells and

enhanced tissue tolerance to various types of damage. As cellular stress increases, the secretions of cells tend to change towards pro-inflammatory cytokines, pro-inflammatory eicosanoids and ceramides which contributes to the development of insulin resistance [547, 548].

In general, the analysis of these theories and concepts further explains the subdividing of tissue stress dynamics into several stages, which includes the version of this classification presented in section 1.1.9.

5.2. The Principle of the Division of General Pathological Processes Based on their Relationship to Tissue Stress

The various forms of TS that possess signs of a pro-inflammatory secretory phenotype can be divided into 2 main categories: proper inflammation and para-inflammatory processes (Table **1**). The basis of any inflammatory process lies in the phenomenon of inflammatory microcirculation. The phenomenon of classical inflammation is realized locally in the focus, and in systemic inflammation at the level of the organism (Fig. **2**) [25]. Concurrently, there are several independent general pathological processes associated with para-inflammation. Quasi-inflammation shares close similarity to classic inflammation. This form of TS manifests itself locally as a cluster of phagocytes (usually macrophages), this could be observed in an atherosclerotic plaque without the reaction of microvessels typical of classical inflammation. Quasi-inflammation In invertebrates is a typical local reaction to an infection in the form of the accumulation of parasites) [549]. Both open and closed hemolymph circulation systems in invertebrates may consist of contractile vessels, and an extensive capillary network with an endothelial lining in some cases [550]. This system in invertebrates differs from the system of microcirculatory units inherent in vertebrate animals, with their characteristic morphofunctional differentiation of microvascular regions responsible for leukocyte migration and exudative-vascular reactions during inflammation, and the special role of postcapillary venules [551, 552].

The absence of such differentiation of TS can make it rather difficult to clearly separate pathological from some physiological processes. In addition, while almost all somatic diseases can acquire the inflammatory status, the pathogenesis of many somatic diseases cannot be considered from the traditional view of inflammation but could possibly be considered from the position of pro-inflammatory TS [553, 554]. In addition, the lack of a clear separation between classical inflammation and other forms of pro-inflammatory TS could lead to the collapse of the concepts of inflammation that have emerged in general pathology as a general pathological process.

As shown above, para-inflammatory mechanisms and other forms of TS are closely related to tumor growth in some particular circumstances. It was shown that tumor tissues have a large set of mechanisms which include the influence on scavenger receptor, regulating the development of cellular stress in the tumor cells and their microvessels, TAM and surrounding tissues [13-15, 26, 175, 555]. This integral general pathological process underlies the pathogenesis of a large number of nosologies and clinical syndromes. This article focuses on the general pathological processes that have a closer connection with the TS.

5.3. Classical Inflammation

The strategy of inflammation involves the isolation and removal of damaging factor even at the deteriment of additional cell damage in the focus of inflammation by phlogogenic factors.

The focus of inflammation is characterized by two main interrelated processes that determine the external signs of inflammation, namely the exudative-vascular reaction and leukocyte infiltration of the damage zone. Depending on the predominance of these processes, inflammation can be divided into three main options: 1) productive or proliferative cell inflammation; 2) exudative inflammation caused by immediate hypersensitivity; 3) exudative-destructive (purulent) inflammation.

5.3.1. Productive Inflammation

The inflammatory focus is characterized by the large variety of cell composition and the functional orientation of these cells [12, 25]. The competitive and cooperative interrelations of CD4 + T-helpers (Th) and macrophages (M) which are formed from monocytes migrating to the inflammatory focus play the focal role in cell orientation [556-558]. Studies in mammals revealed that there are 4 main types of Th, namely Th1, Th2, Th17, and natural regulatory T-cells (Treg) [559]. The macrophages have two differentiation poles: M1 and M2 [557]. The modern classification of the directions of differentiation of macrophages formed from monocytes under the influence of various *in vitro* stimuli includes 10 subpopulations in the M1-M2 range [560]. However, *in vivo* studies found that macrophages differentiation may occur at a more difficult level [561]. Noteworthy to state that the difference in the expression of the markers M1 and M2 is qualitative in nature. Therefore, only in a simplified way, M can be divided into 4 subpopulations

In a more simplified form, the macrophages can be divided into 4 subpopulations namely Th: 1) Th1-M1; 2) Th2-M2a; 3) Th17-M2b; 4) Treg-M2c with each interacting with other complementary subpopulations [557]. Respectively, these 4 subpopulations form 4 vectors of the immune response (i1, i2, i3, i-reg), and each of these vector effect the development of productive inflammation [562]. Concurrently, various vectors of immune reactions can possess zones of functional overlap [563]. Additionally, Th differentiation is plastic under the influence of certain cytokine spectrum, such as the possible transformation of 1) Treg - into Th17 or Th2, 2) Th17 - into Th1, 3) Th2 - into CD4 + T cells, all these differentiations can simultaneously produce competitive cytokines types i: IL-4 (i2) and IFN-γ (i1) [564, 565]. Similar to M1 and M2, Th1 and Th2 subpopulations are heterogeneous and can be divided into more particular subpopulations [566]. The phenotypic features of stromal macrophages of atherosclerotic plaques and other pathologies of the cardiovascular system may not perfectly fit into the M1-M2 axis paradigm, this has prompted suggestions by different authors to switch into non-linear, and more complex models that are capable of evaluating these cells [567]. However, to some degree, the vector approach has allowed the switching from a linear (bipolar) consideration of the Th and M1 phenotype to a planar or even a multiplane (bulk) scheme. Different vectors of the immune response may be implicated in the pathogenesis of the same inflammatory diseases, with some taking indistinct or dominant positions at some specific stages during the development of the inflammatory process [568]. All these factors contribute to the dynamics of inflammation, its adaptation to the damaging factor, the state of the organ and the organism as a whole, as well as the assessment of the *in vivo* complexity of inflammation.

It was found that naive T-cells must receive an antigen-specific signal from antigen-presenting cells, several signals through different cytokine receptors and contact receptors for the differentiation into mature Th to occur [564]. The diversity of the cellular composition and characteristics of the cytokine network allow productive inflammation processes to adapt to the damaging factor, as an infection that uses various pathogenic mechanisms, productive inflammation is able to counteract the immune system through the production of various pathogenicity factors [569]. Additionally, the orientation of productive inflammation has organ specificity and depends on the stage of inflammation [12].

The vector i1. Th1 cells are the main producers of IFN-γ, this cytokine promotes the differentiation and activation of M1 macrophages [570]. The pathway of productive inflammation associated with Th1, M1, CTL, NK is usually effective when infected with intracellular parasites, antitumor immunity, allograft rejection, the

development of a mononuclear delayed-type hypersensitivity reaction, and some autoimmune processes [12, 571, 572]. This response may damage its own tissues due to the secretion of M1 free radicals and hydrolases.

The vector i2 mutually competes with i1. It was reported that Th2 are the main producers of IL-4 and other cytokines that limit the development of i1 [570]. In conjunction with Th2 and M2a, eosinophils, basophils, and mast cells can also play a role in the i2 process. The i2 response is most appropriate in cases of metazoic infection, some types of chronic inflammation, post-inflammatory regeneration and tissue repair, inflammatory processes in tissues that are susceptible to damage (*e.g.* placenta), however, they can also contribute to the fibrosis of internal organs and the development of allergic processes [563, 573].

The i3 response is determined by the interrelation of cells: Th17 (producing IL-17), M2b and neutrophils [562]. This response is less controversial as compared to other vectors, and is prominent in a state such as extracellular bacterial and fungal infections, the development of autoimmune inflammation, delayed-type hypersensitivity, graft rejection, antitumor immunity, and wound healing of epithelial tissues [563, 574].

The i-reg response in parallel with other variants of the immune response acts as a restrictive mechanism that prevents the pathological development of pro-inflammatory mechanisms. It was reported that cells of the immunosuppressive response are natural Treg, secreting IL-10, and TGF-β [563, 575]. The excessive response of i-reg leads to the suppression of inflammation that is dependent on i1 and i3, whereas an insufficient response contributes to the development of autoimmune diseases.

5.3.2. Exudative Reaction and Exudative-destructive Inflammation

In contrast to the generation of antibodies and T-cells, the exudative-vascular reaction does not require an antigen-specific signal and does not have a large variety of its manifestations. The exudative-vascular complex consists of several links: microvessels, the complement system, hemostasis and kallikrein-kinin system, and mast cells. All these links are interconnected and the primary activation of any link leads to the reaction of the entire complex [12]. An exudative reaction can form the initial phase of inflammation and precedes the migration to the focus of inflammation of neutrophils, lymphocytes and monocytes. Purulent inflammation is the quintessence of inflammatory reactivity driven by the reaction of neutrophils and exudative-vascular complex. This type of inflammation to the greatest extent damage own tissues, and it is the last defense line against extracellular infection.

5.3.3. Systemic Level of Classical Inflammation

In this case, typical TS triggers are usually cytokines and other phlogogenic factors penetrating into the bloodstream from the focus of inflammation. An organism response in the form of a stress reaction of the neuroendocrine system, the development of psychasthenia, fever, activation of the hypothalamic-pituitary-adrenal axis, the acute phase of the liver, the mobilization of metabolic cycles, and the enhancement of leukocytopoiesis in the bone marrow [12, 25]. This level of TS reaction is aimed at the resource support of the processes in the focus of inflammation, and mobilization of catabolic processes, a limitation the severity and time of adaptive changes in homeostasis to the complete resolution of acute inflammation. Thus, the systemic level of TS in classical inflammation is closer to the systemic manifestations of para-inflammation than to the processes of the inflammatory focus.

5.4. Typical Pathological Manifestations of Para-inflammation

The main strategy of para-inflammation is to eliminate pathologically changed cells, which are dangerous for its own organism, and to ensure the survival of less injured cells, and full or partial preservation of physiological organ functions. In a position where these tasks are underperformed, the intensity of the TS increases to the formation of a relatively stable allostasis, and the TS acquires dysfunctionality, driving the inclusion of its individual mechanisms into the vicious pathogenetic circle.

5.4.1. The Role of Scavenger Receptors in the Development of Para-inflammation

The secretion factors (primarily cytokines) and the receptor cell phenotype are of significant importance in the implementation of adaptive and maladaptive properties of TS. Among the mechanisms implicated in the maladaptive properties of TS, the scavenger receptor (SR) plays a crucial role. These receptors are predominantly expressed on stromal macrophages and other stromal, and numerous parenchymal cells. Authors reported that some unique SRs are characteristic markers of macrophages M2, primarily SR-A1 (CD204), SR-I1 (CD163), SR-E3 (206) [165-167, 576, 577]. The common features of SR involve the ability to bind apoptotic, damaged and senescent cells, quasi-cells (platelets and erythrocytes), aberrant lipoproteins (especially oxLDL), other unnaturally modified proteins, and their uptake by macrophages, and metabolites by other cells [3, 165, 167]. Additionally, SR is able to form complicate receptor complexes (for example, with TLR), as well as to regulate in the development of the pro-inflammatory functions of the cells expressing them in different directions the. Furthermore, an increase in the expression of SRs on cells in direct proportion to the concentration of their ligands [165-167]. SR is able to bind the immune and proinflammatory functions of cells with changes in homeostasis, limit the severity of TS in physiological conditions but contributes to the formation of stable allostasis in pathology. A number of SRs, such as SR-E1 (LOX-1) contribute to the development of resistant pathological activation of endotheliocytes (endotheliosis) in various somatic diseases [578, 579]. It was found that SR dysfunction is associated with the development of hepatosis (the development of para-inflammation in the liver) [580-581], and pathological changes in other organs [165-167]. SR is also multidirectional involved in the polarization of macrophages, but mainly in the direction of M2. The differentiation of macrophages in the direction of M2 is more related to the function of Th2, and that of the development of para-inflammation it is associated with homeostatic changes and features of the cell microenvironment. A wide range of cytokines and other phlogogenic factors are implicated in the development of TS or its restriction on the mechanism of negative feedback. Numerous SRs in association with other mechanisms of cellular and tissue stress can situationally contribute to both the development of antitumor immunity and the growth of various tumors [582].

While the participation of TS mechanisms in the development of somatic diseases is global, several typical manifestations of these pathologies are distinguishable where the TS value has a definitive pathogenetic meaning.

5.4.2. Low-grade Inflammation

Low-grade inflammation has shown to be associated with low SIR; an increase in blood levels of pro-inflammatory cytokines that is usually not more than 2–4 times, and borderline concentrations of C-reactive protein (3-10 mg / l) [31, 583].

Directly, this pathological phenomenon includes the development of para-inflammation in adipose tissue, liver, and muscles due to obesity, and the development of metabolic syndrome and type 2 diabetes. The development of para-inflammation in optional glycolyzing tissues is accompanied by increased insulin resistance and dysfunction of metabolic cycles. (1.9). Sequentially, these changes which include the phenomenon of lipotoxicity (2.2.), contribute to the spread of para-inflammation to other tissues, mostly in the cardiovascular system. The immediate complications of low-grade inflammation may be NAFLD (nonalcoholic steatohepatitis, or NASH), insulin deficiency (partial death of β-cells, in the termi-

nal stage of type 2 diabetes), sarcopenia with the impaired contractile and metabolic function of skeletal muscles.

It was reported that in some forms of NAFLD (nonalcoholic steatohepatitis, or NASH) in the presence of foci of necrosis, may present similar signs of hepatitis (leukocyte infiltration, microvascular reactions) [584, 585]. The other complication of NAFLD is the liver fibrosis that is not obligatorily associated with hepatitis signs. Authors have reported on the role of the activation of liver cells such as the hepatic stellate cells (Ito cells), without the participation of blood leukocytes, in the development of liver fibrosis [586]. It was suggested that in the general view, there is no reason to believe that fibrosis of the internal organs is undoubtedly associated with classical inflammation [535]. However, the outcome of classical inflammation of parenchymatous organs can be fibrosis of damaged tissues as well as its whole reparation, including aseptic inflammation [587].

The complex of pathological processes of low-grade inflammation is associated with aging, this correlation is not strictly linear though.

With respect to the aging process, there is an increase in two interrelated processes:

1) The accumulation of cells with genome and proteome microdamage, and mitochondrial damage capable of causing chronic cellular stress before the development of stage 2-3 of TS with impaired many physiological functions [588].
2) Reduced energy needs of the body and changes in metabolism which lead to the accumulation of blood levels of free fat acids (FFA), glucose, individual amino acids, atherogenic lipoproteins, glycated and oxidized proteins (including oxLDL), damaged cells and other cellular and metabolic debris which are independent causes of endothelial stress and other tissues stress [213, 589-594].

Metabolites such as FFA, lipids and cell derivatives that are toxic to cells, hydrophobic amino acids with branched radical (Leu, Ile, Val) could damage cell mitochondria, resulting in the development of mitochondrial and oxidative stress (section 2.2). Additionally, the modified proteins, protein complexes and damaged blood cells interact with vascular macrophages and endothelial cells mainly through SR. It was reported that many pathologies of the cardiovascular system develop with and increased level of SR ligands in the blood and a regular increase in SR expression on the endothelium [165-167].

Individual metabolites at high concentrations can directly activate external PRRs. It was shown that high concentrations of FFA (palmitate) can increase insulin resistance by acting on myoblasts through TLR2 [595]. Tissue damage, pathological activation and dysfunction of various cells that occur on the 2-3 stages of TS can lead to a pathogenetical vicious circle, authors reported that oxLDL in the blood is associated with oxidative stress, and are triggers of cellular and tissue stress and also act as a link in the vicious pathogenic circle [596].

The TS mechanisms have both pathological and adaptive properties which can be presented in different processes, an example of such can be shown from the relative and gradual progression of the pathological manifestations of low-grade inflammation. Additionally, there is no clear connection between these processes with chronic diseases that have a much higher level of pro-inflammatory TS (*e.g.* systemic autoimmune diseases) [597]. It remains difficult to establish the contribution of cellular stress mechanisms acting cooperatively with other factors (FFA, lipokines) for the enhancement of insulin resistance [598]. Concurrently, insulin resistance limits the synthesis and accumulation of fat in the fat depot during obesity, which could be classified as a protective value.

Studies have shown the involvement of various subpopulations of Th and morphofunctional polarization of stromal macrophages in the development of obesity and type 2 diabetes mellitus [599]. The autoimmune mechanisms of generation and migration of Th1 and Th17 into adipose tissue have also been implicated in the pathogenesis of obesity and type 2 diabetes mellitus [600, 601]. However, in order to consider obesity from an autoimmune prospective or another type of productive inflammation, more weighty arguments are needed:

1) Experimental data demonstrate that this pathological condition is not a classical autoimmune disease, but could be considered as latent manifestations of an autoimmune process that is not specific to adipose tissue (the presence of autoimmune antibodies and T cells do not accurately indicate the presence of an autoimmune disease).
2) Unlike aging and metabolic dysfunctions, there is no proven direct association between this pathologic condition and known systemic autoimmune and infectious diseases.
3) The concentration of lymphoid cells in adipose tissue is insignificant, while the number of stromal macrophages manifested in obese condition can reach 50% [600, 601].

Migration of leukocytes (memory T-cells) to various tissues occurs constantly but in normal physiological state and during inflammation [602]. Even at low concentrations, pro-inflammatory cytokines and other stimuli can participate in the development of TS during para-inflammation with an increase in the tissue based concentrations of these factors. It remains a subject for debate whether fatty tissues should be associated with a focus of classical inflammation in obesity.

From the abovementioned cases, the pathologies of low-grade inflammation can be considered as a very complex, multifactorial system, where the mechanisms of TS are not the root cause, but the consequence of the gradual accumulation of latent tissue damage at the cellular and tissue levels. Concomitantly, the mechanisms of TS are involved in the formation and stabilization of vicious pathogenetic circles, and pathological changes in homeostasis. However, the TS simultaneously perform a wide range of functions that are of protective value to the body, these are usually aimed at ensuring the survival of moderately damaged cells, utilizing irreversibly damaged and tumor cells, and preserving the function of damaged organs in whole or in part. In general, low-grade inflammation is doubtful to consider from the standpoint of classical inflammation. From the current study point of view, the main manifestations of the complex processes of low-grade inflammation can be classified as para-inflammation.

The phenomenon of pathological insulin resistance makes only a small fraction of the general process of gradual cell aging associated with multiple factors of low damage, and development of TS. Additionally, the mechanisms of TS contribute to the survival of cells and prevent their malignancy, and could also act as direct participants in dysfunctional systems in the formation of a vicious pathogenetic circle. Apparently, the duality and complexity of the cellular and tissue stress mechanisms to a certain extent limit the effectiveness of the use of anti-inflammatory drugs for systemic pathologies associated with aging. Presently, there is an emergence of prospective drugs that directly target specific molecular mechanisms of cellular and tissue stress in the treatment of hypertension [603], neurodegenerative diseases [604, 605], metabolic syndrome and type 2 diabetes [606-608]. However, the pharmacological control of therapeutics on the inconsistent TS processes at the multilevel is far more complex in the theoretical and practical view as compared to their effects on specific mechanisms directly involved in changes of various parameters of homeostasis (*e.g.* blood glucose and arterial pressure levels).

5.4.3. Atherosclerosis

Atherosclerosis can be considered as an independent type of a general pathological process that occupies an intermediate position between para-inflammation and classical inflammation (4.2). This

pathological condition arises through the combined effects of macrophage infiltration - cholesterol-filled foam cells, and the migration of foam cells into the arterial wall of monocytes predominantly occurs through the endothelial lining of the arteries. The pathogenesis of atherosclerosis is associated with three SR binding oxLDL with distinct functional differences: SR-E1 (LOX-1) activates the endothelium and promotes the migration of monocytes, SR-A1 (CD204) is responsible for the active uptake of oxLDL by monocytes and macrophages with the formation of foamy cells, SR-B2 (CD36) activates macrophages [De Paoli 2014]. The progression of atherosclerosis substantially depends on the morphofunctional features of the macrophages and their ratios. Macrophages with M2 phenotype express SR-E3 (CD206) and SR-I1 (CD163), and they are located mainly on the periphery of the center of atherosclerosis in the area of the annulus fibrosis. In contrast, the highly expressing SR-B2, TLR and proinflammatory cytokines are locally located in the central region and shoulder of the plaque directed into the lumen of the vessel [609]. The macrophages with M1 phenotype have a higher pro-inflammatory and procoagulant potential and are connected to the strengthening of pro-inflammatory mechanisms, the activation of the blood clotting system, the formation of atheromas, and other complications of atherosclerosis [610, 611]. Hemoglobin-associated macrophages (M-Hb) which have a high expression of CD163 play a protective role in atherosclerosis. These M-Hb have anti-inflammatory properties, possess mechanisms for the reverse transport of cholesterol from the cell, and are capable of actively absorbing haptoglobin-hemoglobin complexes via the CD163 receptor [610].

5.4.4. Hypertension

The pathogenesis of hypertension include the following main blocks: 1) Dysfunction of the neuroendocrine system such as the disruption of the relationship of the limbo-reticular complex and the hypothalamus, and increased tone of the sympathetic innervation of the vessels. 2) Local dysregulation of contractile vascular tone. 3) Dysfunction of the renin-angiotensin-adrenal system.

Numerous pathogenetic factors have been implicated in the development of hypertension, one of which is the development of TS in the CNS. The development of TS in the CNS involves microglia and neurons which are regulated by many factors, as well as astrocytes and other cells [611]. Mediators such as adrenomedullin may limit the activation of microglia and the development of oxidative stress in neurons, while hypoxia and proinflammatory cytokines exhibit an opposite effect [612]. Generally, the reduction of pro-inflammatory activity and the degree of polarization of microglia in the M1 direction acts as protective from hypertension [613].

The development of TS in the blood microcirculation system and contractile vessels contributes to hypertension, and vasoconstrictor factors (such as endothelin-1 and angiotensin-II) are involved in the vicious pathogenetic circle linking hypertension and local TS. Vasodilators adrenomedullin and NO were found to reduce the severity of proinflammatory cellular stress of endotheliocytes and contractile vessels myocytes [613].

SR plays an important role in the development of the central (in the CNS) and local TS. It was found that endothelin-1 and LOX-1 mutually activate the expression of each other and enhance the absorption of oxLDL by the endothelium [614]. The soluble form of LOX-1 increases in blood and can act as a biomarker in the treatment of patients with hypertension and metabolic syndrome [614].

5.4.5. Neurodegeneration

Neurodegeneration can be considered as a typical pathological process associated with para-inflammation of brain tissue. This process is characterized by the deposition of abnormal proteins (β-amyloids, prions and prion-like protein) in neurons and intercellular substance, proinflammatory stress of neurons and microglial cells, a gradual increase in apoptosis and program necrosis of neurons and their replacement with astrocytes, and increased brain dysfunction. Latent manifestations of neurodegeneration are characteristic features of normal aging but could acquire specific signs of specific neurodegenerative diseases in the pathological sense [615-617].

The brain is a barrier-free tissue and has a number of characteristic features that increase and decrease the sensitivity of this tissue to TS:

1) Under normal conditions, the brain consumes about a quarter of the oxygen required by the body and it is also an insulin-independent obligately glycolizing tissue. Neurons rarely use glycolysis and fatty acid oxidation to compensate for their energy needs, this makes them very sensitive to hypoxia and prone to developing mitochondrial and oxidative stress (section 2.1.). The neurons could evade the phenomenon of lipotoxicity, which is a strong inducer of mitochondrial stress in many other cells of the body (section 2.2.). In conditions of ischemia and other causes of hypoxia, cellular stress develops in neurons with a high probability of apoptosis and program necrosis [618]. During hypoxia, proapoptotic pathways are activated in the inhibition of anti-apoptotic factors such as BCL-2 [619]. Chronic ischemia is an unfavorable factor in the development of neurodegeneration.
2) The process of protein biosynthesis which is necessary for the survival and fulfillment of the specialized functions of these cells is intensively and constantly proceeding in neurons. During the onset of ER-stress, the UPRer mechanisms cannot significantly block protein biosynthesis in these cells, and this contributes to the formation and deposition of abnormal proteins in neurons (section 2.3). Typical causes of the appearance of abnormal proteins are mutations of the genome, mitochondrial and oxidative stress, the ineffectiveness of UPRmt and UPRer, autophagy, and other protective mechanisms of cellular stress. At a certain degree of proteome impairment, mitochondrial and oxidative stress, and triggering apoptotic pathways are pathologically enhanced [620].
3) Neurons are postmitotic cells, in which the mechanisms of DNA (section - 2.7.) exhibit a certain tolerance to damage to the genome. This unique feature leads to the programmed death of neurons against the background of significant changes in the proteome, and this is characteristic of many neurodegenerative diseases [621].
4) Microglial cells may have the least pro-inflammatory potential compared to other stromal macrophages but they express many types of SR that are capable of binding amyloid proteins. At the initial stages of neurodegeneration, this mechanism contributes to the absorption and utilization of soluble β-amyloids in microglia and astrocytes but promote microglia activation and development of TS in the CNS when insoluble β-amyloids are formed [622, 623].

In humans, pronounced manifestations of neurodegeneration are observed with the development of genetic or infectious prion diseases [623]. These diseases are associated with conformational changes in the normal protein of neuronal membranes — PrPC, and its transformation into the PrPSc isoform, which is extremely resistant to proteolysis and degradation and causes further transformations such as PrPC into PrPSc [623, 624]. The probability of the deposition of β-amyloid and prion-like protein in neurons and intercellular substance increases with hereditary predisposition and with aging. In Alzheimer's disease, phosphorylated tau- protein and β-amyloid are deposited, while in Parkinson's disease, α-synuclein and tau-protein are deposited [621]. Additionally, during neurodegeneration, atherogenic forms of LDL can penetrate the blood-brain barrier, act on neurons through SR-E1 (LOX-1), which can promote DNA regeneration by the activation of DDR mechanisms. However, in less favorable cases this mechanism could cause apoptosis

of neurons through the associated SR- E1 signaling pathway: transcription factor - p53 / caspase-3 [621].

Ineffectiveness of autophagy and HSP-response can be manifested in the accumulation of amyloid cells and prion diseases. In humans, prion encephalopathies are associated with a normal neuronal membrane protein, PrPC, which under certain conditions (congenital and acquired) can be transformed into a pathological prion isoform of PrPC (the PrPSc), which is extremely resistant to proteolysis and degradation [624]. This pathological form differs from the normal molecule only in their spatial, but not the primary structure. If the prion forms do not effectively bind to chaperones and are not utilized on time, they could be converted to other PrPCs, and the process acquires a self-developing character; the PrPSc aggregates are deposited in neurons in the form of granules similar to β-amyloid. The process of prion distribution in the brain leads to the pathogenesis of prion diseases [624]. The probability of the deposition of different types of amyloid prion-like protein in neurons increases with the presence of a hereditary predisposition, and with age. In addition to classical genetic and infectious prion encephalopathies (mediated by PrPSc) [622], the deposition of prion-like proteins in neurons and in the intercellular substance of the brain can be observed in other neurodegenerative pathologies, such as the Alzheimer's disease (deposition of Tau-protein, β-Amyloid) and Parkinson (α-Synuclein deposition) [620].

6. SYSTEMIC INFLAMMATION

Authors suggested that it could be essential to characterize systemic inflammation (SI) as an independent variant of the general pathological process, different from classical inflammation [9, 25]. Without clarifying the real meaning of SI, it will remain difficult to solve numerous diagnostic problems or the prediction of complications and pathogenetic therapy in sepsis and other critical conditions. There is no standard definition of the concept of SI, this concept is usually used as an analog for the concept SIR; the concept SIR covers signs of a large number of general pathological processes and diseases, in addition to those not directly related to critical medical states. Considering the aforementioned, the description of the heuristic model of SI as an independent form of non-classical inflammation, which can be named super inflammation or metainflammation, we have dedicated a separate chapter.

The essence of SI is shifting of basic foci mechanisms to the organism level.

At the tissue level, SI leads to the development of abnormal blood microcirculation [625, 626]. Under physiological conditions, the main function of the endothelium is to prevent the intravascular coagulation of the blood, ensure the adequate blood perfusion in microvessels and normal metabolic processes between the inside and the extravascular medium [627]. When the SI processes are disturbed, the function of the microvessels will be oriented in the direction to ensure the exudation processes that are characteristic of the inflammatory focus but detrimental to the body during systemic activation.

6.1. Pathogenetic Core and Clinic of Systemic Inflammation

At the system level, the phenomenon of inflammatory microcirculation is manifested as follows:

1) Microcirculatory disorders and disorders of oxygen transport critical for life [628, 629].
2) Adaptive changes (centralization of blood circulation), and critical macrohemodynamic disorders [630, 631], such as life-critical manifestations of hypovolemia and hypotension [631].
3) Pathological cellular stress of endotheliocytes that produce high concentrations of NO and other inducible factors of "inflammatory" microcirculation [632].
4) Microthrombus formation on the surface of the postcapillaries endothelium [633].
5) Intravascular activation of the complement system and the kallikrein-kinin system, with the formation of complement anaphylaxins (C5a, C3a) and kinins [634].
6) Systemic activation and degranulation of mast cells [635, 636].
7) Organ dysfunctions [637].
8) At the cellular level, oxidative and mitochondrial stress, as well as mitochondrial dysfunction and program cell necrosis, play an important role in the pathogenesis of organ dysfunctions [638].

Generally, it was found that unlike SI, the acute phase response of the liver and bone marrow, the stress response of the neuroendocrine system and other systemic manifestations of classical inflammation are of protective benefits to the body [9, 639]. They provide resources for inflammation and create an additional barrier for the generalization of damage factors, thereby preventing the development of SI. Organs such as the brain, liver, kidney, myocardium, and lungs that are heavily dense with the capillary network, a high concentration of stromal, especially vascular macrophages are the most vulnerable to the development of microcirculatory disorders [640-645].

The main clinical manifestations of SI include thus:

1) Severe septic and aseptic shock conditions that are resistant to treatment with vasopressive drugs, and with a high probability of fatal outcome even under intensive therapy. These are the most obvious external manifestations of SI [9, 25]. In most cases, patients in the intensive care unit exhibit less clear signs of SI, more characteristic of the "gray zone" of systemic pro-inflammatory tissue stress (Fig. **4**), the clinical manifestations of the phenomenon of inflammatory microcirculation in such state are not so fuzzy.
2) A complex of resuscitation syndromes such as capillary leak syndrome [646], disseminated intravascular coagulation syndrome (DIC) [647], multiple organ dysfunction syndrome (MODS), syndromes of dysfunction of individual organs [648], acute respiratory distress syndrome that it is not associated with primary lung injury, and critical complications of postoperative syndrome [649].
3) SIR syndrome is not specific for critical conditions [650-652] and does not have absolute sensitivity to these conditions [652, 653]. The more recent class of sepsis (sepsis-3, 2016) excludes SIR syndrome and defines sepsis using the formula, infection + MODS [652, 654]. In this case, MOD is registered using the SOFA scale, and for screening purposes, the simplified version (the quick SOFA (qSOFA)) which does not require instrumental and hardware examination is employed.
4) In young patients with initially high levels of functional reserves, the presence of MODS is not an attribute of SI as they could proceed without signs of organ dysfunctions at the stage of sub compensation (in the "gray zone"). The development of a critical state does not always begin with the manifestation of MODS [652]. Furthermore, SI is not the only cause of organ dysfunctions [9, 25]; the presence of premorbid (in relation to an acute critical condition) chronic pathologies could play a significant role in organ dysfunctions [652]. Noteworthy, sepsis can be considered as a life-critical infection requiring intensive pathogenetic and etiological therapy [652], but having different pathogenetic scenarios that are not always taken into account. In the most severe cases (primarily, with septic shock), these scenarios include SI mechanisms which have shown to be characterized by a variety of manifestations.

6.2. Etiology of Systemic Inflammation

A common cause of the development of SI is systemic damage in its intensity comparable to local damage during the development of classical inflammation, this severe shock spreading in the in-

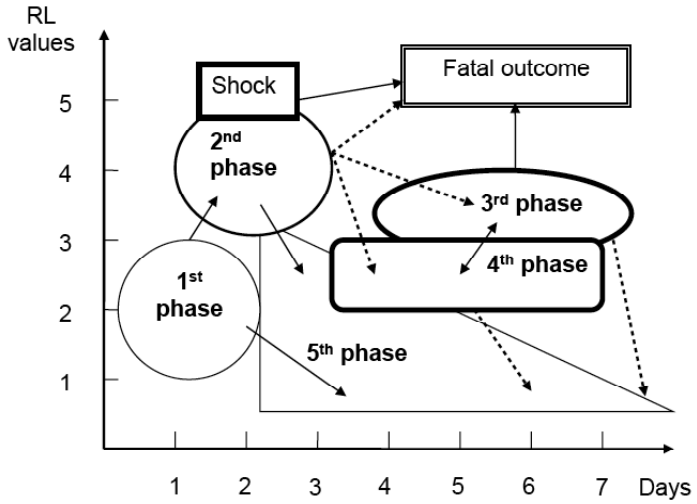

Fig. (4). Phases of SI: pushing scenario
Phases: 1st – a phase of SI development; 2nd – a phase of primary phlogogenic impact; 3rd - a phase of secondary phlogogenic impact; 4th - a depressive phase; 5th- SI resolution phase. The solid arrows indicate the main directions of SI development, dotted - less likely.

travascular environment often lead to a systemic response of the exudative-vascular complex, which is sufficient for the development of the phenomenon of inflammatory microcirculation. SI can also be caused by various infectious and non-infectious factors such as:

1) The release of PAMP into the bloodstream in sepsis, and DAMP in tissue breakdown products in the case of crash syndrome [655].
2) Various causes of large-scale intravascular hemolysis [656].
3) Systemic hypoxia, in cases of cardiogenic shock [657], or untimely relief of hypovolemia in the initial stages of hemorrhagic shock [658, 659].
4) The primary reaction of mast cells, such as in the development of anaphylactic shock [660].
5) Different causes of primary coagulopathy (type DIC) such as amniotic fluid embolism (rich in tissue factors) [661], crash syndrome [655], intravascular hemolysis with the development of DIC syndrome [656], the entry of biological poisons into bloodstream, pathological active hemostasis system [662], receipt from the center of a purulent inflammation of active hemostasis, and complement factors.
6) Individual pro-inflammatory cytokines can cause the pathological activation of endothelial cells and vascular macrophages, and anti-inflammatory cytokines (IL-10) that inhibits the protective function of vascular macrophages [663-665]. These cytokines can enter the bloodstream from the inflammation focus and could accumulate in the blood during systemic activation of endotheliocytes and macrophages.

6.3. Principal Differences and Similarities of Systemic Inflammation and Classical Inflammation

The principal differences between SI and classical inflammation lie in the nature of the effect of the damaging factor, and the absence of a division of the tissue stress program into local and systemic levels. Additionally, the main cellular effectors of classical inflammation are leukocytes and motile macrophages of the cell infiltrate of the inflammatory focus, and for SI, the endothelial cells and vascular stromal macrophages.

Classical inflammation acts as a protective process for the organism, and during autoimmune reactions, this process can acquire the property of a dysfunctional system. Contradictory, SI is initially designed as a dysfunctional process in nature since the systemic response of microvessels, hemostasis system and complement, mast cells, intravascular activation of neutrophils and other leukocytes has no protective properties for the organism. These mechanisms are aimed at the localization of the damaging factor and are not targeted for large-scale systemic use under the action of damage factors in the intravascular environment.

While classical inflammation characterizes the pathogenesis of inflammatory diseases, SI is not an attribute of the pathogenesis of diseases and other clinical definitions, but their critical complications. SI is a terminal stage of the manifestations of classical inflammation, such as purulent inflammation during the development of septic shock.

Septic shock was experimentally modelled through the intravenous administration of LPS or other PAMP to the animals [666, 667], it was reported that SI could be alternatively developed without the presence of a primary focus of inflammation in condition such as blood transfusion shock [668]; this attribute distinguishes SI from classical inflammation as it does not only depend on the presence of an inflammatory focus. Furthermore, this unique characteristic of SI cannot be attributed to the category of canonical inflammation.

Despite this unique attribute of SI, it remains noteworthy to state that there are no fundamental differences between the mechanisms of classical inflammation and SI. In both cases of inflammation, the molecular and cellular components of the exudative-vascular complex react in response to severe damage, however, these responses are localized in classical inflammation, and systemic in SI.

6.4. Definition of Systemic Inflammation as a General Pathological Process

Authors defined SI as a typical multi-syndrome, a phase-specific pathological process, evolving from systemic injury and characterized by the total inflammatory reactivity of the endotheliocytes, plasma and blood cell factors, connective tissue, and at the terminal stage, microcirculatory disorders in vital organs and tissues [669].

6.5. Secondary System Damage

The SI dynamics is largely determined by the development of the phenomenon of secondary systemic damage which contributes

to the development of SI even after the cessation of the primary damaging factor. There are several causes that act in conjunction with each other and contribute to the prolongation of severe systemic damage:

1) A direct result of microcirculatory and macrohemodynamic disorders in SI such as systemic hypoxia, ischemia, hypovolemia, dysproteinemia, respiratory and metabolic acidosis, and other changes in homeostasis [634, 670].
2) Tissue destruction associated with cell necrosis and the entry of DAMP and other toxic products from tissue breakdown into the blood [671, 672].
3) Pathological activation of intravascular leukocytes and vascular macrophages, and the release of cytotoxic factors into the bloodstream [673-675].
4) Poisoning of the body with excretory toxins and other factors associated with hepatic and renal failure [676, 677].
5) Increased intestinal permeability to PAMP and microbial toxins as a result of impaired intestinal barrier function [678]. In various cases of SI (sepsis, acute injury), this phenomenon is further aggravated due to hypoperfusion of mucous membranes and other disorders associated with microcirculatory disturbances [679, 680].
6) The increase in the blood levels of thrombin, complement anaphylaxins, and various inflammatory mediators in toxic amounts (excitotoxicity), which in turn increases the development of pathological stress of endothelial cells, vascular and intravascular phagocytes, other cells [634, 670, 681, 682].
7) Systemic cellular stress initiates intravascular netosis of neutrophils (section 1.1.3.), enhance extracellular DNA traps that lead to endothelium and platelets damage [683], facilitate the migration ROS, NO, proteinases, cationic proteins, other molecules into the blood which increase the damage to the cell membranes, and the activation of pro-inflammatory effects in blood plasma proteins.
8) Metabolic dysfunctions that are related to the stress response of the neuroendocrine system, and the development of tissue stress in other tissues which can cause the reduction of glutathione levels, thereby enhancing the development of oxidative stress [684]. The stress response of the neuroendocrine system, activation of metabolic cycles, increased insulin resistance, and the hypermetabolism and hypercatabolism phenomena can exhibit both protective (mobilization of nutrient reserves) and dysfunctional value [685]. These reactions could either enhance the accumulation of FFA, glucose, different changes in the concentration of amino acids, and many other metabolites in the blood or lead to the deficiency of essential amino acids, vitamins and other metabolites. It was found that oxygen transport disorders, mitochondrial stress, and mitochondrial dysfunction lead to oxidative phosphorylation disturbance and overproduction of lactate [686]. The development of hypermetabolism and hypercatabolism syndromes chiefly arises as an adverse consequence of the use of hormone therapy (such as insulin preparations) and metabolic therapy (nutritional support), this is evidential from the possible pathological effects of aberrant metabolome in burn disease [687, 688], sepsis, and other versions of MODS [687, 689].

The accumulation of aberrant metabolites in the bloodstream of SI could activate microvascular endothelium cells through the interaction with certain SRs, and this contributes to an unfavorable course of the process. It was found that mice that lacked SR-E1 (LOX-1) expression showed improved survival from sepsis as a result of reduced indices and the degree of damage to the internal organs [690]. The association between the pathological role of SR-E1 in sepsis and a high level of oxLDL in the blood was also highlighted [690].

6.6. The Main Phenomena of Systemic Inflammation

The lack of a holistic image of the pathogenetic core of sepsis and aseptic has posed as a hurdle in solving specific clinical problems [652, 691, 692]. The main phenomena of SI include the following:

1) A shock that is resistant to vazopressive drugs and infusion therapy. As aforementioned, this shock symbolizes the external and obvious manifestation of SI arising from various origins. The manifestations of the "gray zone" of SI may occur clinically prior to the formation of secondary systemic damage at the latter stages of SI [25, 669].
2) MODS and dysfunction of individual organ systems are also characteristic manifestations of SI at the stage of decompensation, however, organ dysfunctions could also arise as a consequence from other pathogenetic mechanisms beside SI, thereby limiting the manifestation of SI at the stage of the "gray zone" as a critical state [25].
3) The phenomenon of secondary systemic damage manifests itself from the accumulation of tissue decay products in the blood (*e.g.* troponin I that are not associated with myocardial infarction), and myoglobin [25].
4) The reaction of the hypothalamic-pituitary-adrenal axis and some other manifestations of classical inflammation. According to Selye [536], these reactions could be observed as the general adaptation syndrome, and have a very broad physiological and pathological significance.
5) Metabolic changes such as the elevated levels of glucose and lactate in the blood during sepsis [693, 694]. In most cases, these signs are associated with the stress response of the neuroendocrine system, TS in other organs, or act as molecular manifestations of damaged organs dysfunction. This phenomenon is not strictly specific to the SI particularly if it is not associated with the development of the shock state.
6) The phenomenon of systemic autophagocytic pathology associated with the activation of vascular and intravascular phagocytes, which presents itself as one of the causes of secondary systemic damage [652].
7) Phenomena of dysfunction of the immune system, barrier functions of the mucous membranes, blockade of leukocyte migration to the inflammatory focus due to their intravascular activation outside the inflammatory focus, contribute to the development of secondary infectious complications (*e.g.* post-traumatic sepsis).
8) Microcirculatory disorders that develop in a mosaic manner at the level of individual microcirculatory units in SI, and can be studied *in vivo* using the dark-beam low-field microscopy [695, 696]. A separate component of this phenomenon is the process of microthrombogenesis, which is clinically fixed using the criteria of the syndrome DIC [697]. It was reported that the disturbances of microcirculation, systemic activation of endotheliocytes and hemostasis factors are closely interrelated with the intravascular activation of the systems of kallikrein-kinins and complement [698]. Similarly, it was found that an increase in the blood of complement anaphylaxin and kinins, and depletion of plasma kallikreinogen can also be explained by the phenomenon of microcirculation disorders [699].
9) The phenomenon of systemic activation and mast cell degranulation. Mast cells are interconnected with the reaction of blood vessels, the system of complement and hemostasis, and other pro-inflammatory mechanisms [12, 700, 701]. In living cells, this phenomenon can be presented as the high blood concentrations of histamine or mast cell indicator enzymes (primarily tryptase) [701, 702]. This phenomenon can also manifest in sepsis [703], and systemic anaphylactic processes [12, 702].

10) For the development of SI damaging factors, it is necessary to overcome the barriers of anti-inflammatory resistance such as the antioxidant and antiproteinase systems of blood plasma, as well as the function of SR macrophages of the reticuloendothelial system (RES) which is realized with the aid of protein factors of blood plasma, liver microvessels macrophages and some other organs. Some factors of systemic anti-inflammatory resistance are the acute phase proteins, which include α1-proteinase inhibitor (α1-antitrypsin), α1-antichymotrypsin, haptoglobin, α1-acid glycoprotein, ceruloplasmin and some others. These factors of systemic anti-inflammatory resistance also include conditional anti-inflammatory cytokine TGF-β, which are present in the blood high concentrations under normal conditions. These plasma proteins can also characterize SIR to a certain extent. It was reported that rather than an increase in the concentration of these proteins in the blood, the depletion of their barrier function in the process of developing systemic damage can be considered as a relative specific phenomenon to SI [9, 669].

The homeostatic functions of SR RES are generally associated with blood purification from metabolic and cellular debris. This function is overlapping in many SRs, but some types of these receptors have their functional accents [165-167]:

- blood purification from apoptotic cells - SR-F1 [76] and others;
- blood purification from PAMP - SR-A6 (MARCO) and others;
- blood purification from aberrant metabolites - SR-A1 (CD204) and others;
- inhibition of endothelial cell stress - SR-B1 [704, 705] and others;
- formation of regulatory complexes with TLR - SR-B2 (CD36) and others;
- aberrant platelet removal - SR-E4 (AMR) [706, 707];
- DAMP binding (S-100, HMGB1) - SR-J1 (RAGE) [708];
- protease / antiprotease complex uptake - SR-L1 (CD91) [709];
- haptoglobin / hemoglobin complexes uptake - SR-I1 (CD163) [610].

11) In the narrow sense, the phenomena of the secretory phenotype of the systemic TS or the SIR. This is characterized by the accumulation of cellular stress products in the blood, and it is strictly specific to the SI when a strong systemic response of the entire mass of the vascular endothelium is observed [25, 669].

It is worthy to note that each phenomenon is a complex system consisting of more subsystems. The hierarchy of the subsystems has both vertical integrated, and horizontal (network) links that integrate the main SI processes into a single whole. Furthermore, owing to the different characteristics of the etiological factors of SI (genotype, environmental factors *etc*.), the course of SI is characterized by a high degree of diversity; this also applies to the various variants of combinations of SI phenomena.

6.7. Systemic Inflammatory Response, a Methodology for its Assessment

The usage of the integral SIR criterion by combining at least three to five separate indicators on an alternative basis is necessary due to the complexity and non-linearity of the changes in the values of SIR in the blood in SI and other variants of inflammation [25, 669]. However, these indicators must meet the following requirements:

1. Be associated with systemic activation of microvascular cells, platelets and pro-inflammatory systems of blood plasma (hemostasis, complement and kallikrein-kinin systems), and with the clinical manifestations of microcirculation disorders (shock). Alternatively, they should reflect some probability of the development of other key SI phenomena. Concurrently, the individual pathogenetic factors can act as indicators of several phenomena depending on the specific patterns of their use.
2. Have a biological and clinical significance.
3. Show a sufficiently high amplitude of quantitative changes in the blood in pathological states, as well as exhibiting clear control intervals of their concentrations under normal condition.
4. They must differ in their relatively short half-life in the bloodstream to allow the assessment of the process dynamics.
5. The empirical indicators for the integral criterion should reflect the integrity of the SIR.
6. The quantitative range of their concentrations in the blood can be determined from other indicators. These ranges should be comparable in pathogenetic significance and reflect the likelihood of development of various qualitative levels of systemic cellular and tissue stress. Alternatively, comparable ranges of different indicators should equally identify specific SIR levels, reflecting in different degrees the likelihood of SIR development. These indicators make it unnecessary to use only formal logic (such as “yes” is a definite truth, and “no” is its absence) to determine SIR levels, rather, the use of rational multiple probabilistic logic such as in the following sequence of variants of the SI signs: 1) “no”; 2) “rather not”; 3) neither “no” nor “yes” (zone of uncertainty); 4) “rather yes” and 5) “yes” is also required [28].

These ranges of reactivity levels (RL) of SIR are expressed by different numerical values since different levels have a different pathogenetic and diagnostic value listed as follows [25, 669]:

0 - a standard level which includes borderline manifestations of SIR typical for para-inflammation, such as the C-reactive protein concentrations in the range of 3-10 mg / l (these borderline SIR values require separate classification).

1 - SIR level excluding the development of acute SI, and usually characterizes acute and chronic classical inflammation, as well as the development of systemic para-inflammation.

2 - The typical level for SIR in classical inflammation in an expressed purulent process, as well as in relatively rare hypoergic (depressive) variants of the development of SI. It is usually not typical but could be possible for systemic manifestations of some variants of para-inflammation.

3 – The ambiguity area that does not ease the differentiation between classical and systemic inflammation, and requires monitoring and evaluation of other SI criteria.

4 - Typical for hyperergic SI variants (phase of phlogogenic impact) that are less likely with classical inflammation.

5 - Confirms the development of SI and characterizes the critical state of the patient's condition regardless of the SOFA scale values and the general indicators of state assessment.

The blood concentration ranges for the corresponding RL values for each indicator are calculated; for RL-0, the upper limit of the norm is calculated. When using the 5 indicators for each patient, there are 3 indicators showing the highest values of RL, and they are averaged to the value of integral RL [25]. The integral criterion allows to correct individual indicators, their randomness, and the non-linear changes in the blood concentration of these indicators. The exclusion of weak links allows to adapt the integral indicator of RL to a patient. Furthermore, the integral criterion allows the uniformity of separate indicators, and the integration of indicators with different functional orientation into a single system. However, the integral indicator SIR does not reflect the pathogenetic picture of SI as this requires more complex scales that consider other SI phenomena [25, 669].

6.8. Potential SIR Criteria for Calculating RL Scale

The number of potential SIR indicators in blood plasma is vast and could serve as an alternative means of calculating the integral criterion of RL.

A clinical practice and *in vivo* experiment tested chemokine markers of two subfamilies 1) CXCL1 (NAP-3), CXCL2 (MIP-2α) and CXCL8 (IL-8); 2) CCL2 (MCP-1), CCL3 (MIP-1α) and CCL5 (RANTES) , and it was found that their strength is directly related to the activation of endotheliocytes and platelet degranulation, the high amplitude of the changes, and the mild anomaly distribution of their concentrations in the blood [693, 710-712].

Members of the families of cytokines interleukin 1 (IL-1β) and tumor necrosis factor (TNF-α) are very significant in the development of SI. Despite the importance of these cytokines in the pathogenesis of diseases, they cannot be used as prognostic criteria for the development of critical complications due to feedback mechanisms that limit the increase in these cytokines in the blood [669, 694]. Meanwhile, other cytokines, mainly those secreted by macrophages (IL-12, IL-18, MIF, GM-CSF) can be used to estimate SIR [694, 710, 711, 713].

One of the most important cytokine markers of SIR is IL-6, this factor is excreted in large quantities during SI by vascular macrophages and endothelial cells (considering the total mass of these cells), and has a very significant range of changes in blood concentration (more than 1000-fold changes relative to the upper normal level) which are associated with the severity of patients [669, 694].

Two anti-inflammatory cytokines, IL-10 and interleukin-1 receptor antagonist (IL-1ra) are described as SIR markers, their blood levels have been found to be very high in sepsis, and has implicated in the development of critical complications [694, 711, 712]. The change in the blood concentration of the growth factors secreted by activated endotheliocytes, platelet growth factor (PDGF) [694], and cytokines of the vascular endothelial growth factor (VEGF) family [714] can be criteria of SIR. Proadrenomedullin concentration in the blood has a good prognostic value in sepsis [715]. Soluble forms of cytokine receptors for IL-2 (sIL-2R) and the TNF family can equally serve as criteria for SIR [694, 695, 716].

The accumulation of desquamated endothelial cells (CD144 + cells) in the blood, as well as soluble forms of some adhesive receptors (endocan, E-selectin, VCAM-1 and ICAM-1), can be considered as signs of systemic activation of microvessels [27, 694, 717, 718]. Several inducible heat shock proteins can be considered as promising markers of SIR [694]. Soluble fragments of some PRRs, namely presepsin (fragment of the CD14 co-receptor TLR-4) and soluble trigger receptor expressed on myeloid cells-1 (sTREM-1, which is another co-receptor TLR-4) acts as markers of sepsis [710]. The soluble forms of some SR-sCD163 [610] and sCD206 [679] can also be effectively used for this purpose. Among the protein factors that are not SIR cytokine, the non-histone chromosomal protein HMGB1 can be identified, and its blood level may correlate with the criticality of the patient's condition [694, 719]. Procalcitonin can be secreted into the blood by various stromal cells, but its pathogenetic role remains unclear. Authors found that procalcitonin, just like presepsin, is relatively (but not absolutely) specific for a bacterial infection, but exhibits a longer period of accumulation in the blood [720].

Some of the acute phases of the liver proteins have traditionally been used as SIR markers [694, 710, 717], their concentrations increase in the blood during various inflammatory processes, but they have a relatively long lag-period of accumulation and half-life in the bloodstream. The most popular protein of the acute phase is C-reactive protein.

Neopterin, some lipid mediators (eicosanoids) [711, 721] and platelet activating factor [722], as well as the factor of vasodilation and microvascular permeability (NO-radical) and its metabolic products, can be considered as potential non-protein SIR markers [694, 723].

6.9. Examples of using the SIR integral criterion (RL)

For the calculation of the RL criterion, 5 blood plasma SIR indicators with an established upper limit of normal is used: C-reactive protein (normal ≤ 10 mg / l), TNF-α (≤8pg / ml), IL-6 (≤5 pg / ml), IL-8 (≤10 pg / ml), IL-10 (≤5 pg / ml). For each indicator, the ranges of pathogenetic significant concentrations exceeding the limit values of the norm were individually calculated. To calculate the RL for each patient, 3 indicators with the highest values of the pathogenetic significance ranges were averaged to determine the integral RL [25]. The values of RL in three groups with criteria for sepsis-3 in the acute period of the disease (1-2 days) are presented in Table **2** and discussed thus:

1) Phlegmon of the shin of the 3rd degree (usually affects the muscle tissue) in men aged 18-21 years who are undergoing treatment in the surgical department without intensive therapy; despite the presence of MOD signs, the score on the SOFA scale (mean ± σ) was 3.6 ± 1.14.
2) Patients of the intensive care unit (peritonitis, pneumonia); the score on the SOFA scale (mean ± σ) was 5.5 ± 2.30.
3) Septic shock (also verified by the criteria of sepsis-3).

Also, patients with a high SI probability were identified considering other SI phenomena such as stress response of the neuroendocrine system, DIC, systemic damage [25]. The probability was expressed in% of the total number of patients in the groups.

The presented data confirm that SI is associated with shock state and the fact that not any variant of sepsis-3 can be viewed from the position of SI. At the same time, a certain number of patients without the formal criteria of MODS undergoing intensive therapy may have signs of SI [25].

The RL distribution ranges between groups varies (Table **2**). However, for individual indicators, the degree of fluctuations and parameters of distribution abnormalities are much greater. In general, the values of RL in the acute period of sepsis correlate with the severity of the patients' state, such as the maximum values of RL occur in resuscitation patients with septic shock. Similar regularities are characteristic of the development of critical states in acute trauma and postoperative complications [25].

6.10. Dynamics of Systemic Inflammation

The dynamics of SI strongly correlates with the intensity of systemic damage and not on its nature nor the response to this damage. The development of pro-inflammatory tissue stress is an energy-intensive process. Authors reported on the possible manifestation of hyperergic and hypoergic variants of SI development [25]; it was also found that during the development of critical states, the daily energy consumption may exceed 10,000 kilocalories, however, there could be a state of low energy consumption [724]. At the stage of sub compensation, blood circulation is centralized with a relatively high level of perfusion and oxygen transport in the internal organs, however, at the stage of critical decompensation and pathological decentralization of hemodynamics, these processes are grossly disturbed [725-727]. In SI, hyperergic status can provide high levels of SIR (RL-4 and RL-5) during the development of a critical state. It remains noteworthy to state that a decrease in SIR is not always a favorable sign. Additionally, it was found that the most critical shock development can occur at relatively small SIR values (RL-2 and RL-3), and this phase of SI could be termed the depressed phase. This depressed phase is characterized by the inability of cells to support physiological functions, as well as a strong stress response against damage.

Two main SI dynamic scenarios are possible depending on the intensity of the damaging factor effect:

Table 2. Frequency of RL distribution (%), the incidence of SI and lethal outcomes (LO) in three groups of acute sepsis (sepsis-3 criteria) and conditionally healthy people (control).

Groups	N	RL-0	RL -1	RL -2	RL -3	RL -4	RL -5	SI	LO
Control (18-55 ages)	50	100	0	0	0	0	0	0	0
Non-esuscitation sepsis, (phlegmon of the leg 3 degrees)	40	0	27.5	55	17.5	0	0	10	0
Resuscitation sepsis (peritonitis, pneumonia)	46	0	4.3	10.9	41.3	30.4	13.1	73.9	23.9
Septic shock	14	0	0	7.1	14.3	42.9	35.7	100	78.6

RL denotes the level of systemic pro-inflammatory reactivity, SI is a systemic inflammation determined using an integral criterion [87].

1) The breakthrough scenario which is super-sharp, relatively rare, and unfavorable to the development of SI.
2) The pushing scenario which is characterized by a gradual transformation of classical inflammation into SI, such as in sepsis, with the exception of its rare variant (fulminant sepsis).

The breakthrough SI dynamic scenario is rare, develops spontaneously, has a vibrant dynamic, and requires multiple monitoring for its assessment in the first few days of its development. The clinical assessment of this dynamic scenario is rather complicated. Several of such cases were monitored, and named thus: 1) 3 cases of embolism of amniotic fluid with fulminant development of consumption coagulopathy, and to the extent of complete non-coagulation of blood; 2) A case of fulminant sepsis, several cases of acute injury with massive blood loss. Generally, the regularities of these processes are the achievement of the peak of a very pronounced phase of phlogogenic impact (RL-5) after 6-12 hours from the onset of the damaging factor action, and the development of the depressive phase before 24hrs of the manifestation of the process. In the overwhelming majority of cases, this variant of the SI is fatal. Despite being non-specific for SI manifestations of SIR, the verification of the depressive phase of SI is not difficult. Authors reported that this depressive phase of SI is characterized by extreme severe shock processes with a high degree of manifestation of other SI phenomena [25]. The development of the "breakthrough" variant is not related to the classical inflammatory focus, and its role in the development of this SI variant is equally insignificant.

The pushing scenario is the most typical and more multifaceted variant of the SI (Fig. **4**). The manifestations of SI grow gradually through the passage of the "gray zone", and in this zone, SI can be resolved. The phase of the SI development (RL-2, RL-3), which is the most typical phases corresponds to the border state of the "gray zone", and with a further progression, a phase of primary phlogogenic impact (UR-4, less often RL-5) occurs. The phase of primary phlogogenic impact can last up to several days and can be accompanied by shock and MODS with high SOFA values and death, or could possible show a more favorable scenario with a transition to the SI resolution phase (RL-2, RL-3) within 3-10 days of the process (some signs of SIR can last longer).

A less favorable and rare variant of pushing scenario is the phase of secondary phlogogenic impact, this phase is associated with the registration RL-4 after 5-8 days from the onset of the development of a critical condition. This phase may manifest either through an interphase transition (light window type), a progredient process or in the form of a plateau during the direct transition of the primary phlogogenic impact phase to the secondary phlogogenic impact phase. This less favorable variant of pushing scenario was presented in five patients with acute injury, four out of which showed a fatal outcome, the only survivor had no signs of MODS during hospitalization. Similarly, 6 of such cases were identified in sepsis-3, and 4 of 6 patients showed a fatal outcome.

The depressive phase is not typical of the pushing variant, however, it appears as an interphase transition. The exceptions of the depressive phase occur in the protracted and subacute course of sepsis (tertiary peritonitis), in these cases, the torpid flow of MODS could be complicated by a severe shock condition with the dominance of the depressive phase of the SI. Authors observed the depressive phase 17 patients with tertiary peritonitis, 16 of which showed signs of the depressive phase and the remaining patient had a phlogogenic impact phase, a 94% mortality rate was reported. Noteworthy, it can be stated that with the breakthrough variant, the SI process bursts into the depressive phase through a short-term and very rapid development of the phlogogenic impact phase, but with protracted/subacute sepsis the progression to the depressive phase is rather slower.

The SI dynamics acts as a variable both in the intensity of the SIR, and the manifestation of other signs of SIR process [25]. Furthermore, these features of the dynamics of SI should be taken into account for the differentiated use of intensive care products, mostly, glucocorticoids and other anti-inflammatory drugs.

6.11. Is there Chronic Systemic Inflammation?

Some chronic diseases can be associated with the strong systemic effect of infectious and non-infectious damaging factors, some of them are listed thus:

1) Chronic renal failure of the 5th stage requiring a replacement therapy, and the use of program hemodialysis. Factors of systemic damage, in this case, include the action of renal toxins, contact blood and a foreign surface, and the factors of the underlying disease.
2) Systemic autoimmune diseases such as immunocomplex pathology, other mechanisms of endothelium activation and its damage.
3) Atherosclerotic gangrene of the toes during stenosis of the femoral artery, the migration of tissue breakdown products from ischemic tissues into the blood.
4) Severe chronic infections with secondary atrophic and sclerotic changes in the internal organs.

In contrast to the acute processes in the aforementioned chronic diseases, there are no reliable clinical criteria for SI. The causes of chronic disorders of internal organs are different; and the mechanisms of chronic systemic inflammation (ChrSI) can only accelerate the development of these processes. However, the assessment of these changes requires verified ChrSI criteria, large-scale prospective studies, and meta-analysis. The inability to verify ChrSI criteria, coupled with the fact that ChrSI is not independently recognized in practical medicine, pose as an obstacle in its use as an assessment tool.

We suggest that patients with a high probability of developing ChrSI could be attributed to those who have constant or periodical high SIR levels (RL≥3, not associated with acute inflammation) or

Table 3. Frequencies of RL values and D-dimer registration (DIC value) for various chronic diseases.

Groups	n	RL-0	RL -1	RL -2	RL -3	RL -4	RL -5	D-d
Conditionally healthy people over 65	18	88.9	11.1	0	0	0	0	0
Chr. adnexitis	16	75	25	0	0	0	0	0
Chr. flegmons of the lower extremities	42	19	78.6	2.4	0	0	0	9.5
Hypertension, post menstrual syndrome	16	93.7	6,3	0	0	0	0	0
> 65 years, stage 2-3 chr. heart failure, encephalopathy	49	53.1	36.7	10.2	0	0	0	32.7
Atherosclerotic stenosis of the femoral artery, chr. gangrene toes	38	5.3	31.6	52.6	10.5	0	0	47.4
Autoimmune thyroiditis	29	79.3	20.7	0	0	0	0	0
Ankylosing Spondylitis	27	44.5	33.3	22.2	0	0	0	11.1
Psoriasis, arthritis	12	33.3	50	16.7	0	0	0	8.3
Valvular heart disease	15	53.5	33.3	13.2	0	0	0	13.3
Reactive arthritis	30	46.7	33.3	20	0	0	0	23.3
Rheumatoid arthritis	42	31	47.6	19	2.4	0	0	54.8
Systemic lupus erythematosus	49	8.2	4.1	16.3	32.6	34.7	4.1	40.8
Stage 5 chr. renal failure[1] before hemodialysis	42	4.8	16.6	54.8	21.4	2.4	0	38.1
Stage 5 chr. renal failure[1] after hemodialysis	42	14.3	33.3	45.3	7.1	0	0	16.6
Chr. kidney transplant dysfunction[2]	23	8.7	69.6	17.4	4.3	0	0	21.7
Normal kidney transplant function	24	58.3	25	16.7	0	0	0	2.4

The frequency of registration of the value of D-dimer (D-d)> 500 ng / ml; 1 signifies disease conditions such as chr. glomerulonephritis, diabetes mellitus, and chr. pyelonephritis before and after hemodialysis process, patients in these groups received anticoagulants. 2 indicates that there was no correlation between SI with other variants of morphological changes during a biopsy of the kidney. In groups with no age grade indicated signified patients that were younger than 65 years.

RL-2 in the presence of individual signs of latent DIC (D-dimers > 500 ng / ml) or chronic microcirculatory disorders according to intravital microscopic examination. In chronic microcirculatory disorders, a more precise verification of the detected changes, the release of the stages of microcirculatory bed change, blood saturation and perfusion could be required.

The distribution of the RL and the detection rate of the DIC criterion (D-dimers> 500 ng / ml) for some chronic diseases are presented in Table **3**. The tabulated data substantiate the viewpoint on the possible development of ChrSI as a complication of the underlying disease in some systemic autoimmune diseases, chronic atherosclerotic gangrene of the toes, and chronic renal failure of the 5th stage (Table **3**). From the data obtained in systemic lupus erythematosus patients, RL-5 was detected in two patients which were denoted as A and B (Table **3**). In acute processes, the presence of RL-5 is typical of hyperergic shock state and other critical complications.

We suggested on the specific values of plasma cytokines in these patients as thus: IL-6 pg / ml: A) 12560, B) 3648; IL-8 pg / ml: A) 35350, B) 8230; TNF-α pg / ml: A) 848, B) 1654; IL-10 pg / ml: A) 6.5, B) 16.2. Obviously, in these patients, a partial adaptation to the potentially damaging effect of high concentrations of pro-inflammatory cytokines in the blood was observed, and this adaptation is not directly related to the overproduction of IL-10, as it has no significance in these patients. It could be possible that therapy such as glucocorticoids and other anti-inflammatory drugs plays certain roles in this adaptation. The dynamics of SLE is characterized by different phases of exacerbation and remission, lesions of the skin, mucous membranes, joints, internal organs (mostly the kidneys and brain) [728]. SLE is usually characterized by impaired blood microcirculation and endothelial dysfunction [729], intravascular activation of the hemostasis system [730], complement [731], and activation of the kallikrein-kinin system [732]. Authors reported on the possible role of mast cell activation in the pathogenesis of several other systemic autoimmune diseases [582].

Thus, the development of SIR in chronic pathologies differs from para-inflammation, likewise low-grade inflammation. It remains factual that ChrSI could exist as an independent form in the general pathological process of SI, the chronic variant of this process is not an attribute of the pathogenesis of specific diseases, but their complications. The contribution of ChrSI to the development of chronic organ dysfunctions and thrombohemorrhagic complications is currently not evaluated.

CONCLUSION

The information obtained from the general regularities, underlying specific problems, allows to resolve them successfully. Models of some general pathologic processes exhibit general regularities of clinical definitions (Fig. **3**), and these general pathologic processes are based on the universal regularities of cellular and tissue stress. Additionally, cellular stress acts like an elementary functional chain of different pathologies and certain physiological processes associated with cell and organ response to various extreme effects of real or potential damaging factors. Cellular stress is realized by a complex of typical reactions of proteome and genome, including transcriptional, posttranscriptional and posttranslational changes in original genetic information. These genomic and proteomic reactions lead to the transformation of the cell information field. Cellular stress includes interconnected processes that are associated with oxidative stress and the stress response of individual cellular compartments. Extremal functions of cells are synchronized by changing the receptor and secretory phenotype of these cells; certain programs of tissue stress switch on during the cellular synchronization process.

Furthermore, a certain program of tissues is also switched on by a strong local injury program of classical inflammation. The delocalization of the mechanisms of the exudative-vascular complex arises from strong systemic damage, and systemic inflammation develops with life-critical microcirculatory disorders in the internal organs from this process. In case of injuries of low intensity that are highly associated with cell aging, the action of aberrant metabolome factors, other adverse changes in homeostasis, para-inflammatory processes develop. These injuries can also cause various pathologies associated with insulin resistance, neurodegenerative processes and other diseases that do not demonstrate attribute signs of classical inflammation.

Cellular stress programs include both general and specific components depending on the type of cells, their initial state, and particularities of the action of stress signals. There are also diverse directions and outcomes of cellular stress, these include the development of various programs of cellular suicide, tumor transformation, cell aging, and other morphofunctional transformations of cells. Depending on the correlation of these trends, a complex of general pathological processes is formed at the tissue level, simultaneously, pathologies acquire specific contours characteristic of various clinical definitions.

Growth and development processes and the accumulation of functional reserves of cells increase the resistance of the tissue to the action of damaging factors of low intensity which usually occur at the initial stage of tissue stress development. Functional cells enhance resistance to apoptosis, while an irreversibly altered, and dysfunctional cells are eliminated from healthy tissue.

With a further increment of the effect of damaging factors, oxidative and mitochondrial stress enhance the intracellular network of regulatory factors and the secretory phenotype of the cells and increase their pro-inflammatory properties. The processes of tissue atrophy and sclerosis are becoming prominent due to the replacement of the parenchyma of internal organs by cells and the extracellular matrix of connective tissue, which are more resistant to the action of damaging factors. Aging of cells with a gradual increase in their dysfunction is not the worst scenario in the development of tissue stress. Less favorable pathways in the aging process of cells are processes of tissue malignancy, and those leading to massive death of parenchymal cells through apoptosis and programmed necrosis. The mechanisms of cellular and tissue stress play a dual role either stabilizing an already changed homeostasis (allostasis) or participate in various dysfunctional systems that form vicious pathogenetic circles.

With the development of classical inflammation, the main events of tissue stress occur in the focus of inflammation, the main task of tissue stress in these states is aimed at the localization and elimination of the damaging factor, and not geared towards the preservation of the integrity and function of the damaged tissue. The main cellular elements, in this case, are leukocytes migrating from the bloodstream, and inflammatory macrophages formed from monocytes. Macrophages and T-cells interact with these cellular elements and adapt to the features of the damaging factor through their directional differentiation into a various morphofunctional pole. With further enhancement of the action of damaging factors, such as the development of purulent inflammation, the role of neutrophils and the mechanisms of the exudative-vascular complex increases. However, during the course of the development of systemic inflammation, the role of this complex becomes prominent in the development of systemic microcirculatory disorders. The process of acute classical inflammation is completed by post-inflammatory regeneration or scar repair of damaged tissue. At the stages of acute classical inflammation, there is a reversion of the mechanisms of tissue stress in the direction of reducing its pro-inflammatory properties. Hence, the balance between the damaging factors and the mechanisms of cellular and tissue stress will determine the occurrence, course, and outcome of almost all human pathologies.

The mechanisms of cellular and tissue stress are structured into complex systems, which include the network of information exchange with multidirectional signaling pathways that make these systems internally complex, and the effects of their activation, unpredictable. The primary effects of a targeted impact on these systems inevitably generate a vast of secondary effects that may have a different target from the goal of the primary impact. The transition from unidirectional use of therapeutic agents (such as the effect on specific mechanisms of vascular tone or antimicrobial effects) for the regulation of cellular and tissue stress as a holistic process is rather complex; an alternate solution to this problem requires new theoretical and methodological approaches. The integral criteria can plausibly reflect the holistic image of the complex processes since the results obtained from the analysis are accurate in detail, but not in assessing the holistic state. Furthermore, the introduction of integral criteria for various variants of tissue stress will require a higher level of patient examination costs, determination of indications for these examinations, use of programs associated with computer networks of medical institutions, new capabilities for analyzing electronic databases, and employing the use of artificial intelligence. One step in this direction involves the isolation and formalization of the general patterns of human pathologies in the form of abstract models of general pathological processes, as well as the development of methods and methodological approaches for their evaluation.

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REFERENCES

[1] Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 2014; 69(1): S4-9.

[2] Pietzner M, Kaul A, Henning AK, *et al*. Comprehensive metabolic profiling of chronic low-grade inflammation among generally healthy individuals. BMC Med 2017; 15: 210.

[3] Castro AM, Concha LEM, Pantoja-Meléndez CA. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Rev Med Hosp Gen Méx 2017; 80(2): 101-5.

[4] Kültz D. Molecular and evolutionary basis of the cellular stress response. Annu Rev Physiol 2005; 67: 225-67.

[5] Muralidharan S, Mandrekar P. Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation. J Leukoc Biol 2013; 94 (6): 1167-84.

[6] Kültz D. Evolution of the cellular stress proteome: from monophyletic origin to ubiquitous function. J Exp Biol 2003; 206: 3119-24.

[7] Egiazaryan GG, Sudakov KV. Theory of functional systems in the scientific school of P.K. Anokhin. J Hist Neurosci 2007; 16(1-2): 194-205.

[8] Fulda S, Gorman AM, Hori O, Samali A. Cellular Stress Responses: Cell Survival and Cell Death. Int J Cell Biol 2010; 2010: ID 214074.

[9] Gusev EYu, Chereshnev VA. Systemic inflammation: theoretical and methodological approaches to the description of the general pathological process model. Part I. General characteristics of the process. Pathol Physiol Exp The 2012; 4: 3-14.

[10] Guido M; Isabelle J. Cells, Tissues and Disease: Principles of General Pathology. Oxford University Press (OUP) 2004; 1040.

[11] McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav 2003; 43(1): 2-15.

[12] Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology, 9th Ed. Elsevier, 2018. 579 p.

[13] Motoshima T, Miura Y, Wakigami N, *et al*. Phenotypical change of tumor-associated macrophages in metastatic lesions of clear cell renal cell carcinoma. Med Mol Morphol 2018; 51(1): 57-63.

[14] Zhang H, Zhang W, Sun X, *et al*. Class A1 scavenger receptor modulates glioma progression by regulating M2-like tumor-associated macrophage polarization. Oncotarget 2016; 7(31): 50099-116

[15] Kubota K., Moriyama M, Furukawa S, *et al*. $CD163^{+}CD204^{+}$ tumor-associated macrophages contribute to T cell regulation via interleukin-10 and PD-L1 production in oral squamous cell carcinoma. Sci Rep 2017; 7(1): 1755.

[16] Jones DP. Redefining oxidative stress. *Antioxid Redox Signal* 2006; 8(9-10): 1865-79.

[17] Meusser B, Hirsch C, Jarosch E, Sommer T. ERAD: the long road to destruction. Nat Cell Biol 2005; 7: 766-72.

[18] Yan F, Mo X, Liu J, *et al*. Thymic function in the regulation of T cells, and molecular mechanisms underlying the modulation of cytokines and stress signaling. Mol Med Rep 2017; 16(5): 7175-84.

[19] Lei-Leston AC, Murphy AG, Maloy KJ. Epithelial cell inflammasomes in intestinal immunity and inflammation. Front Immunol 2017; 8: 1168.

[20] Peake J, Della Gatta P, Suzuki K, Nieman D. Cytokine expression and secretion by skeletal muscle cells : regulatory mechanisms and exercise effects. Exerc Immunol Rev 2015; 21: 8-25.

[21] Nielsen S, Pedersen BK. Skeletal muscle as an immunogenic organ. Curr Opin Pharmacol 2008; 8(3): 346-51.

[22] Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 2008; 88(4): 1379-406.

[23] Senf SM. Skeletal muscle heat shock protein 70: diverse functions and therapeutic potential for wasting disorders Front Physiol 2013; 4: 330.

[24] Kim ML, Chae JJ, Park YH, *et al*. Aberrant actin depolymerization triggers the pyrin inflammasome and autoinflammatory disease that is dependent on IL-18, not IL-1. J Exp Med 2015; 212(6): 927-38.

[25] Zotova NV, Chereshnev VA, Gusev EYu. Systemic inflammation: methodological approaches to identification of the common pathological process. PLoS ONE 2016; 11: e0155138.

[26] Chimal-Ramírez GK, Espinoza-Sánchez NA, Chávez-Sánchez L, *et al*. Monocyte Differentiation towards Protumor Activity Does Not Correlate with M1 or M2 Phenotypes. J Immunol Res. 2016; 2016: 6031486.

[27] Polisak B, Milisav I. Clinical implications of cellular stress responses. Bosn J Basic Med Sci 2012; 12(2): 122-6.

[28] Bergmann M. An introduction to many-valued and fuzzy logic: semantics, algebras, and derivation systems. Cambridge, MA: Cambridge University Press, 2008. 342 p. 740

[29] Milisav I, PoljšakB, Ribarič S. Reduced risk of apoptosis: mechanisms of stress responses. Apoptosis 2017; 22(2): 265-83.

[30] Randle PJ, Garland PB, Hales CN, EAN The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; 1(7285): 785-9.

[31] Minihane AM, Vinoy S, Russel WR, *et al*. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr 2015; 114(7): 999-1012.

[32] Milisav I, Poljsak B, Suput D. Adaptive response, evidence of cross-resistance and its potential clinical use. Int J Mol Sci 2012: 13(9): 10771-806.

[33] Polisak B, Milisav I. Clinical implications of cellular stress responses. Bosn J Basic Med Sci 2012; 12(2): 122-6.

[34] Kroemer G, Levine B. Autophagic cell death: the story of a misnomer. Nat Rev Mol Cell Biol 2008; 9(12): 1004-10.

[35] Elmore S. Apoptosis: A review of programmed cell death. Toxicol Pathol 2007; 35(4): 495-516.

[36] Shimamatsu K, Wanless IR. Role of Ischemia in Causing Apoptosis, Atrophy, and Nodular. Hepatology 1997; 26(2): 343-50.

[37] Dupont-Versteegden EE. Apoptosis in skeletal muscle and its relevance to atrophy. Worid J Gastroenterol 2006; 12(46): 7463-6.

[38] Chipuk JE, Green DR. Do inducers of apoptosis trigger caspase-independent cell death? Nat Rev Mol Cell Biol 2005; 6: 268-75.

[39] Kroemer G, Martin SJ. Caspase-independent cell death. Nat Med 2005; 11: 725-730.

[40] Wajant H. The Fas signaling pathway*:* more than a paradigm. Science 2002; 296: 1635-36.

[41] Schutze S, Tchikov V, Schneider-Brachert W. Regulation of TNFR1 and CD95 signalling by receptor compartmentalization. Nat Rev Mol Cell Biol 2008; 9: 655-62.

[42] Arya R, White K. Cell death in development: signaling pathways and core mechanisms. Semin Cell Dev Biol 2015; 39: 12-9.

[43] Adams JM, Cory S. The Bcl-2 Protein Family: Arbiters of Cell Survival. Science 1998; 281: 1322-26.

[44] Jin Z, El-Deiry WS. Overview of cell death signaling pathways. Cancer Biol Ther 2005; 4(2): 147-71.

[45] Eefting F, Rensing B, Wigman J. Role of apoptosis in reperfusion injury. Cardiovasc Res 2004; 61(3): 414-26.

[46] Baig S, Seevasant I, Mochamad J, *et al*. Potential of apoptotic pathway-targeted cancer therapeutic research: Where do we stand? Cell Death Dis 2016; 7: 2058.

[47] Pećina-Šlaus N. Wnt signal transduction pathway and apoptosis: A review. Cancer Cell Int 2010; 10: 22.

[48] Eroglu M, Derry WB. Your neighbours matter - non-autonomous control of apoptosis in development and disease. Cell Death Differ 2016; 23: 1110-8.

[49] Moreno-Gonzalez G, Vandenabeele P, Krysko DV. Necroptosis: A novel cell death modality and its potential relevance for critical care medicine. Am J Respir Crit Care Med 2016; 194(4): 415-28.

[50] Galluzzi L, Vitale I, Abrams JM, Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012; 19(1): 107-20.

[51] Sansonetti PJ, Phalipon A, Arondel J, et al. Caspase-1 activation of IL-1beta and IL-18 are essential for Shigella flexneri-induced inflammation. Immunity 2000; 12: 581-90.

[52] Bergsbaken T, Fink SL, Cookson BT. Pyroptosis*:* host cell death and inflammation. Nat Rev Microbiol 2009; 7: 99-109.

[53] De Gassart A, Martinon F. Pyroptosis: Caspase-11 Unlocks the Gates of Death. Immunity 43(5), 2015; 43: 835-7.

[54] Brinkmann V, Reichard U, Goosmann C, *et al*. Neutrophil extracellular traps kill bacteria. Science 2004; 303(5663): 1532-5.

[55] Boe DM, Curtis BJ, Chen MM, *et al*. Extracellular traps and macrophages: new roles for the versatile phagocyte. J Leukoc Biol 2015; 97(6): 1023-35.

[56] Uribe Echevarría L, Leimgruber C, García González J, *et al*. Evidence of eosinophil extracellular trap cell death in COPD: does it represent the trigger that switches on the disease? Int J Chron Obstruct Pulmon Dis 2017; 12: 885-96.

[57] Fuchs TA, Abed U, Goosmann C, *et al*. Novel cell death program leads to neutrophil extracellular traps. J Cell Biol 2007; 176(2): 231-41.

[58] Yousefi S, Gold JA, Andina N, *et al.* Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. Nat Med 2008; 14: 949-53.
[59] Remijsen Q, Kuijpers TW, Wirawan E, *et al*. Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. Cell Death Differ 2011; 18: 581-8.
[60] Granger V, Faille D, Vfrani V, *et al*. Human blood monocytes are able to form extracellular traps. J Leukoc Biol 2017; 102(3): 775-81.
[61] Lipińska-Gediga M. Neutrophils, NETs, NETosis - old or new factors in sepsis and septic shock? Anaesthesiol Intensive Ther 2017; 49(3): 235-24.
[62] Hakkim A, Furnrohr BC, Amann K, *et al*. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci USA 2010; 107(21): 9813-8.
[63] Wong SL, Demers M, Martinod K, *et al*. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med 2015; 21: 815-9.
[64] Chen L, Zhao Y, Lai D, *et al*. Neutrophil extracellular traps promote macrophage pyroptosis in sepsis. Cell Death Dis 2018; 9(6): 597.
[65] Pietronigro EC, Della Bianca V, Zenaro E, Constantin G. NETosis in Alzheimer's disease. Frontiers in Immunology. 2017; 8: 211.
[66] Candi E, Schmidt R, Melino G. The cornified envelope*:* A model of cell death in the skin. Nat Rev Mol Cell Biol 2005; 6: 328-340.
[67] Boya P, Gonzalez-Polo RA, Casares N, et al. Inhibition of macroautophagy triggers apoptosis. Mol Cell Biol 2005; 25: 1025-1040.
[68] Weinlich R, Oberst A, Beere HM, Green DR. Necroptosis in development, inflammation and disease. Nat Rev Mol Cell Biol 2017; 18: 127-36.
[69] Galluzzi L, Kroemer G. Necroptosis: A Specialized Pathway of Programmed Necrosis. Cell 2008; 135: 1161-3.
[70] Linkermann A, Green DR. Necroptosis. N Engl J Med 2014; 370(5): 455-65.
[71] Degterev A, Huang Z, Boyce M, *et al*. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nat Chem Biol 2005; 1(2): 112-9.
[72] Gunther C, Martini E, Wittkopf N, *et al*. Caspase-8 regulates TNF-alpha-induced epithelial necroptosis and terminal ileitis. Nature 2011; 477(7364): 335-9.
[73] Wyllie AH, Kerr JF, Currie AR Cell death: the significance of apoptosis. Int Rev Cytol. 1980; 68: 251-306.
[74] Garg AD, Romano E, Rufo N, Agostinis P. Immunogenic versus tolerogenic phagocytosis during anticancer therapy: mechanisms and clinical translation. Cell Death Differ 2016; 23(6): 938-51.
[75] Mahajan A, Herrmann M, Muñoz LE. Clearance Deficiency and Cell Death Pathways: A Model for the Pathogenesis of SLE. Front Immunol 2016; 7: 35.
[76] Patten D.A. SCARF1: A multifaceted, yet largely understudied, scavenger receptor. Inflamm Res 2018; 67 (8): 627-32.
[77] Sachet M, Liang YY, Oehler R. The immune response to secondary necrotic cells. Apoptosis 2017; 22: 1189-1204.
[78] Galluzzi L, Maiuri MC, Vitale I, *et al.* Cell death modalities*:* classification and pathophysiological implications. Cell Death Differ 2007; 14: 1237-43.
[79] Kroemer G, Galluzzi L, Vandenabeele P, *et* al. Classification of cell death*:* recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ 2009; 16: 3-11.
[80] Vakifahmetoglu H, Olsson M, Zhivotovsky B. Death through a tragedy*:* mitotic catastrophe. Cell Death Differ 2008; 15: 1153-1162.
[81] Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe*:* A mechanism for avoiding of genomic instability. Nat Rev Mol Cell Biol 2011; 12: 385-92.
[82] Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. Nature 2015; 517(7534): 311-20.
[83] Man SM, Karki R, Kanneganti T-D. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev 2017; 277(1): 61-75.
[84] Jog NR, Caricchio R. The Role of Necrotic cell death in the pathogenesis of immune mediated nephropathies. Clin Immunol 2014; 153(2): 243-53.
[85] Hernander C, Hernander P, Schwade RF. Damage-associated molecular patterns in cancer: A double-edged sword. Oncogene 2016; 35(46): 5931-41.
[86] Ohshima H, Tazawa H, Sylla BS, Sawa T. Prevention of human cancer by modulation of chronic inflammatory processes. Mutat Res 2005; 591: 110-22.
[87] Chircop M, Speidel D. Cellular Stress Responses in Cancer and Cancer Therapy. Front Oncol 2014; 4: 304.
[88] Kantono M, Guo B. Inflammasomes and Cancer: The Dynamic Role of the Inflammasome in Tumor Development. Front Immunol 2017; 8: 1132.
[89] Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010; 464: 529-35.
[90] Kourtis N, Tavernarakis N. Cellular stress response pathways and ageing: intricate molecular relationships. EMBO J 2011; 30(13): 2520-31.
[91] Rodier F, Campisi J. Four faces of cellular senescence. J Cell Biol 2011; 192(4): 547-56.
[92] Mather KA, Jorm AF, Parslow RA, Christensen H. Is telomere length a biomarker of aging? A review. J Gerontol Series A Biol Sci Med Sci 2011; 66(2): 202-13.
[93] Bratic A, Larsson NG. The role of mitochondria in aging. J Clin Invest 2013; 123: 951-7.
[94] Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell 2011; 146: 682-695.
[95] Yun M, Han YH, Yoon SH, *et al*. *p31comet induces cellular senescence through p21 accumulation and Mad2 disruption*. Mol Cancer Res 2009; **7**: 371-82.
[96] Schroen B, Heymans S. Small but smart-microRNAs in the centre of inflammatory processes during cardiovascular diseases, the metabolic syndrome, and ageing. Cardiovasc Res 2012; 93(4): 605-13.
[97] Jung Y, Brack AS. Cellular Mechanisms of Somatic Stem Cell Aging. Curr Top Dev Biol 2014; 107: 405-38.
[98] Chen F, Liu Y, Wong N-K, *et al*. Oxidative Stress in Stem Cell Aging. Cell Transplant 2017; 26(9): 1483-95.
[99] Yadav UCS, Aguilera-Aguirre L, Ramana KV, *et al*. Aldose Reductase Inhibition Prevents Metaplasia of Airway Epithelial Cells. PLoS One 2010; 5(12): e14440.
[100] Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Fertil Steril 2001; 76(1): 1-10.
[101] Scutiero G, Iannone P, Bernardi G, *et al.* Oxidative Stress and Endometriosis: A Systematic Review of the Literature. Oxid Med Cell Longev 2017; 2017: 7265238.
[102] Freeman TA, Parvizi J, Valle CJD, Steinbeck MJ. Mast cells and hypoxia drive tissue metaplasia and heterotopic ossification in idiopathic arthrofibrosis after total knee arthroplasty. Fibrogenesis Tissue Repair 2010; 3: 17.
[103] Park YH, Kim N. Review of Atrophic Gastritis and Intestinal Metaplasia as a Premalignant Lesion of Gastric Cancer. J Cancer Prev 2015; 20(1): 25-40.
[104] Shennib H, Lough J, Klein HW, Hampson LG. Gastric carcinoma: intestinal metaplasia and tumor growth patterns as indicators of prognosis. Surgery 1986; 100(4): 774-80.
[105] Cregg JM, DePaul MA, Filous AR, *et al*. Functional regeneration beyond the glial scar. Exp Neurol 2014; 253: 197-207.
[106] Anderson MA, Ao Y, Sofroniew MV. Heterogeneity of reactive astrocytes. Neurosci Lett 2014; 565: 23-29.
[107] Kapetanaki MG, Mora AL, Rojas M. Influence of age on wound healing and fibrosis. J Pathol 2013; 229: 310-22.
[108] Bone RC, Balk RA, Cerra FB *et al*. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 100(6): 1644-55.
[109] Martindale JL, Holbrook NJ. Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol 2002; 192 (1): 1-15.
[110] Gupta RK, Patel AK, Shah N, *et al*. Oxidative stress and antioxidants in disease and cancer: A review. Asian Pac J Cancer Prev 2014; 15(11): 4405-9.
[111] Rahal A, Kumar A, Singh V, *et al*. Oxidative Stress, Prooxidants, and Antioxidants: The Interplay. BioMed Res Int 2014; 2014: ID 761264.
[112] Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. Eur J Med Chem 2015; 97: 55-74.
[113] Sies H. Oxidative stress: A concept in redox biology and medicine. Redox Biol 2015; 4: 180-3.
[114] Sinha N, Dadla PK. Oxidative stress and antioxidants in hypertension-a current review. Curr Hypertens Rev 2015; 11(2): 132-42.

[115] Nita M, Grzybowski A. The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults. Oxid Med Cell Longev 2016; 2016: 3164734.
[116] Cabello-Verrugio C, Ruiz-Ortega M, Mosqueira M, Simon F. Oxidative Stress in Disease and Aging: Mechanisms and Therapies. Oxid Med Cell Longev 2016; 2016: 8786564.
[117] Ciccia A, Elledge SJ. The DNA damage response: making it safe to play with knives. Mol Cell 2010; 40(2): 179-204.
[118] Polo SE, Jackson SP. Dynamics of DNA damage response proteins at DNA breaks: A focus on protein modifications. Genes Dev 2011; 25: 409-33.
[119] Mouw KW, Goldberg MS, Konstantinopoulos PA, D'Andrea AD. DNA Damage and Repair Biomarkers of Immunotherapy Response. Cancer Discov 2017; 7(7): 675-93.
[120] Cao Y, Long J, Liu L, *et al*. A review of endoplasmic reticulum (ER) stress and nanoparticle (NP) exposure. Life Sci 2017; 186: 33-42.
[121] Hetz C. The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol 2012; 13: 89-102.
[122] Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. Nat Rev Neurol 2017; 3: 477-91.
[123] Srivastava P. Roles of heat-shock proteins in innate and adaptive immunity. Nat Rev Immunol 2002; 2: 185-94.
[124] Richter K, Haslbeck M, Buchner J. The Heat Shock Response: Life on the Verge of Death. Mol Cell 2010; 40: 253-66.
[125] Tkacova J. Angelovicova M. Heat Shock Proteins (HSPs): A Review. Anim Sci Biotechnol 2012; 45(1): 349-53.
[126] Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol 2013; 13: 397-411.
[127] Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signaling. Nat Rev Immunol 2016; 16: 407-20.
[128] Prochnichnicki T, Latz E. Inflammasomes on the Crossroads of Innate Immune Recognition and Metabolic Control. Cell Metab 2017; 26: 71-93.
[129] Kroemer G, MarinoG, Levine B. Autophagy and the integrated stress response. Mol Cell 2010; 40(2): 280-93.
[130] Singh R, Cuervo AM Autophagy in the Cellular Energetic Balance. Cell Metab 2011; 13: 495-504.
[131] Ravanan P. Srikumal IF, Talwar P. Autophagy: The spotlight for cellular stress responses. Life Sci 2017; 188: 53-67.
[132] Samali A, Fulda S. Corman AM. Cell Stress and Cell Death. Int J Cell Biol 2010; 2010: 245803.
[133] Portt L. Norman G, Clapp C, *et al*. Anti-apoptosis and cell survival: A review. Biochim Biophys Acta 2011; 1813(1): 238-59.
[134] Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. Biochim Biophys Acta 2013; 1833: 3448-59.
[135] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med. 2010; 49(11): 1603-16.
[136] Haigis MC, Yankner BA. The Aging Stress Response. Mol Cell 2010; 40(2): 333-44.
[137] Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative Stress in Atherosclerosis. Gurr Atheroscler Rep 2017; 19(11): 42.
[138] Yang X, Li Y, Li Y, *et al*. Oxidative Stress-Mediated Atherosclerosis: Mechanisms and Therapies. Front Physiol 2017; 8: 600.
[139] Marré1 ML, James EA, Piganelli JD. β cell ER stress and the implications for immunogenicity in type 1 diabetes. Front Cell Dev Biol 2015; 3: 67.
[140] Wright E, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. Int J Clin Pract 2006; 60(3): 308-14.
[141] Rodrigo R, Gonzalez J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res 2011; 34: 413-40.
[142] Dinh QN, Drummond GR, Sobey CG, Chrissobolis S. Roles of Inflammation, Oxidative Stress, and Vascular Dysfunction in Hypertension. BioMed Res Int 2014; 2014: 406960.
[143] Tilg H., Moschen A. R. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 2010; 52(5): 1836-46.
[144] Ginaldi L, DiBenedetto MC, DeMartinis M. Osteoporosis inflammation and ageing. Immun Ageing 2005; 2: 14.
[145] Yuan Z, Jiang G, Fu S, *et al*. Correlation between autophagy of osteoblasts and oxidative stress of osteoporosis rats. Int J Clin Exp Pathol 2016; 9(10): 9907-9915.
[146] Adamczyk B, Adamczyk-Sowa M. New Insights into the Role of Oxidative Stress Mechanisms in the Pathophysiology and Treatment of Multiple Sclerosis. Oxid Med Cell Longev 2016; 2016: 1973834.
[147] Pohanka M. Alzheimer´s disease and oxidative stress: A review. Curr Med Chem 2014; 21(3): 356-64.
[148] Dias V, Junn E, Mouradian MM. The Role of Oxidative Stress in Parkinson's disease. J Parkinsons Dis 2013; 3(4): 461-91.
[149] Schiavone S, Jaquet V, Trabace L. Krause K-H. Severe Life Stress and Oxidative Stress in the Brain: From Animal Models to Human Pathology. Antioxid Redox Signal 2013; 18(12): 1475-90.
[150] Hayashi T. Conversion of psychological stress into cellular stress response: Roles of the sigma-1 receptor in the process. Psychiatry Clin Neurosci 2015; 69: 179-91.
[151] Naidoo N. "Cellular Stress/The Unfolded Protein Response: Relevance to Sleep and Sleep Disorders." Sleep Med Rev. 2009; 13(3): 195-204.
[152] Takeuchi O, Akira S. Pattern Recognition Receptors and Inflammation. Cell 2010; 140(6): 805-20.
[153] Vance RE, Isberg RR, Portnoy DA. Patterns of Pathogenesis: Discrimination of Pathogenic and Nonpathogenic Microbes by the Innate Immune System. Cell Host Microbe 2009; 6: 10-21.
[154] Land WG. The Role of Damage-Associated Molecular Patterns in Human Diseases: Part I - Promoting inflammation and immunity. Suldan Qaboos Univ Med J 2015; 15(1): e9-21.
[155] Oppenheim JJ, Yang D. Alarmins: chemotactic activators of immune responses. Curr Opin Immunol 2005; 17(4): 359-65.
[156] Bianchi M. DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 2007; 81(1): 1-5.
[157] Yang D, de la Rosa G, Tewary P, Oppenheim JJ. Alarmins link neutrophils and dendritic cells. Trends Immunol 2009; 30(11): 531-37.
[158] Fukata M, Vamadevan AS, Abreu MT. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) in inflammatory disorders. Semin Immunol 2009; 21(4): 242-53.
[159] Park JS, Gamboni-Robertson F, He Q. High mobility group box 1 protein interacts with multiple Toll-like receptors. Am J Physiol Cell Physiol 2006; 290(3): 917-24.
[160] Mogensen TH. Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses. Clin Microbiol Rev 2009; 22(2): 240-73.
[161] Tan RST, Ho B, Leung BP, Ding J-L. TLR Cross-talk Confers Specificity to Innate Immunity. Int Rev Immunol 2014; 33(6): 443-53.
[162] Cao X. Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease. Nat Rev Immunol 2016; 16: 35-50.
[163] Barry M, Bleackley RC. Cytotoxic T lymphocytes: All roads lead to death. Nat Rev Immunol 2002; 2: 401-9.
[164] Ve T, Williams SJ, Kobe B. Structure and function of Toll/interleukin-1 receptor/resistance protein (TIR) domains. Apoptosis 2015; 20(2): 250-61.
[165] Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. Nat Rev Immunol 2013; 13: 621-34.
[166] PrabhuDas MR, Baldwin CL, Bollyky PL, *et al*. A Consensus Definitive Classification of Scavenger Receptors and Their Roles in Health and Disease. J Immunol 2017; 198(10): 3775-89.
[167] Zani IA, Stephen SL, Mughal NA, *et al*. Scavenger Receptor Structure and Function in Health and Disease. Cells 2015; 4(2): 178-201.
[168] Boullier A, Bird DA, Chang MK, *et al*. Scavenger receptors, oxidized LDL, and atherosclerosis. Ann N Y Acad Sci 2001; 947: 214-22.
[169] Stephen SL, Freestone K, Dunn S, *et al*. Scavenger Receptors and Their Potential as Therapeutic Targets in the Treatment of Cardiovascular Disease. Int J Hypertens 2010; 2010: ID 646929.
[170] Liliensiek B, Weigand MA, Bierhaus A. *et al*. Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. J Clin Invest 2004; 113(11): 1641-50.
[171] Sparvero LJ, Asafu-Adjei D, Kang R, *et al*. RAGE (Receptor for Advanced Glycation Endproducts), RAGE Ligands, and their role in Cancer and Inflammation. J Transl Med 2009; 7: 17.
[172] Eugenin J, Veccohiola A, Murgas P, *et al*. Expression Pattern of Scavenger Receptors and Amyloid-β Phagocytosis of Astrocytes

and Microglia in Culture are Modified by Acidosis: Implications for Alzheimer's Disease. J Alzeimer Dis 2016; 53(3): 857-73.
[173] Qian L, Li X, Fang R, *et al*. Class A scavenger receptor deficiency augments angiotensin II-induced vascular remodeling. Biochem Pharmacol 2014; 90(3): 254-64.
[174] Ma K, Xu Y, Wang C, *et al*. A cross talk between class A scavenger receptor and receptor for advanced glycation end-products contributes to diabetic retinopathy. Am J Physiol Endocrinol Metab 2014; 307(12): E153-65.
[175] Vasquez M., Simões I., Consuegra-Fernández M., *et al*. Exploiting scavenger receptors in cancer immunotherapy: Lessons from CD5 and SR-B1. Eur J Immunol 2017; 47 (7): 1108-18.
[176] Chen F, Wang CC, Kim E, Harrison LE. Hyperthermia in combination with oxidative stress induces autophagic cell death in HT-29 colon cancer cells. Cell Biol Int 2008; 32(7): 715-23.
[177] Bouquet F, Ousset M, Biard D. A DNA-dependent stress response involving DNA-PK occurs in hypoxic cells and contributes to cellular adaptation to hypoxia. J Cell Sci 2011; 124: 1943-51.
[178] Finan JD, Guilak F. The effects of osmotic stress on the structure and function of the cell nucleus. J Cell Biochem 2010; 109(3): 460-67.
[179] Hardie DG. AMP-activated protein kinase: An energy sensor that regulates all aspects of cell function. Genes Dev 2011; 25: 1895-908.
[180] Rouhanizadeh M, Takabe W, Ai L, *et al*. Monitoring oxidative stress in vascular endothelial cells in response to fluid shear stress: from biochemical analyses to micro- and nanotechnologies. Methods Enzymol 2008; 441: 111-50.
[181] Raulet D.H. Roles of the NKG2D immunoreceptor and its ligands. Nat Rev Immunol 2003; 3(10): 781-90.
[182] Zwirner N, Fuertes M, Girart M-V, *et al*. Cytokinedriven regulation of NK cell function in tumor immunity: role of the MICA-NKG2D system. Cytokine Growth Factor Rev 2007, 18: 159-70.
[183] Shyy JY-J, Chien S. Role of integrins in cellular responses to mechanical stress and adhesion. Curr Opin Cell Biol 1997; 9(5): 707-13.
[184] Fouquet S, Lugo-Martínez V-H, Faussat A-M, *et al*. Early Loss of E-cadherin from Cell-Cell Contacts Is Involved in the Onset of Anoikis in Enterocytes. J Biol Chem 2004; 279(41): 43061-69.
[185] Parnaud G, Gonelle-Gispert C, Morel Ph, *et al*. Cadherin Engagement Protects Human β-Cells from Apoptosis. Endocrinology 2011; 152(12): 4601-09.
[186] Geng F, Zhu W, Anderson RA, *et al*. Multiple post-translational modifications regulate E-cadherin transport during apoptosis. J Cell Sci 2012; 125(11): 2615-25.
[187] Wolfl M, Greenberg PD. Antigen-specific activation and cytokine-facilitated expansion of naive, human $CD8^+$ T cells. Nat Protoc 2014; 9(4): 950-66.
[188] Ermak G, Davies KJ. Calcium and oxidative stress: from cell signaling to cell death. Mol Immunol 2002; 38(10): 713-21.
[189] Cerella C, Diederich M, Ghibelli L. The Dual Role of Calcium asMessenger and Stressor in Cell Damage, Death, and Survival. Int J Cell Biol 2010; 2010: 546163.
[190] Gangwar R, Meena AS, Shukla PK. Calcium-mediated oxidative stress: A common mechanism in tight junction disruption by different types of cellular stress. Biochem J 2017; 474(5): 731-49.
[191] Pétrilli V, Papin S, Dostert C, *et al*. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ 2007; 14: 1583-89.
[192] Lee H, Song M, Shin N. Diagnostic Significance of Serum HMGB1 in Colorectal Carcinomas. PLoS ONE 2012; 7: e34318.
[193] Biswas SK. Does the Interdependence between Oxidative Stress and Inflammation Explain the Antioxidant Paradox? Oxid Med Cell Longev 2016; 2016: 5698931.
[194] Butterfield DA, Drake J, Pocernich C, Castegna A. Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β-peptide. Trends Mol Med 2001; 7(12): 548-54.
[195] Onyango IG. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Neurochem Res 2008; 33(3): 589-97.
[196] Kim JI, S. Cho I, Kim NH, *et al*. Oxidative stress and neurodegeneration in prion diseases. Ann N Y Acad Sci 2001; 928: 182-6.
[197] Tezel G. Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 2006; 25(5): 490-513.
[198] Tabner B.J, El-Agnaf OMA., German MJ, *et al*. Protein aggregation, metals and oxidative stress in neurodegenerative diseases. Biochem Soc Trans 2005; 33(5): 1082-6.
[199] Miller MW, Lin AP, Wolf EJ, Miller DR. Oxidative Stress, Inflammation, and Neuroprogression in Chronic PTSD. Harv Rev Psychiatry 2018; 26(2): 57-69.
[200] Finkel T, Holbrook NJ. Oxidants, oxidative stress and thebiology of ageing. Nature 2000; 408: 239-47.
[201] Beigrezaei S, Nasri H. Oxidative stress in chronic kidney disease; an updated review on current concepts. J Renal Endocrinol 2017; 3: e01.
[202] Tan BL, Norhaizan ME, Liew WPP. Nutrients and Oxidative Stress: Friend or Foe? Oxid Med Cell Longev 2018; 2018: 9719584.
[203] *England K*, *Cotter CT*. Direct oxidative modifications of signalling proteins in mammalian cells and their effects on apoptosis. *Redox Rep 2005; 10*: *237-45*.
[204] Powers SK, Radak Z, Ji LL. Exercise-induced oxidative stress: past, present and future. J Physiol 2016; 15; 594(18): 5081-92.
[205] Schieber M, Chandel NS. ROS Function in Redox Signaling and Oxidative Stress. Curr Biol 2014; 24: R453-62.
[206] Solaini G, Baracca A, Lenaz G, Sgarbi G. Hypoxia and mitochondrial oxidative metabolism. Biochim Biophys Acta 2010; 1797(6-7): 1171-77.
[207] Movafagh S, Crook S, Vo K. Regulation of hypoxia-inducible factor-1a by reactive oxygen species: new developments in an old debate. J Cell Biochem 2015; 116(5): 696-703.
[208] Birben E, Sahiner UM, Sackesen C, *et al*. Oxidative Stress and Antioxidant Defense. World Allergy Organ J 2012; 5(1): 9-19.
[209] Cargnello M, Philippe P. Activation and Function of the MAPKs and Their Substrates, the MAPK-Activated Protein Kinases. Microbiol Mol Biol Rev 2011; 75(1): 50-83.
[210] Barakat DJ, Dvoriantchikova G, Ivanov D, Shestopalov VI. Astroglial NF-κB mediates oxidative stress by regulation of NADPH oxidase in a model of retinal ischemia reperfusion injury. J Neurochem 2012; 120(4): 586-97.
[211] Connery AH. Pharmacological implications of microsomal enzyme induction. Pharmacol Rev 1967; 19(3): 317-66.
[212] McDonnell AM, Dang CH. Basic Review of the Cytochrome P450 System. J Adv Pract Oncol 2013; 4(4): 263-8.
[213] Hauck AK, Bernlohr DA. Oxidative stress and lipotoxicity. J Lipid Res 2016; 57: 1976-86.
[214] Grimsrud PA, Xie H, Griffin TJ, Bernlohr DA. Oxidative stress and covalent modification of protein with bioactive aldehydes. J Biol Chem 2008; 283: 21837-41.
[215] Marinhoa HS, Reala C, Cyrnea L, *et al*. Hydrogen peroxide sensing, signaling and regulation of transcription factors. Redox Biol 2014; 2: 535-62.
[216] Peng Q, Deng Z, Pan H, *et al*. Mitogen-activated protein kinase signaling pathway in oral cancer (Review). Oncol Lett 2018; 15: 1379-88.
[217] Broom OJ, Widjaya B, Troelsen J, *et al*. Mitogen activated protein kinases: A role in inflammatory bowel disease? Clin Exp Immunol 2009; 158(3): 272-80.
[218] Manna PR, Stocco DM. The Role of Specific Mitogen-Activated Protein Kinase Signaling Cascades in the Regulation of Steroidogenesis. J Signal Transduct 2011; 2011: 821615.
[219] Lu Z, Xu S. ERK1/2 MAP kinases in cell survival and apoptosis. IUBMB Life 2006; 58(11): 621-31.
[220] Lenassi M, Plemenitaš A. The role of p38 MAP kinase in cancer cell apoptosis. Radiol Oncol 2006; 40(1): 51-6.
[221] Beyfuss K, Hood DA. A systematic review of p53 regulation of oxidative stress in skeletal muscle. Redox Rep 2018; 23(1): 100-17.
[222] Webster GA, Perkins ND. Transcriptional Cross Talk between NF-κB and p53. Mol Cell Biol 1999; 19(5): 3485-95.
[223] Tanaka T, Tsuchiya R, Hozumi Y, *et al*. Reciprocal regulation of p53 and NF-κB by diacylglycerol kinase ζ. Adv Biol Regul 2016; 60: 15-21.
[224] Chittiboyina S, Bai Y Lelievre SA. Microenvironment-Cell Nucleus Relationship in the Context of Oxidative Stress. Front Cell Dev Biol 2018; 6: 23.
[225] Pyo CW., Choi JH., Oh SM., Choi S.Y. Oxidative stress-induced cyclin D1 depletion and its role in cell cycle processing. Biochim Biophys Acta 2013; 1830(11): 5316-25.

[226] Konczol M, Weiss A, Stangenberg E, *et al*. Cell-Cycle Changes and Oxidative Stress Response to Magnetite in A549 Human Lung Cells. *Chem Res Toxicol* 2013; 26(5): 693-702.
[227] Jones DP, Go Y-M. Redox compartmentalization and cellular stress. Diabetes Obes Metab 2010; 12(2): 116-25.
[228] Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci 2014; 39(4): 199-218.
[229] Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorder. Mutat Res 2010; 690(1-2): 12-23.
[230] Tan SM, de Haan JB. Combating oxidative stress in diabetic complications with Nrf2 activators: How much is too much? Redox Rep 2014; 19(3): 107-17.
[231] Veal EA, Day AM, Morgan BA. Hydrogen Peroxide Sensing and Signaling. Mol Cell 2007; 26(1): 1-14.
[232] Luiking YC, Engelen MPKJ, Deutz NEP. Regulation of nitric oxide production in health and disease. Curr Opin Clin Nutr Metab Care 2010; 13(1): 97-104.
[233] Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation. Int J Chron Obsruct Pulmon Dis 2011; 6: 413-21.
[234] Runke ED, Baumeister R, Schulze E. Mitochondrial stress: Balancing friend and foe. Exp Gerontol 2014; 56: 194-201.
[235] Fu X, Zhang H. Signaling pathway of mitochondrial stress. Front Lab Med 2017; 1(1): 40-2.
[236] Melber A, Haynes CM. UPR^{mt} regulation and output: A stress response mediated by mitochondrial-nuclear communication. Cell Res 2018; 28(3): 281-95.
[237] Balaban RS. The Mitochondrial Proteome: A Dynamic Functional Program in Tissues and Disease States. Environ Mol Mutagen 2010; 51(5): 352-59.
[238] Hu F, Liu F. Mitochondrial stress: A bridge between mitochondrial dysfunction and metabolic diseases? Cellular Signal 2011; 23(10): 1528-33.
[239] Hill S, Remmen H. Mitochondrial stress signaling in longevity: A new role for mitochondrial function in aging. Redox Biol 2014; 2: 936-44.
[240] Quirós PM, Prado MA, Zamboni N, *et al*. Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals. J Cell Biol 2017; 216(7): 2027.
[241] Zhao Q, Wang J, Levichkin IV. A mitochondrial specific stress response in mammalian cells. EMBO J 2002; 21: 4411-19.
[242] Nakahira K, Haspel JA, Rathinam VA, *et al*. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011, 12: 222-30.
[243] Pinti M, Cevenini E, Nasi M, *et al*. Circulating mitochondrial DNA increases with age and is a familiar trait: implications for 'inflamm-aging". Eur J Immunol 2014; 44: 1552-62.
[244] Khan NA, Nikkanen J, Yatsuga S, *et al*. mTORC1 regulates mitochondrial integrated stress response and mitochondrial myopathy progression. Cell Metab 2017; 26: 419-28.
[245] Kelly G. A review of the sirtuin system, its clinical implications, and the potential role of dietary activators like resveratrol: part 1. Altern Med Rev. 2010; 15(3): 245-63.
[246] Jovaisaite V, Mouchiroud L, Auwerx J. The mitochondrial unfolded protein response, a conserved stress response pathway with implications in health and disease. J Exp Biol 2014; 217: 137-43.
[247] Houtkooper RH, Mouchiroud L, Ryu D, *et al*. Mitonuclear protein imbalance as a conserved longevity mechanism. Nature 2013; 497: 451-57.
[248] Schulz AM, Haynes CM. UPR (mt)-mediated cytoprotection and organismal aging. Biochim Biophys Acta 2015; 1847(11): 1448-56.
[249] Norddahl GL, Pronk CJ, Wahlestedt M, *et al*. Accumulating mitochondrial DNA mutations drive premature hematopoietic aging phenotypes distinct from physiological stem cell aging. Cell Stem Cell 2011; 8: 499-510.
[250] Ahlqvist KJ, Hamalainen RH, Yatsuga S, *et al*. Somatic progenitor cell vulnerability to mitochondrial DNA mutagenesis underlies progeroid phenotypes in Polg mutator mice. Cell Metab 2012; 15: 100-9.
[251] Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol 2003; 14: 281-7.
[252] Yuzefovych LV, Solodushko VA, Wilson GL, Rachek LI. Protection from palmitate-induced mitochondrial DNA damage prevents from mitochondrial oxidative stress, mitochondrial dysfunction, apoptosis, and impaired insulin signaling in rat l6 skeletal muscle cells. Endocrinology 2012; 153: 92-100.
[253] Tumova J, Andel M, Trnka J. Excess of Free Fatty Acids as a Cause of Metabolic Dysfunction in Skeletal Muscle. Physiol Res 2016; 65: 193-207.
[254] Zambo V, Simon-Szabo L, Szelenyi P, *et al*. Lipotoxicity in the liver. World J Hepatol 2013; 5(10): 550-7.
[255] Drosatos K, Schulze PC. Cardiac Lipotoxicity: Molecular Pathways and Therapeutic Implications. Curr Heart Fail Rep 2013; 10(2): 109-21.
[256] Virkamaki A, Korsheninnikova E, Seppala-Lindroos A, *et al*. Intramyocellular lipid is associated with resistance to *in vivo* insulin actions on glucose uptake, antilipolysis, and early insulin signaling pathways in human skeletal muscle. Diabetes 2001; 50: 2337-43.
[257] Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. Biochim Biophys Acta 2010; 1801(3): 338-49.
[258] Prieur X, Mok CYL, Velagapudi VR, *et al*. Differential Lipid Partitioning Between Adipocytes and Tissue Macrophages Modulates Macrophage Lipotoxicity and M2/M1 Polarization in Obese Mice. Diabetes 2011; 60(3): 797-809.
[259] Duncan JG. Mitochondrial dysfunction in diabetic cardiomyopathy. Biochim Biophys Acta 2011; 1813(7): 1351-9.
[260] Aon MA, Foster DB. Diabetic Cardiomyopathy and the Role of Mitochondrial Dysfunction: Novel Insights, Mechanisms, and Therapeutic Strategies. Antioxid Redox Signal 2015; 22(17): 1499-501.
[261] Wajner M, Amaral AU. Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animalstudies. Biosci Rep 2016; 36(1): e00281.
[262] Bugger H, Chen D, Riehle C, *et al*. Tissue-Specific Remodeling of the Mitochondrial Proteome in Type 1 Diabetic Akita Mice. Diabetes 2009; 58(9): 1986-97.
[263] Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic beta cells. Trends Endocrinol Metab 2012; 23: 477-87.
[264] Begriche K, Massart J, Robin MA. Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease. Hepatology 2013; 58(4): 1497-507.
[265] Sunny NE, Bril F, Cusi K. Mitochondrial Adaptation in Nonalcoholic Fatty Liver Disease: Novel Mechanisms and Treatment Strategies. Trends Endocrinol Metab 2017; 28(4): 250-60.
[266] Rubattu S, Stanzione R, Volpe M. Mitochondrial Dysfunction Contributes to Hypertensive Target Organ Damage: Lessons from an Animal Model of Human Disease. Oxid Med Cell Longev 2016; 2016: 1067801.
[267] Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther 2012; 342(3): 619-30.
[268] Jiao H, Zhou K, Zhao J, *et al*. A high-caloric diet rich in soy oil alleviates oxidative damage of skeletal muscles induced by dexamethasone in chickens. Redox Rep 2017, 23(1): 68-82.
[269] Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. Cell Mol Life Sci 2016; 73: 79-94.
[270] Van Meer G, Voelker DR, Feigenson GW. Membrane lipids: where they are and how they behave. Nat Rev Mol Cell Biol 2008; 9: 112-24.
[271] Schroder M. Endoplasmic reticulum stress responses. Cell Mol Life Sci 2008; 65: 862-94.
[272] Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. J Clin Invest 2005; 115(10): 2656-64.
[273] Yang L, Zhao D, Ren J, Yang J. Endoplasmic reticulum stress and protein quality control in diabetic cardiomyopathy. Biochim Biophys Acta 2015; 1852: 209-18.
[274] Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. Science 2011; 334: 1081-6.
[275] Vabulas RM., Raychaudhuri S, Hayer-Hartl M, Hartl FU. Protein folding in the cytoplasm and the heat shock response. Cold Spring Harb Perspect Biol 2010; 2: A004390.
[276] Szegezdi E, Logue SE, Gorman AM, Samali A. Mediators of endoplasmic reticulum stress-induced apoptosis. EMBO Rep 2006; 7: 880-5.
[277] Scull CM, Tabas I. Mechanisms of ER Stress-induced Apoptosis in Atherosclerosis. Arterioscler Thromb Vasc Biol 2011; 31(12): 2792-7.

[278] Sano R, Reed JC. ER stress-induced cell death mechanisms. Biochim Biophys Acta 2013; 1833: 3460-70.
[279] Bernales S, McDonald KL, Walter P. Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response. PLoS Biol 2006; 4: e423.
[280] Taru H, Suzuki T. Regulation of the physiological function and metabolism of AbetaPP by AbetaPP binding proteins. J Alzheimer Dis 2009; 18 (2): 253-65.
[281] Fonseca SG, Burcin M, Gromada J, Urano F. Endoplasmic reticulum stress in beta-cells and development of diabetes. Curr Opin Pharmacol 2009; 9(6): 763-70.
[282] Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. Trends Mol Med 2012; 18: 59-68.
[283] Vendrell J, Maymo-Masip E, Tinahones F, *et al*. Tumor necrosis-like weak inducer of apoptosis as a proinflammatory cytokine in human adipocyte cells: up-regulation in severe obesity is mediated by inflammation but not hypoxia. J Clin Endocrinol Metab 2010; 95: 2983-92.
[284] Lefterova MI, Mullican SE, Tomaru T, *et al*. LazarEndoplasmic reticulum stress regulates adipocyte resistin expression. Diabetes 2009; 58: 1879-86.
[285] Buchanan J, Mazumder PK, Hu P, *et al*. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 2005; 146: 5341-49.
[286] Todd DJ, Lee AH, Glimcher LH. The endoplasmic reticulum stress response in immunity and autoimmunity. Nat Rev Immunol 2008; 8(9): 663-74.
[287] Koliński T, Marek-Trzonkowska N, Trzonkowski P, Siebert J. Heat shock proteins (HSPs) in the homeostasis of regulatory T cells (Tregs). Cent Eur J Immunol 2016; 41(3): 317-23.
[288] Morimoto RI. The Heat Shock Response: Systems Biology of Proteotoxic Stress in Aging and Disease. Cold Spring Harb Symp Quant Biol 2011; 76: 91-9.
[289] Stetler RA, Gan Y, Zhang W, *et al*. Heat Shock Proteins: Cellular and molecular mechanisms in the CNS. Prog Neurobiol 2010; 92(2): 184-211.
[290] Tóth ME, Gombos I, Sánth M. Heat shock proteins and their role in human diseases. Acta Biologica Szegediensis 2015; 59(Suppl.1): 121-41.
[291] Dubinska-Magiera M, Jablonska J, Saczko J, *et al*. Contribution of small heat shock proteins to muscle development and function. FEBS Letters 2014; 588: 517-30.
[292] Kim JS, Lee YH, Choi DY, Yi HK. Expression of Heat Shock Proteins (HSPs) in Aged Skeletal Muscles Depends on the Frequency and Duration of Exercise Training. J Sports Sci Med 2015; 14(2): 347-53.
[293] Scroggins BT, Robzyk K, Wang D, *et al*. An acetylation site in the middle domain of Hsp90 regulates chaperone function. Mol Cell 2007; 25: 151-59.
[294] Gorenberg EL, Chandra SS. The Role of Co-chaperones in Synaptic Proteostasis and Neurodegenerative Disease. Front Neurosci 2017; 11: 248.
[295] Ikwegbue PC, Masamba P, Oyinloye BE, Kappo AP. Roles of Heat Shock Proteins in Apoptosis, Oxidative Stress, Human Inflammatory Diseases, and Cancer. Pharmaceuticals 2018; 11(1): e2.
[296] Beere HM. The stress of dying': The role of heat shock proteins in the regulation of apoptosis. J Cell Sci 2004; 117: 2641-51.
[297] Mymrikov EV, Seit-Nebi AS, Gusev NB. Large potentials of small heat shock proteins. Physiol Rev 2011; 91(4): 1123-59.
[298] McIlwain, D.R.; Berger, T.; Mak, T.W. Caspase functions in cell death and disease. Cold Spring Harb 2013; Perspect Bio. 2013; 5: a008656.
[299] Wang X-Y, Subjeck JR. High Molecular Weight Stress Proteins: Identification, Cloning, and Utilization in Cancer Immunotherapy. Int J Hyperthermia 2013; 29(5): 364-75.
[300] Wilhelmus MM, Otte-Holler I, Wesseling P, *et al*. Specific association of small heat shock proteins with the pathological hallmarks of Alzheimer's disease brains. Neuropathol Appl Neurobiol 2006; 32: 119-30.
[301] Kusaczuk M, Cechowska-Pasko M. Molecular chaperone ORP150 in ER stress-related diseases. Curr Pharm Des 2013; 19(15): 2807-18.
[302] Gao X, Carroni M, Nussbaum-Krammer C, *et al*. Human Hsp70 disaggregase reverses Parkinson's-linked α-synuclein amyloid fibrils. Mol Cell 2015; 59: 781-93.
[303] Nagle MW, Latourelle JC, Labadorf A, *et al*. The 4p16.3 Parkinson Disease Risk Locus Is Associated with GAK Expression and Genes Involved with the Synaptic Vesicle Membrane. PLoS One 2016; 11(8): e0160925.
[304] Dattilo S, Mancuso C, Koverech G, *et al*. Heat shock proteins and hormesis in the diagnosis and treatment of neurodegenerative diseases. Immun Ageing 2015; 12: 20.
[305] Akerfelt M, Morimoto RI, Sistonen L. Heat shock factors: integrators of cell stress, development and lifespan. Nat Rev Mol Cell Biol 2010; 11(8): 545-55.
[306] Klionsky DJ, Baehrecke EH, Brumell JH, *et al*. A comprehensive glossary of autophagy-related molecules and processes (2nd edition). Autophagy 2011; 7(11): 1273-94.
[307] Esclatine A, Chaumorcel M, Codogno P. Macroautophagy signaling and regulation. Curr Top Microbiol Immunol 2009; 335: 33-70.
[308] Tsukada M, Ohsumi Y. Isolation and characterization of autophagy-defective mutants of Saccharomyces cerevisiae. FEBS Lett 1993; 333: 169-74.
[309] Mizushima N, Levine B, Cuervo AM, Klionsky DJ. *Autophagy fights disease through cellular self-digestion*. Nature 2008; 451: 1069-75.
[310] Lee J, Giordano S, Zhang J. Autophagy, mitochondria and oxidative stress: cross-talk and redox signaling. Biochem J 2012; 441(2): 523-40.
[311] Huang J, Klionsky DJ. *Autophagy and human disease*. Cell Cycle 2007; 6: 1837-49.
[312] Chen Y, Klionsky DJ. The regulation of autophagy - unanswered questions. J Cell Sci 2011; 124: 161-70.
[313] Burger AM, Seth AK. The ubiquitin-mediated protein degradation pathway in cancer: therapeutic implications. Eur J Cancer 2004; 40: 2217-29.
[314] Lilienbaum A. Relationship between the proteasomal system and autophagy. Int J Biochem Mol Biol 2013; 4(1): 1-26.
[315] Klionsky DJ. Look people, "Atg" is an abbreviation for "autophagy-related." That's it. Autophagy 2012; 8(9): 1281-82.
[316] Sengupta S, Peterson TR, Sabatini DM. Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. Mol Cell 2010; 40: 310-22.
[317] Farrell F, Rustem TE, Stenmark H. Phosphoinositide 3-kinases as accelerators and brakes of autophagy. FEBS J 2013; 280(24): 6322-37.
[318] Rafalski VA, Brunet A. Energy metabolism in adult neural stem cell fate. Prog Neurobiol 2011; 93(2): 182-203.
[319] Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR signaling in Cancer. Front Oncol 2014; 4: 64.
[320] Pattingre S, Espert L, Biard-Piechaczyk M, Codogno P. Regulation of macroautophagy by mTOR and Beclin 1 complexes. Biochimie 2008; 90: 313-23.
[321] Kroemer G, Marino G, Levine B. Autophagy and the integrated stress response. Mol Cell 2012; 40: 280-93.
[322] Hashimoto M, Rockenstein E, Crews L, Masliah E. Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases. Neuro Mol Med 2003; 4: 21-36.
[323] Yu WH, Cuervo AM, Kumar A, *et al*. Macroautophagy: A novel beta-amyloid peptide-generating pathway activated in Alzheimer's disease. J Cell Biol 2005; 171: 87-98.
[324] Chimin P, Andrade ML, Belchior T, *et al*. Adipocyte mTORC1 deficiency promotes adipose tissue inflammation and NLRP3 inflammasome activation via oxidative stress and de novo ceramide synthesis. J Lipid Res 2017; 58(9): 1797-807.
[325] Shacka JJ, Roth KA, Zhang J. The autophagy-lysosomal degradation pathway: role in neurodegenerative disease and therapy. Front Biosci 2008; 13: 718-36.
[326] Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nat Rev Mol Cell Biol 2007; 8(9): 741-52.
[327] Kuballa P, Nolte WM, Castoreno AB, Xavier RJ. Autophagy and the immune system. Annu Rev Immunol 2012; 30: 611-46.
[328] Subauste CS. Autophagy as an antimicrobial strategy. Expert Rev Anti Infect Ther 2009; 7(6): 743-52.
[329] Sanjuan MA, Dillon CP, Tait SW, *et al*. Tait Toll-like receptor signalling in macrophages links the autophagy pathway to phagocytosis. Nature 2007; 450(7173): 1253-7.
[330] Zhou R, Yazdi AS, Menu P, Tshopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature 2011; 469(7329): 221-5.

[331] Shi CS, Shenderov K, Huang NN, *et al*. Activation of autophagy by inflammatory signals limits IL-1β production by targeting ubiquitinated inflammasomes for destruction. Nat Immunol 2012; 13(3): 255-63.
[332] Chiu HW, Chen CH, Chang JN, *et al*. Far-infrared promotes burn wound healing by suppressing NLRP3 inflammasome caused by enhanced autophagy. J Mol Med (Berl) 2016; 94(7): 809-19.
[333] Lamkanfi M, Dixit VM. Mechanisms and Functions of Inflammasomes. Cell 2014; 157, 1013-22.
[334] Indramohan M, Stehlik C, Dorfleutner A. COP и POPs Patrol Inflammasome Activation. J Mol Biol 2018; 430(2): 153-73.
[335] Rathinam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol. 2012; 13: 333-2.
[336] Dos Santos G, Kutuzov MA, Ridge KM. The inflammasome in lung diseases. Am J Physiol Lung Cell Mol Physiol 2012; 303: L627-L633.
[337] Nasti TH, Timares L. Inflammasome activation of IL-1 family mediators in response to cutaneous photodamage. Photochem Photobiol 2012; 88(5): 1111-25.
[338] Khare S, Ratsimandresey RA, de Almeida L, *et al*. *The PYRIN domain-only protein POP3 inhibits ALR inflammasomes and regulates responses to infection with DNA viruses*. Nat Immunol 2014; 15: 343-53.
[339] Cox DJ, Field RH, Williams DG, *et al*. DNA sensors are expressed in astrocytes and microglia *in vitro* and are upregulated during gliosis in neurodegenerative disease. Glia 2015; 63(5): 812-25.
[340] Rathinam VA, Fitzgera KA. Inflammasome Complexes: Emerging Mechanisms and Effector Functions. Cell 2016; 165: 792-800.
[341] Hornung V, Bauernfeind F, Halle A, *et al*. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008; 9: 847-56.
[342] Zhou R, Tardivel A, Thorens B, *et al*. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 2011; 11: 136-40.
[343] Bauernfeind F, Bartok E, Rieger A, *et al*. Cutting edge: reactive oxygen species inhibitors block priming, but not activation, of the NLRP3 inflammasome. J Immunol 2011; 187: 613-17.
[344] Nakaya Y, Lilue J, Stavrou S, *et al*. AIM2-Like Receptors Positively and Negatively Regulate the Interferon Response Induced by Cytosolic DNA. MBio 2017; 8(4): e00944-17.
[345] Rathinam VAK, Jiang Z, Waggoner SN, *et al*. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat Immunol 2010; 11: 395-402.
[346] Kerur N, Veettil MV, Sharma-Walia N, *et al*. IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection. Cell Host Microbe 2011; 9(5): 363-75.
[347] Chavarria-Smith J, Vance RE. The NLRP1 inflammasomes. Immunol Rev 2015; 265(1): 22-34.
[348] Arthur JC, Lich JD, Ye Z, *et al*. Cutting edge: NLRP12 controls dendritic and myeloid cell migration to affect contact hypersensitivity. J Immunol 2010; 185(8): 4515-9.
[349] Khare S, Dorfleutner A, Bryan NB, *et al*. An NLRP7-Containing Inflammasome Mediates Recognition of Microbial Lipopeptides in Human Macrophages. Immunity 2012; 36(3): 464-76.
[350] Hari A, Zhang Y, Tu Z, *et al*. Activation of NLRP3 inflammasome by crystalline structures via cell surface contact. Sci Rep 2014; 4: 7281.
[351] Heid ME, Keyel PA, Kamga C, *et al*. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. J Immunol 2013; 191(10): 5230-8.
[352] Franchi L, Munoz-Planillo R, Nunez G. Sensing and reacting to microbes through the inflammasomes. Nat Immunol 2012; 13: 325-32.
[353] Harris J, Lang T, Thomas JPW, *et al*. Autophagy and inflammasomes. Mol Immunol 2017; 86: 10-15.
[354] Levin TC, Wickliffe KE, Leppla SH, Moayeri M. Heat shock inhibits caspase-1 activity while also preventing its inflammasome-mediated activation by anthrax lethal toxin. Cellular Microbiol 2008; 10(12): 2434-46.
[355] Yao Y, Chen S, Cao M, *et al*. Antigen-specific $CD8^+$ T cell feedback activates NLRP3 inflammasome in antigen-presenting cells through perforin. Nat Commun 2017; 8: 15402.
[356] Dostert C, Ludigs K, Guarda G. Innate and adaptive effects of inflammasomes on T cell responses. Curr Opin Immunol 2013; 25(3): 359-65.
[357] Arbore G, West EE, Spolski R, *et al*. T helper 1 immunity requires complement-driven NLRP3 inflammasome activity in $CD4^+$ T cells. Science 2016; 352(6292): Aad1210.
[358] Ali MF, Dasari H, Van Keulen VP, Carmona EM. Canonical Stimulation of the NLRP3 Inflammasome by Fungal Antigens Links Innate and Adaptive B-Lymphocyte Responses by Modulating IL-1β and IgM Production. Front Immunol 2017; 8: 1504.
[359] Nakamura Y, Kambe N, Saito M, *et al*. Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria. J Exp Med 2009; 206(5): 1037-46.
[360] Lin H, Li Z, Lin D, *et al*. Role of NLRP3 Inflammasome in Eosinophilic and Non-eosinophilic Chronic Rhinosinusitis with Nasal Polyps. Inflammation 2016; 39(6): 2045-52.
[361] Bakele M, Joos M, Burdi S, *et al*. Localization and functionality of the inflammasome in neutrophils. J Biol Chem 2014; 289(8): 5320-9.
[362] Davis BK, Wen H, Ting JP. *The inflammasome NLRs in immunity, inflammation, and associated diseases*. Annu Rev Immunol 2011; 29: 707-35.
[363] Chen GY, Nunez G. *Inflammasomes in intestinal inflammation and cancer*. Gastroenterology 2011; 141: 1986-99.
[364] Dupaul-Chicoine J, Yeretssian G, Doiron K, *et al*. *Control of intestinal homeostasis, colitis, and colitis-associated colorectal cancer by the inflammatory caspases*. Immunity 2010; 32: 367-78.
[365] Guo B, Fu S, Zhang J, Liu B, Li Z. *Targeting inflammasome/IL-1 pathways for cancer immunotherapy*. Sci Rep 2016; 6: 36107.
[366] Xia M, Boini KM, Abais JM, *et al*. Endothelial NLRP3 Inflammasome Activation and Enhanced Neointima Formation in Mice by Adipokine Visfatin. Am J Pathol 2014; 184(5): 1617-28.
[367] Chen Y, Wang L. Pitzer AL, *et al*. Contribution of redox-dependent activation of endothelial Nlrp3 inflammasomes to hyperglycemia-induced endothelial dysfunction. J Mol Med (Berl) 2016; 94(12): 1335-47.
[368] Wang S, Xie X, Lei T, *et al*. Statins Attenuate Activation of the NLRP3 Inflammasome by Oxidized LDL or TNFα in Vascular Endothelial Cells through a PXR-Dependent Mechanism. Mol Pharm 2017; 92(3): 256-64.
[369] Zhou Z, Wang Z, Guan Q, *et al*. PEDF Inhibits the Activation of NLRP3 Inflammasome in Hypoxia Cardiomyocytes through PEDF Receptor/Phospholipase A2. Niessen HWM, ed. Int J Mol Sci 2016; 17(12): 2064.
[370] Lippai D, Bala S, Petrasek J, *et al*. Alcohol-induced IL-1β in the brain is mediated by NLRP3/ASC inflammasome activation that amplifies neuroinflammation. J Leukoc Biol 2013; 94(1): 171-82.
[371] Song L, Pei L, Yao S, Wu Y, Shang Y. NLRP3 Inflammasome in Neurological Diseases, from Functions to Therapies. Front Cell Neurosci 2017; 11: 63.
[372] Tan MS, Tan L, Jiang T, *et al*. Amyloid-β induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease. Cell Death Dis 2014; 5: e1382.
[373] Salminen A, Ojala J, Kaarniranta K, Kauppinen, A. Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. Cell Mol Life Sci 2012; 69: 2999-3013.
[374] Wu PJ, Liu HY, Huang TN, Hsueh YP. AIM 2 inflammasomes regulate neuronal morphology and influence anxiety and memory in mice. Sci Rep 2016; 6: 32405.
[375] Varghese GP, Folkersen L, Strawbridge RJ, *et al*. NLRP3 Inflammasome Expression and Activation in Human Atherosclerosis. J Am Heart Assoc 2016; 5(5): e003031.
[376] Hoseini Z, Sepahvand F, Rashidi B, *et al*. NLRP3 inflammasome: Its regulation and involvement in atherosclerosis. J Cell Phisiol 2018; 233(3): 2116-32.
[377] Cannito S, Morello E, Bocca C, *et al*. Microvesicles released from fat-laden cells promote activation of hepatocellular NLRP3 inflammasome: A pro-inflammatory link between lipotoxicity and non-alcoholic steatohepatitis. PLoS ONE 2017; 12(3): e0172575.
[378] Wree A, Eguchi A, McGeough MD, *et al*. NLRP3 inflammasome activation results in hepatocyte pyroptosis, liver inflammation and fibrosis. Hepatology 2014; 59(3): 898-910.
[379] DeSantis DA, Ko C-W, Wang L, *et al*. Constitutive Activation of the Nlrc4 Inflammasome Prevents Hepatic Fibrosis and Promotes Hepatic Regeneration after Partial Hepatectomy. Mediators Inflamm 2015; 2015: Article ID 909827.

[380] Jourdan T, Godlewski G, Cinar R, *et al*. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. Nat med 2013; 19(9): 1132-40.
[381] Stienstra R, Joosten LA, Koenen T, *et al*. The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin sensitivity. Cell Metab 2010; 12(6): 593-605.
[382] Artlett CM, Sassi-Gaha S Rieger JL, *et al*. The inflammasome activating caspase 1 mediates fibrosis and myofibroblast differentiation in systemic sclerosis. Arthritis Rheum 2011; 63(11): 3563-74.
[383] Li Y, Zheng J-Y, Liu J-Q, *et al*. Succinate/NLRP3 Inflammasome Induces Synovial Fibroblast Activation: Therapeutical Effects of Clematichinenoside AR on Arthritis. Front Immunol 2016; 7: 532.
[384] Feldmeyer L, Werner S, Frencha LE, Beer HD. Interleukin-1, inflammasomes and the skin. Eur J Cell Biol 2010; 89(9): 638-44.
[385] Dai X, Tohyama M, Murakami M, Sayama K. Epidermal keratinocytes sense dsRNA via the NLRP3 inflammasome, mediating interleukin (IL)-1β and IL-18 release. Exp Dermatol 2017; 26(10): 904-11.
[386] Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol 2009; 27: 229-65.
[387] Bendtzen K. Danger signals and inflammasomes in autoinflammatory and autoimmune diseases. Ugeskr Laegter 2011; 173(38): 2340-3.
[388] Pinkerton JW, Kim RY, Robertson AAB, *et al*. Inflammasomes in the lung. Mol Immunol 2017; 86: 44-55.
[389] Hosseinian N, Cho Y, Lockey RF, Kolliputi N. The role of the NLRP3 inflammasome in pulmonary diseases. Ther Adv Respir Dis 2015; 9(4): 188-97.
[390] Shahzad K, Bock F, Dong W, *et al*. Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy. Kidney Int 2015; 87: 74-84.
[391] Chang A, Ko K, Clark MR. The Emerging Role of the Inflammasome in Kidney Diseases. Curr Opin Nephrol Hypertens 2014; 23(3): 204-10.
[392] Oh JY, Ko JH, Lee YJ, *et al*. Mesenchymal stem/stromal cells inhibit the NLRP3 inflammasome by decreasing mitochondrial reactive oxygen species. Stem Cells 2014; 32(6): 1553-63.
[393] Ranson N, Eri R. The Role of Inflammasomes in Intestinal Inflammation. Am J Med Biol Res 2013; 1(3): 64-76.
[394] Elinav E, Strowig T, Kau AL, *et al*. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell 2011; 145(5): 745-57.
[395] Wlodarska M, Thaiss CA, Nowarski R, *et al*. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. Cell 2014; 156(5): 1045-59.
[396] Zmora N, Levy M, Pevsner-Fishcer M, Elinav E. Inflammasomes and intestinal inflammation. Mucosal Immunol 2017; 10(4): 865-83.
[397] Elinav E, Strowig T, Kau AL, *et al*. NLRP6 inflammasome is a regulator of colonic microbial ecology and risk for colitis. Cell 2011; 145(5): 745-57.
[398] Anand PK, Kanneganti TD. NLRP6 in Infection and Inflammation. Microbes infect 2013; 15(10-11): 661-8.
[399] Liao KC, Mogridge J. Expression of Nlrp1b Inflammasome components in human fibroblasts confers susceptibility to anthrax lethal toxin. Infect immune 2009; 77(10): 4455-62.
[400] Anand PK, Malireddi RK, Lukens JR, *et al*. NLRP6 negatively regulates innate immunity and host defence against bacterial pathogens. Nature 2012; 488: 389-93.
[401] Neven B, Callebaut I, Prieure AM. Molecular basis of the spectral expression of CIAS1 mutations assotiated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS and FCU. Blood 2004; 103: 2809-15.
[402] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature 2009; 461(7267): 1071-78.
[403] Delia D, Mizutani S. The DNA damage response pathway in normal hematopoiesis and malignancies. Int J Hematol 2017; 106: 328-34.
[404] Lindahl T, Barnes DE. Repair of endogenous DNA damage. Cold Spring Harb Symp Quant Biol 2000; 65: 127-33.
[405] Khanna KK, Jackson SP. DNA double-trand breaks: signaling, repair and the cancer connection. Nat Genet 2001; 27: 247-54.
[406] Elledge SJ. The DNA Damage Response - Self-awareness for DNA. JAMA 2015; 314(11): 1111-12.
[407] Bartek J, Lukas J. DNA damage checkpoints: from initiation to recovery or adaptation. Curr Opin Cell Biol 2007; 19: P. 238-245.
[408] O'Hagan HM, Mohammad HP, Baylin SB. Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island. PLoS Genet 2008; 4(8): e1000155.
[409] Loeb LA, Monnat RJ Jr. DNA polymerases and human disease. Nat Rev Genet 2008; 9(8): 594-604.
[410] Barnum KJ, O'Connell MJ. Cell Cycle Regulation by Checkpoints. Methods Mol Biol 2014; 1170: 29-40.
[411] Bernstein H, Payne CM, Bernstein C, *et al*. (2008). Cancer and aging as consequences of un-repaired DNA damage. In: New Research on DNA Damages (Editors: Honoka Kimura and Aoi Suzuki) Nova Science Publishers, Inc., New York, 2008; Chapter 1: 1-47.
[412] Freitas AA, de Magalhães JP. A review and appraisal of the DNA damage theory of ageing. Mutat Res 2011; 728(1-2): 12-22.
[413] Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med 2009; 361(15): 1475-85.
[414] Jiang Y, Qi X, Liu X, *et al*. Fbxw7 haploinsufficiency loses its protection against DNA damage and accelerates MNU-induced gastric carcinogenesis. Oncotarget 2017; 8(20): 33444-56.
[415] Roos WP, Kaina B. DNA damage-induced cell death by apoptosis Trends Mol Med 2006; 12(9): 440-50.
[416] Sun X, Li Y, LiW, *et al*. Selective induction of necrotic cell death in cancer cells by beta-lapachone through activation of DNA damage response pathway. Cell Cyte 2006; 5(17): 2019-35.
[417] Carroll SB, Wessler SR, Griffiths AJFl, Lewontin RC. Introduction to genetic analysis. New York: W.H. Freeman and Co, 2008, p. 534.
[418] Nakad R, Schumacher B. DNA Damage Response and Immune Defense: Links and Mechanisms. Front Genet 2016; 7: 147.
[419] Edifizi D, Schumacher B. Genome instability in development and aging: insights from nucleotide excision repair in humans, mice, and worms. Biomolecules 2015; 5: 1855-69.
[420] Bauer NC, Corbett AH, Doetsch PW. The current state of eukaryotic DNA base damage and repair. Nucleic Acids Res 2015; 43: 10083-101.
[421] Caldecott KW. Single-strand break repair and genetic disease. Nat Rev Genet 2008; 9: 619-31.
[422] Gill G. SUMO and ubiquitin in the nucleus: different functions, similar mechanisms? Genes Dev 2004; 18: 2046-59.
[423] Meulmeester E, Kunze M, Hsiao HH, *et al*. Mechanism and consequences for paralog-specific sumoylation of ubiquitin-specific protease 25. Mol Cell 2008; 30: 610-19.
[424] Jalal D, Chalisserry J, Hassan AH. Genome maintenance in Saccharomyces cerevisiae: the role of SUMO and SUMO-targeted ubiquitin ligases. Nucleic Acids Res 2017; 45(5): 2242-61.
[425] Zilio N, Eifler-Olivi K, Ulrich HD. Functions of SUMO in the Maintenance of Genome Stability. Adv Exp Med Biol 2017; 963: 51-87.
[426] Jiricny J. The multifaceted mismatch-repair system. Nat Rev Mol Cell Biol 2006; 7(5): 335-46.
[427] David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. Nature 2007; 447(714): 941-50.
[428] Brown JS, Jackson SP. Ubiquitylation, neddylation and the DNA damage response. Open Biol 2015; 5(4): 150018.
[429] Lindstrom MS. NPM1/B23: A Multifunctional Chaperone in Ribosome Biogenesis and Chromatin Remodeling. Biochem Res Int 2011; 2011: 195-209.
[430] Colombo E, Alcalay M, Pelicci PG. Nucleophosmin and its complex network: A possible therapeutic target in hematological diseases. Oncogene 2011; 30: 2595-09.
[431] Lee SB., Nguyen TLX, Choi JW, *et al*. Nuclear At interacts with B23/NPM and protects it from proteolytic cleavage, enhancing cell survival. Proc Natl Acad Sci 2008; 105: 16584-9.
[432] Al-Ejeh F, Kumar R, Wiegmans A, *et al*. Harnessing the complexity of DNA-damage response pathways to improve cancer treatment outcomes. Oncogene 2010; 29(46): 6085-98.
[433] Shortt J, Martin BP, Newbold A, *et al*. Combined inhibition of PI3K-related DNA damage response kinases and mTORC1 induces apoptosis in MYC-driven B-cell lymphomas. Blood 2013; 121(15): 2964-74.
[434] Mendoza MC, Er EE, Blenis J. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem Sci 2011; 36(6): 320-8.

[435] Garofalo RS, Orena SJ, Rafidi K, *et al*. Severe diabetes, age-dependent loss of adipose tissue, and mild growth deficiency in mice lacking Akt2/PKB beta. J Clin Invest 2003; 112(2): 197-208.
[436] Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006; 7: 85 -96.
[437] Weinstein-Oppenheimer CR, Blalock WL, Steelman LS, *et al*. The Raf signal transduction cascade as a target for chemotherapeutic intervention in growth factor-responsive tumors. Pharmacol Ther 2000; 88(3): 229-79.
[438] Huang X, Halicka HD, Darzynkiewicz Z. Detection of histone H2AX phosphorylation on Ser-139 as an indicator of DNA damage (DNA double-strand breaks). Curr Protoc Cytom 2004; 7: 7.27.
[439] Kurz EU, Lees-Miller SP. DNA damage-induced activation of ATM and ATM-dependent signaling pathways. DNA Repair (Amst) 2004; 3(8-9): 889-900.
[440] Carr MI, Jones SN. Regulation of the Mdm2-p53 signaling axis in the DNA damage response and tumorigenesis. Transl Cancer Res 2016; 5(6): 707-24.
[441] Centurione L, Aiello FB. DNA Repair and Cytokines: TGF-β, IL-6, and Thrombopoietin as Different Biomarkers of Radioresistance. Front Oncol 2016; 6: 175.
[442] Valentin-Vega YA, Maclean KH, Tait-Mulder J, *et al*. Mitochondrial dysfunction in ataxia-telangiectasia. Blood 2012; 119(6): 1490-500.
[443] Giglia-Mari G, Zotter A, Vermeulen W. DNA Damage Response. Cold Spring Harb Perspect Biol 2011; 3(1): A000745.
[444] Sirbu BM, Cortez D. DNA damage response: three levels of DNA repair regulation. Cold Spring Harb Perspect 2013; 5(8): A012724.
[445] Jazayeri A, Falck J, Lukas C, *et al*. ATM- and cell cycle-dependent regulation of ATR in response to DNA double-strand breaks. Nat Cell Biol 2006; 8(1): 37-45.
[446] Huen MS, Chen J. The DNA damage response pathways: At the crossroad of protein modifications. Cell Res 2008; 18(1): 8-16.
[447] Niida H, Tsuge S, Katsuno Y, *et al*. Depletion of Chk1 leads to premature activation of Cdc2-cyclinB and mitotic catastrophe. J Biol Chem 2005; 280: 39246-52.
[448] O'Driscoll M. Diseases Associated with Defective Responses to DNA Damage. Cold Spring Harbor Perspect Biol 2012; 4(12): A012773.
[449] Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature 2009; 458(7239): 719-24.
[450] Mouw KW, Goldberg MS, Konstantinopoulos PA, D'Andrea AD. DNA Damage and Repair Biomarkers of Immunotherapy Response. Cancer Discov 2017; 7(7): 675-93.
[451] Matzuk MM, Lamb DJ. The biology of infertility: research advances and clinical challenges. Nat Med 2008; 14(11): 1197-213.
[452] Verdun RE, Karlseder J. Replication and protection of telomeres. Nature 2007; 447(714): 924-31.
[453] Longhese MP. DNA damage response at functional and dysfunctional telomeres. Genes Dev 2008; 22(2): 125-40.
[454] Schumacher B, Garinis GA, Hoeijmakers JH. Age to survive: DNA damage and aging. Trends Genet 2008; 24(2): 77-85.
[455] Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. Cellular senescence in aging primates. Science 2006; 311(5765): 1257.
[456] Jeyapalan JC, Sedivy JM. Cellular senescence and organismal aging. Mech Ageing Dev 2008; 129(7-8): 467-474.
[457] Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 2007; 8(9): 729-40.
[458] Rass U, Ahel I, West SC. Defective DNA repair and neurodegenerative disease. Cell 2007; 130(6): 991-1004.
[459] Kulkarni A, Wilson DM 3rd. The involvement of DNA-damage and -repair defects in neurological dysfunction. Am J Hum Genet 2008; 82(3): 539-66.
[460] Higo T, Naito AT, Sumida T, *et al*. DNA single-strand break-induced DNA damage response causes heart failure. Nat Commun 2017; 8: 15104.
[461] International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature 2004; 431(7011): 931-45.
[462] Sharma S, Lu HC. microRNAs in Neurodegeneration: Current Findings and Potential Impacts. J Alzheimer's Dis Parkinsonism. 2018; 8(1): 420.
[463] Esteller M. Non-coding RNAs in human disease. Nat Rev Genet 2011; 12: 861-74.
[464] Finch ML, Marquardt JU, Yeoh GC, Callus BA. Regulation of microRNAs and their role in liver development, regeneration and disease. Int J Biochem Cell Biol 2014; 54: 288-303.
[465] Peterson SM, Thompson JA, Ufkin ML, *et al*. Common features of microRNA target prediction tools. Front Genet 2014; 5: 23.
[466] Ambros V, Bartel B, Bartel DP, *et al*. A uniform system for microRNA annotation. RNA 2003; 9(3): 277-9.
[467] Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009. 19(1): 92-105.
[468] Sohel MH. Extracellular/circulating MicroRNAs: release mechanisms, functions and challenges. Achiev Life Sci 2016; 10(2): 175-86.
[469] Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005; 120(1): 15-20.
[470] Lewis BP, Shih IH, Jones-Rhoades MW, *et al*. Prediction of mammalian microRNA targets. Cell 2003; 115(7): 787-98.
[471] Krek A, Grün D, Poy MN, *et al*. Combinatorial microRNA target predictions. Nat Genet 2005; 37(5): 495-500.
[472] Koscianska E, Starega□Roslan J, Krzyzosiak WJ. The role of Dicer protein partners in the processing of microRNA precursors. PLoS One 2011; 6: e28548.
[473] Macrae I, Zhou K, Li F, *et al*. Structural basis for double-stranded RNA processing by Dicer. Science 2006; 311(5758): 195-8.
[474] Rana TM. Illuminating the silence: understanding the structure and function of small RNAs. Nat Rev Mol Cell Biol 2007; 8(1): 23-36.
[475] Morozova N, Zinovyev A, Nonne N, *et al*. Kinetic signatures of microRNA modes of action. RNA 2012; 18(9): 1635-55.
[476] Tenenbaum SA, Christiansen J, *et al*. The post-transcriptional operon. Methods Mol Biol 2011; 703: 237-45.
[477] Marsit CJ, Eddy K, Kelsey KT. MicroRNA Responses to Cellular Stress. Cancer Res 2006; 66(22): 10843-8.
[478] Babar IA, Slack FJ, Weidhaas JB. miRNA modulation of the cellular stress response. Future Oncol 2008; 4(2): 289-98.
[479] Regazzi R. Diabetes mellitus reveals its micro-signature. Circ Res 2010; 107(6): 686-8.
[480] Srivastava D. Making or breaking the heart: from lineage determination to morphogenesis. Cell 2006; 126(6): 1037-48.
[481] Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. Nature 2011; 469(7330): 336-42.
[482] Bushati N, Cohen SM. MicroRNAs in neurodegeneration. Curr Opin Neurobiol 2008; 18(3): 292-6.
[483] Schober A, Nazari-Jahantigh M, Weber C. MicroRNA-mediated mechanisms of the cellular stress response in atherosclerosis. Nat Rev Cardiol 2015; 12(6): 361-74.
[484] Bu H, Wedel S, Cavinato M, Jansen-Dürr P. MicroRNA Regulation of Oxidative Stress-Induced Cellular Senescence. Oxid Med Cell Longev 2017; 2017: 2398696.
[485] Ibanez□Ventoso C, Driscoll M. MicroRNAs in C. elegans aging: molecular insurance for robustness? Curr Genomics 2009; 10(3): 144-53.
[486] Minones□Moyano E, Porta S, Escaramis G, *et al*. MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR□34b/c which modulate mitochondrial function. Hum Mol Genet 2011; 20: 3067-78.
[487] Olivieri F, Capri M, Bonafe M, *et al*. Circulating miRNAs and miRNA shuttles as biomarkers: Perspective trajectories of healthy and unhealthy aging. Mech Ageing Dev 2017; 165(Pt B): 162-70.
[488] Smith-Vikos T, Liu Z, Parsons C, *et al*. A serum miRNA profile of human longevity: findings from the Baltimore Longitudinal Study of Aging (BLSA). Aging (Albany NY) 2016; 8(11): 2971-87.
[489] Menghini R, Casagrande V, Cardellini M, et al., MicroRNA 217 modulates endothelial cell senescence via silent information regulator 1. Circulation 2009; 120(16): 1524-32.
[490] Bai XY, Ma Y, Ding R, *et al*. miR-335 and miR-34a promote renal senescence by suppressing mitochondrial antioxidative enzymes. J Am Soc Nephrol 2011; 22(7): 1252-61.
[491] Pan Q, Liao X., Liu H, *et al*. MicroRNA-125a-5p alleviates the deleterious effects of ox-LDL on multiple functions of human brain microvessel endothelial cells. Am J Physiol Cell Physiol 2017; 312(2): C119-C130.
[492] Embe A, Hornstein E. miRNAs at the interface of cellular stress and disease. EMBO 2014; 33(13): 1428-37.

[493] Mori MA, Raghavan P, Thomou T, *et al*. Role of microRNA processing in adipose tissue in stress defense and longevity. Cell Metab 2012; 16: 336-47.
[494] Lim DH, Oh CT, Lee L, *et al*. The endogenous siRNA pathway in Drosophila impacts stress resistance and lifespan by regulating metabolic homeostasis. FEBS Lett 2011585: 3079-85.
[495] Cheng S, Zhang C, Xu C, *et al*. Age-dependent neuron loss is associated with impaired adult neurogenesis in forebrain neuron-specific dicer conditional knockout mice. Int J Biochem Cell Biol 2014; 57: 186-96.
[496] Hébert SS, Papadopoulou AS, Smith P, *et al*. Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyperphosphorylation and neurodegeneration. Hum Mol Genet 2010; 19: 3959-69.
[497] Wang X, Guo B, Li Q, Peng J, *et al*. miR□214 targets ATF4 to inhibit bone formation. Nat Med 2013; 19: 93-100.
[498] Byrd AE, Aragon IV, Brewer JW. MicroRNA□30c□2* limits expression of proadaptive factor XBP1 in the unfolded protein response. J Cell Biol 2012; 196: 689-98.
[499] Upton JP, Wang L, Han D, *et al*. IRE1alpha cleaves select microRNAs during ER stress to derepress translation of proapoptotic Caspase□2. Science 2012338: 818-22.
[500] Byrd AE, Brewer JW. Micro(RNA)managing endoplasmic reticulum stress. IUBMB Life 2013; 65: 373-81.
[501] Chitnis N, Pytel D, Diehl JA. UPR□inducible miRNAs contribute to stressful situations. Trends Biochem Sci 2013; 38(9): 447-52.
[502] Maurel M, Chevet E Endoplasmic reticulum stress signaling: the microRNA connection. Am J Physiol Cell Physiol 2013; 304: 1117-26.
[503] Le MTN, Teh C, Shyh-Chang N, *et al*. MicroRNA-125b is a novel negative regulator of p53. Genes Dev 2009; 23(7): 862-76.
[504] Jones MF, Lal A. MicroRNAs, wild-type and mutant p53: More questions than answers. RNA Biol 2012; 9(6): 781-91.
[505] Navarro F, Lieberman J. miR-34 and p53: New Insights into a Complex Functional Relationship. PLoS One 2015; 10(7): e0132767.
[506] Okada N, Lin CP, Ribeiro MC, *et al*. A positive feedback between p53 and miR-34 miRNAs mediates tumor suppression. Genes Dev 2014; 28(5): 438-50.
[507] He L, He X, Lowe SW, Hannon GJ. microRNAs join the p53 network—another piece in the tumour-suppression puzzle. Nat Rev Cancer 2007; 7(11): 819-22.
[508] Liu X, Fu B, Chen D *et al*, miR-184 and miR-150 promote renal glomerular mesangial cell aging by targeting Rab1a and Rab31. Exp Cell Res 2015; 336(2): 192-203.
[509] O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. Nat Rev Immunol 2010; 10: 111-22.
[510] Leung AK, Sharp PA. MicroRNA functions in stress responses. Mol Cell 2010; 40: 205-15.
[511] Bardwell L, Zou X, Nie Q, Komarova NL. Mathematical models of specificity in cell signaling. Biophys J 2007; 92(10): 3425-41.
[512] Benayoun BA, Veitia RA. A post-translational modification code for transcription factors: sorting through a sea of signals. Trends Cell Biol 2009; 19: 189-97.
[513] Jensen ON. Modification-specific proteomics: characterization of post-translational modifications by mass spectrometry. Curr Opin Chem Biol 2004; 8: 33-41.
[514] Duan G, Walther D. The Roles of Post-translational Modifications in the Context of Protein Interaction Networks. PLoS Comput Biol 2015; 11(2): e1004049.
[515] Sakamoto K, Holman GD. Emerging role for AS160/TBC1D4 and TBC1D1 in the regulation of GLUT4 traffic. Am J Physiol Endocrinol Metab 2008; 295(1): E29-E37.
[516] Kousteni S. FoxO1: A molecule for all seasons. J Bone Miner Res 2011; 26(5): 912-7.
[517] Mihaylova MM, Shaw RJ. The AMP-activated protein kinase (AMPK) signaling pathway coordinates cell growth, autophagy, & metabolism. Nat Cell Biol 2011; 13(9): 1016-23.
[518] Zaborske JM, Narashimhan J, Jiang L, *et al*. Genome-wide analysis of tRNA charging and activation of the eIF2 kinase Gcn2p. J Biol Chem 2009; 284(37): 25254-67.
[519] Hotamisligil GS. Endoplasmic Reticulum Stress and the Inflammatory Basis of Metabolic Disease. Cell 2010; 140(6): 900-17.
[520] García MA, Gil J, Ventoso I, *et al*. Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. Microbiol Mol Biol Rev 2006; 70(4): 1032-60.
[521] Anda S, Zach R, Grallert B. Activation of Gcn2 in response to different stresses. PLoS ONE 2017; 12(8): e0182143.
[522] Manieri E, Sabio G. Stress kinases in the modulation of metabolism and energy balance. J Mol Endocrinol 2015; 55(2): R11-22.
[523] Sabio G, Davis RJ. TNF and MAP kinase signalling pathways. Semin Immunol 2014; 26(3): 237-45.
[524] Paul A, Wilson S, Belham CM, *et al*. Stress-activated protein kinases: Activation, regulation and function. Cell Signal 1997; 9(6): 403-10.
[525] Hotamisligil GS. A central role for JNK in obesity and insulin resistance. Nature 2002; 420(6913): 333-6.
[526] Vernia S, Cavanagh-Kyros J, Garcia-Haro L, *et al*. The PPARα-FGF21 hormone axis contributes to metabolic regulation by the hepatic JNK signaling pathway. Cell Metab 2014; 20(3): 512-25.
[527] Sabio G, Cavanagh-Kyros J, Ko HJ, *et al*. Prevention of steatosis by hepatic JNK1. Cell Metab 2009; 10(6): 491-8.
[528] Zhou D, Huang C, Lin Z, *et al*. Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 2014; 26(2): 192-7.
[529] Baker RG, Hayden MS, Ghosh S. NF-κB, inflammation and metabolic disease. Cell Metab 2011; 13(1): 11-22.
[530] Xu H, Barnes GT, Yang Q, *et al*. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112(12): 1821-30.
[531] Yang H, Youm YH, Vandanmagsar B, *et al*. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resistance. J Immunol 2010; 185 (3): 1836-45.
[532] Chiang SH, Bazuine M, Lumen CN, *et al*. The protein kinase IK-Kepsilon regulates energy balance in obese mice. Cell 2009; 138(5): 961-75.
[533] Ke B, Zhao Z, Ye X, *et al*. Inactivation of NF-κB p65 (RelA) in Liver Improves Insulin Sensitivity and Inhibits cAMP/PKA Pathway. Diabetes 2015; 64(10): 3355-62.
[534] Arkan MC, Hevener AL, Greten FR, *et al*. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 2005; 11(2): 191-8.
[535] Lark DS, Wasserman DH. Meta-fibrosis links positive energy balance and mitochondrial metabolism to insulin resistance. F1000Res 2017; 6: 1758.
[536] Selye H. Stress and the general adaptation syndrome. Br Med J 1950; 1: 1383-92.
[537] Goldberg GI, Eisen AZ, Bauer EA. Tissue stress and tumor promotion. Possible relevance to epidermolysis bullosa. Arch Dermatol 1988; 124(5): 737-41.
[538] Besedovsky HO, del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev 1996; 17(1): 64-102.
[539] Borg M, Brincat S, Camilleri G, *et al*. The role of cytokines in skin aging. Climacteric 2013; 16(5): 514-21.
[540] Michaud M, Balardy L, Moulis G, *et al*. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc 2013; 14(12): 877-82.
[541] Herder C, Schneitler S, Rathmann W, *et al*. Low-grade inflammation, obesity, and insulin resistance in adolescents. J Clin Endocrinol Metab 2007; 92(12): 4569-74.
[542] Wedell-Neergaard A-S, Eriksen L, Grønbæk M, *et al*. Low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI. PLoS ONE 2018; 13(1): e0190645.
[543] McPoil TG, Hunt GC. Evaluation and management of foot and ankle disorders: present problems and future directions. J Orthop Sports Phys Ther 1995; 21(6): 381-8.
[544] Mueller MJ, Maluf KS. Tissue adaptation to physical stress: A proposed "Physical Stress Theory" to guide physical therapist practice, education, and research. Phys Ther 2002; 82(4): 383-403.
[545] Elbakidze GM, Elbakidze AG. Principles of Tissue Growth Intratissue Regulation. Collierville, USA, 2009, 163 p.
[546] Gilman AG. G proteins: transducers of receptor-generated signals. Annu Rev Biochem 1987; 56 (1): 615-49.
[547] Basu S. Bioactive eicosanoids: role of prostaglandin F(2α) and F□-isoprostanes in inflammation and oxidative stress related pathology. Mol Cells 2010; 39(5): 383-91.

[548] Hannun YA. Functions of ceramide in coordinating cellular responses to stress. Science 1996; 274(5294): 1855-9.
[549] Williams MJ. Drosophila hemopoiesis and Cellular Immunity. J Immunol 2007; 178(8): 4711-16.
[550] Reiber CL, McGaw IJ. A Review of the "Open" and "Closed" Circulatory Systems: New Terminology for Complex Invertebrate Circulatory Systems in Light of Current Findings. International J Zoology 2009; 2009: 01284.
[551] Palade GE, Simionescu M, Simionescu N. Structural aspects of the permeability of the microvascular endothelium. Acta Physiol Scand Suppl 1979; 463: 11-32.
[552] Kumar P, Shen Q, Pivetti CD, *et al*. Molecular mechanisms of endothelial hypermeability: implications in inflammation. Expert Rev Mol Med. 2009; 11: e19.
[553] Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2012; 20(3): 407-22.
[554] Tanchev P. Osteoarthritis or Osteoarthrosis: Commentary on Misuse of Terms. Reconstructive Review 2017; 7(1): doi: 10.15438/rr.7.1.178.
[555] Yu X, Guo C, Fisher PB, *et al*. Scavenger receptors: emerging roles in cancer biology and immunology. Adv Cancer Res. 2015; 128: 309-64.
[556] Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. J Immunol 2000; 164(12): 6166-73.
[557] Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep 2014; 6: 13.
[558] Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol 2009; 27: 669-92.
[559] Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol 2008; 8(7): 523-32.
[560] Murray PJ, Allen JE, Biswas SK, *et al*. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 2014; 41(1): 14-20.
[561] Geissmann F, Manz MG, Jung S, *et al*. Development of monocytes, macrophages, and dendritic cells. Science 2010; 327(5966): 656-61.
[562] Yamaguchi T, Takizawa F, Fisher U, Dijkstra JM. Along the axis between Type 1 and Type 2 immunity; principles conserved in evolution from fish to mammals. Biology (Basel) 2015; 4: 814-59.
[563] Wang Y, Souabni A, Flavell RA, Wan YY. An intrinsic mechanism predisposes Foxp3-expressing regulatory T cells to Th2 conversion *in vivo*. J Immunol 2010; 185: 5983-92.
[564] Luckheeram RV, Zhou R. Verma AD, Xia B. CD4+T cells: differentiation and functions. Clin Dev Immunol 2012; 2012: 925135.
[565] Olson NC, Sallam R, Doyle MF, *et al*. T Helper Cell Polarization in Healthy People: Implications for Cardiovascular Disease. J Cardiovasc Transl Res 2013; 6(5): 772-86.
[566] Hirahara K, Nakayama T. CD4+ T-cell subsets in inflammatory diseases: beyond the Th1/Th2 paradigm. Int Immunol 2016; 28(4): 163-71.
[567] Nahrendorf M, Swirski FK. Abandoning M1/M2 for a Network Model of Macrophage Function. Circ Res 2016; 119(3): 414-7.
[568] Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol 2010; 10(12): 838-48.
[569] Wu HJ, Wang AHJ, Jennings MP. Discovery of virulence factors of pathogenic bacteria. Cur Opin Chem Biol 2008; 12(1): 93-101.
[570] Romagnani S. Type 1 T helper and type 2 T helper cells: Functions, regulation and role in protection and disease. Int J Clin Lab Res 1992: 21(2-4): 152-8.
[571] Nishimura T, Iwakabe K, Sekimoto M. Distinct role of antigen-specific T helper type 1 (Th1) and Th2 cells in tumor eradication *in vivo*. J Exp Med 1999; 190(5): 617-27.
[572] Dohg C, Flavell RA. Cell fate decision: T-helper 1 and 2 subsets in immune responses. Arthritis Res 2000: 2(3): 179-88.
[573] Georas SN, Guo J, De Fanis U, Casolaro V. T-helper cell type-2 regulation in allergic disease. Eur Respir J 2005; 26(6): 1119-37.
[574] Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity 2008; 28(4): 454-67.
[575] Banchereau J, Pascual V, O'Garra A. From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. Nat Immunol 2012; 13(10): 925-31.
[576] Murthy S, Larson-Casey JL, Ryan AJ, *et al*. Alternative activation of macrophages and pulmonary fibrosis are modulated by scavenger receptor, macrophage receptor with collagenous structure. FASEB J. 2015; 29 (8): 3527-36.
[577] Xu Z, Xu L, Li W, *et al*. Innate scavenger receptor-A regulates adaptive T helper cell responses to pathogen infection. Nat Commun 2017; 8: 16035.
[578] Mehta JL, Li D. Identification, regulation and function of a novel lectin-like oxidized low-density lipoprotein receptor. J Am Coll Cardiol 2002; 39 (9): 1429-35.
[579] De Siqueira J, Abdul Zani I, Russell DA, *et al*. Clinical and Preclinical Use of LOX-1-Specific Antibodies in Diagnostics and Therapeutics. J Cardiovasc Transl Res 2015; 8 (8): 458-65.
[580] Armengol C, Bartolí R, Sanjurjo L, *et al*. Role of scavenger receptors in the pathophysiology of chronic liver diseases. Crit Rev Immunol 2013; 33 (1): 57-96.
[581] Rahman N, Pervin M, Kuramochi M, *et al*. M1/M2-macrophage polarization-based hepatotoxicity in d-galactosamine-induced acute liver injury in rats. Toxicol Pathol 2018; 46 (7): 764-76.
[582] Yu X, Kasprick A, Petersen F. Revisiting the role of mast cells in autoimmunity. Autoimmun Rev 2015; 14(9): 751-9.
[583] Rosvall M, Engstrom G, Janzon L, *et al*. The role of low grade inflammation as measured by C-reactive protein levels in the explanation of socioeconomic differences in carotid atherosclerosis. Eur J Public Health 2007; 17(4): 340-7.
[584] Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. CMAJ 2005; 172(7): 899-905.
[585] Pereira ENGDS, Silvares RR, Flores EEI, *et al*. Hepatic microvascular dysfunction and increased advanced glycation end products are components of non-alcoholic fatty liver disease. PLoS One 2017; 12(6): e0179654.
[586] Van Grunsven LA. 3D *in vitro* models of liver fibrosis. Adv Drug Deliv Rev 2017; 121: 133-46.
[587] Anders HJ, Schaefer L. Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J Am Soc Nephrol 2014; 25(7): 1387-400.
[588] Cui H, Kong Y, Zhang H. Oxidative Stress, Mitochondrial Dysfunction, and Aging. J Signal Transduct 2012; 2012: 646354.
[589] Murea M, Freedman BI, Parks JS, *et al*. Lipotoxicity in Diabetic Nephropathy: The Potential Role of Fatty Acid Oxidation. Clin J Am Soc Nephrol 2010; 5(12): 2373-9.
[590] Schaffer JE. Lipotoxicity: Many Roads to Cell Dysfunction and Cell Death: Introduction to a Thematic Review Series. J Lipid Res 2016; 57(8): 1327-28.
[591] Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab 2012; 15(5): 606-14.
[592] Hu W, Sun L, Gong Y, *et al*. Relationship between Branched-Chain Amino Acids, Metabolic Syndrome, and Cardiovascular Risk Profile in a Chinese Population: A Cross-Sectional Study. Int J Endocrinol 2016; 2016: 8173905.
[593] Catena C, Colussi G, Nait F, *et al*. Elevated Homocysteine Levels Are Associated With the Metabolic Syndrome and Cardiovascular Events in Hypertensive Patients. Am J Hypertens 2015; 28(7): 943-50.
[594] Hohensinner PJ, Niessner A, Huber K, *et al*. Inflammation and cardiac outcome. Curr Opin Infect Dis 2011, 24: 259-64.
[595] Senn JJ. Toll-like receptor-2 is essential for the development of palmitate-induced insulin resistance in myotubes. J Biol Chem 2006; 281(37): 26865-75.
[596] Lara-Guzman OJ, Gil-Izquierdo A, Medina S, *et al*. Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages. Redox Biol 2018; 15: 1-11.
[597] Manzel A, Muller DN, Hafler DA, *et al*. Role of "Western diet" in inflammatory autoimmune diseases. Curr Allergy Astma Rep 2014; 14(1): 404.
[598] Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 2008; 29(24): 2959-71.
[599] Almawi WY, Tamim H, Azar ST. Clinical review 103: T helper type 1 and 2 cytokines mediate the onset and progression of type I (insulin-dependent) diabetes. J Clin Endocrinol Metab 1999; 84(5): 1497-502.
[600] Tsai S, Clemente-Casares X, Revelo XS, *et al*. Are obesity-related insulin resistance and type 2 diabetes autoimmune diseases? Diabetes 2015; 64(6): 1886-97.

[601] Xia C, Rao X, Zhong J. Role of T Lymphocytes in Type 2 Diabetes and Diabetes-Associated Inflammation. J Diabetes Res 2017; 2017: 6494795.
[602] Pennock ND, White JT, Cross EW, *et al*. T cell responses: naive to memory and everything in between. Adv Physiol Educ 2013; 37(4): 273-83.
[603] De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep 2015; 17(1): 507.
[604] Gilgun-Sherki Y, Melamed E, Offen D. Anti-inflammatory drugs in the treatment of neurodegenerative diseases: current state. Curr Pharm Des 2006; 12(27): 3509-19.
[605] Chen X, Pan W. The Treatment Strategies for Neurodegenerative Diseases by Integrative Medicine. Integr Med Int 2014; 1: 223-5.
[606] Esser N, Paquot N, Scheen AJ. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expert Opin Investig Drugs 2015; 24(3): 283-307.
[607] Pollack RM, Donath MY, LeRoith D, Leibowitz G. Anti-inflammatory Agents in the Treatment of Diabetes and Its Vascular Complications. Diabetes Care 2016; 39(2): S244-S252.
[608] Merone L, McDermott R. Nutritional anti-inflammatories in the treatment and prevention of type 2 diabetes mellitus and the metabolic syndrome. Diabetes Res Clin Pract 2017; 127: 238-53.
[609] Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. Circ Res 2016; 118 (4): 653-67.
[610] De Paoli F, Staels B, Chinetti-Gbaguidi G. Macrophage phenotypes and their modulation in atherosclerosis. Circ J 2014; 78 (8): 1775-81.
[611] Carniglia L, Ramírez D, Durand D, *et al*. Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. Mediators Inflamm 2017; 2017: 5048616.
[612] Harwani SC. Macrophages under pressure: the role of macrophage polarization in hypertension. Transl Res 2018; 191: 45-63.
[613] Morawietz H, Duerrschmidt N, Niemann B, *et al*. Induction of the oxLDL receptor LOX-1 by endothelin-1 in human endothelial cells. Biochem Biophys Res Commun 2001; 284 (4): 961-65.
[614] Youg AB. Four decades of neurodegenerative disease research: how far we have come! J Neurosci 2009; 29(41): 12722-8.
[615] Levenson RW, Sturm VE, Haase CM. Emotional and behavioral symptoms in neurodegenerative disease: A model for studying the neural bases of psychopathology. Annu Rev Clin Psychol 2014; 10: 581-606.
[616] Baquero M, Martin N. Depressive symptoms in neurodegenerative diseases. World J Clin Cases 2015; 3(8): 682-93.
[617] Martin LJ, Al-Abdulla NA, Brambrink AM, *et al*. Neurodegeneration in excitotoxicity, global cerebral ischemia, and target deprivation: A perspective on the contributions of apoptosis and necrosis. Brain Res Bull 1998; 46(4): 281-309.
[618] Wang X, Li J, Wu D, Bu X, Qiao Y. Hypoxia promotes apoptosis of neuronal cells through hypoxia-inducible factor-1α-microRNA-204-B-cell lymphoma-2 pathway. Exp Biol Med (Maywood) 2016; 241(2): 177-83.
[619] Akbar M, Essa MM, Daradkeh G, Abdelmegeed MA, Choi Y, Mahmood L, Song BJ. Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress. Brain Res 2016; 1637: 34-55.
[620] Goedert M. NEURODEGENERATION. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. Science 2015; 349(6248): 1255555.
[621] Wilkinson K, El Khoury J. Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int J Alzheimers Dis 2012; 2012: 489456.
[622] Eugenín J, Vecchiola A, Murgas P, Arroyo P, Cornejo F, von Bernhardi R. Expression pattern of scavenger receptors and amyloid-β phagocytosis of astrocytes and microglia in culture are modified by acidosis: implications for Alzheimer's disease. J Alzheimers Dis 2016; 53 (3): 857-73.
[623] Linden R, Martins VR, Prado MAM, *et al*. Physiology of the prion protein. Physiol Rev 2008; 88: 673-728.
[624] Imran M, Mahmood S. An overview of human prion diseases. Virol J 2011; 8: 559.
[625] Creteur J, De Backer D, Sakr Y, Koch M, Vincent J. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med 2006; 32(4): 516-23.
[626] De Backer D, Ospina-Tascon G, Salgado D, *et al*. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. Intensive Care Med 2010; 36(11): 1813-25.
[627] Davies PF. Flow-mediated endothelial mechanotransduction. Physiol Rev 1995; 75(3): 519-60.
[628] Walley KR. Heterogeneity of oxygen delivery impairs oxyge6n extraction by peripheral tissues: theory. J Appl Physiol 1996; 81(2): 885-94.
[629] Yang S, Cioffi WG, Bland KI, *et al*. Differential alterations in systemic and regional oxygen delivery and consumption during the early and late stages of sepsis. J Trauma 1999; 47: 706-12.
[630] Rackow EC, Kaufmann BS, Falk JL, *et al*. Hemodynamic response to fluid repletion in patients with septic shock: evidence for early depression of cardiac performance. Circ Shock 1987; 22(1): 11-22.
[631] Dellinger RP. Cardiovascular management of septic shock. Crit Care Med 2003; 31(3): 946-55.
[632] Karimova A, Pinsky DJ. The endothelial response to oxygen deprivation: biology and clinical implications. Intensive Care Med 2001; 27(1): 19-31.
[633] Vallet B. Microthrombosis in sepsis. Minerva Anestesiol 2001; 67(4): 298-301.
[634] Hotchkiss RS, Moldawer LL, Opal SM, *et al*. Sepsis and septic shock. Nat Rev Dis Primers 2016; 2: 16045.
[635] Seeley EJ, Sutherland RE, Kim SS, Wolters PJ. Systemic mast cell degranulation increases mortality during polymicrobial septic peritonitis in mice. J Leukoc Biol 2011; 90(3): 591-7.
[636] Cai C, Cfo Z, Loughran PA, *et al*. Mast cells play a critical role in the systemic inflammatory response and end-organ injury resulting from trauma. J Am Coll Surg 2011; 213(5): 604-15.
[637] Deutschman CS, Tracey KJ. *Sepsis: Current dogma and new perspectives*. Immunity 2014; 40(4): 463-75.
[638] Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence 2014; 5(1): 66-72.
[639] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340(6): 448-54.
[640] Taccone FS, Su F, Pierrakos C, He X, *et al*. Cerebral microcirculation is impaired during sepsis: An experimental study. Crit Care 2010; 14(4): R140.
[641] Sharshar T, Polito A, Checinski A, Stevens RD. Septic-associated encephalopathy - everything starts at a microlevel. Crit Care 2010; 14(5): 199.
[642] Soleimanpour H, Safari S, Rahmani F, *et al*. Hepatic Shock Differential Diagnosis and Risk Factors: A Review Article. Hepat Mon 2015; 15(10): e27063.
[643] Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol 2011; 22(6): 999-1006.
[644] Jentzer JC, Chonde MD, Dezfulian C. Myocardial Dysfunction and Shock after Cardiac Arrest. Biomed Res Int 2015; 2015: 314796.
[645] Cortés DO, Rahmania L, Irazabal M, *et al*. Microvascular reactivity is altered early in patients with acute respiratory distress syndrome. Respir Res 2016; 17: 59.
[646] Siddall E, Khatri M, Radhakrishnfn J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int 2017; 92(1): 37-46.
[647] Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev Dis Primers 2016; 2: 16037.
[648] Fujishima S. Organ dysfunction as a new standard for defining sepsis. Inflamm Regen 2016; 36: 24.
[649] Roumen RM, Hendriks T, van der Ven-Jongekrijg J, *et al*. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993; 218(6): 769-76.
[650] Drewry AM, Hotchkiss RS. Sepsis: Revising definitions of sepsis. Nat Rev Nephrol 2015; 11: 326-8.
[651] Takala A, Jousela I, Olkkola KT, *et al*. Systemic inflammatory response syndrome without systemic inflammation in acutely ill patients admitted to hospital in a medical emergency. Clin Sci (Lond) 1999; 96: 287-95.
[652] Richter DC, Heininger A, Brenner T, *et al*. Bacterial sepsis: Diagnostics and calculated antibiotic therapy. Anaesthesist 2017; 66(10): 737-61.
[653] Kaukonen KM, Bailey M, Pilcher D, *et al*. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015; 372(17): 1629-38.

[654] Singer M, Deutschman CS, Seymour CW, *et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-10.
[655] Rajagopalan S. Crush Injuries and the Crush Syndrome. Med J Armed Forces India 2010; 66(4): 317-20.
[656] Hardaway RM, Dumke R, Gee T, *et al*. The danger of hemolysis in shock. Ann Surg 1979; 189(3): 373-6.
[657] Khalid L, Dhakam SH. A review of cardiogenic shock in acute myocardial infarction. Curr Cardiol Rev 2008; 4(1): 34-40.
[658] Bouglé A, Harrois A, Duranteau J. Resuscitative strategies in traumatic hemorrhagic shock. Ann Intensive Care 2013; 3(1): 1.
[659] Haljamae H. Microcirculation and hemorrhagic shock. Am J Emerg Med 1984; 2(1): 100-7.
[660] Kemp SF, Lockey RF. Anaphylaxis: A review of causes and mechanisms. J Allergy Clin Immunol 2002; 110(3): 341-48.
[661] Kaur K, Bhardwaj M, Kumar P, *et al*. Amniotic fluid embolism. J Anaesthesiol Clin Pharmacol 2016; 32(2): 153-9.
[662] Hifumi T, Sakai A, Kondo Y, *et al*. Venomous snake bites: clinical diagnosis and treatment. J Intensive Car 2015; 3(1): 16.
[663] Chaudhry H, Zhou J, Zhong Y, *et al*. Role of cytokines as a double-edged sword in sepsis. *In Vivo* 2013; 27(6): 669-84.
[664] Schulte W, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets - an updated view. Mediators Inflamm 2013; 2013: 165974.
[665] Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol 2009; 78(6): 539-52.
[666] Wise WC, Cook JA, Temhel GE, *et al*. The rat in sepsis and endotoxic shock. Prog Clin Biol Res 1989; 299: 243-52. ---(703
[667] Fink MP, Heard SO. Laboratory models of sepsis and septic shock. J Surg Res 1990; 49(2): 186-96. ---(704
[668] Elmer L. DeGowin MD. Hemolytic shock following blood transfusion. JAMA 1936; 107(8): 605-6. ---(705
[669] Gusev EY, Yurchenko, L.N., Chereshnev, V.A., Zotova, N.V., Kopalova, Yu.A. The method for diagnosis and prognosis of Systemic Inflammation with phases and stages verification. In: RAS IoiapU, editor. Bulletin N28. IPC7 G01N 33/53 ed. Russian Federation: Institute of immunology and physiology UB RAS. 2008. p. 56.
[670] Bonanno FG. Physiopathology of shock. J Emerg Trauma Shock 2011; 4(2): 222-32.
[671] Schaefer L. Complexity of danger: the diverse nature of damage-associated molecular patterns. J Biol Chem 2014; 289(51): 35237-45.
[672] Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, *et al*. The pathogenesis of sepsis. Annu Rev Pathol 2011; 6: 19-48.
[673] Tennenberg SD, Solomkin JS. Neutrophil activation in sepsis. The relationship between fmet-leu-phe receptor mobilization and oxidative activity. Arch Surg 1988; 123(2): 171-5.
[674] Wang X, Qin W, Sun B. New strategy for sepsis: Targeting a key role of platelet-neutrophil interaction. Burns Trauma 2014; 28; 2(3): 114-20.
[675] Finsterbusch M, Hall P, Li A, *et al*. Patrolling monocytes promote intravascular neutrophil activation and glomerular injury in the acutely inflamed glomerulus. Proc Natl Acad Sci USA 2016; 113(35): E5172-81.
[676] Nesseler N, Launey Y, Aninat C, *et al*. Clinical review: The liver in sepsis. Crit Care 2012; 16(5): 235.
[677] Bilgili B, Haliloglu M, Cinel I. Sepsis and Acute Kidney Injury. Turk J Anaesthesiol Reanim 2014; 42(6): 294-301.
[678] Fukui H. Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation? Inflamm Intest Dis 2016; 1: 135-45.
[679] Sertaridou E, Papaioannou V, Kolios G, Pneumatikos I. Gut failure in critical care: old school versus new school. Ann Gastroenterol 2015; 28(3): 309-22.
[680] Bischoff SC, Barbara G, Buurman W, *et al*. Intestinal permeability - a new target for disease prevention and therapy. BMC Gastroenterol 2014; 14: 189.
[681] Okusawa S, Gelfand JA, Ikejima T, *et al*. Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. J Clin Invest 1988; 81(4): 1162-72.
[682] Mallick AA, Ishizaka A, Stephens KE, *et al*. Multiple organ damage caused by tumor necrosis factor and prevented by prior neutrophil depletion. Chest 1989; 95(5): 1114-20.
[683] Luo L, Zhang S, Wang Y, *et al*. Proinflammatory role of neutrophil extracellular traps in abdominal sepsis. Am J Physiol Lung Cell Mol Physiol 2014; 307(7): L586-96.
[684] Pravda J. Metabolic theory of septic shock. World J Crit Care Med 2014; 3(2): 45-54.
[685] Preiser JC, Ichai C, Orban JC, Groeneveld AB. Metabolic response to the stress of critical illness. Br J Anaesth 2014; 113(6): 945-54.
[686] Kimmoun A, Novy E, Auchet T, *et al*. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. Crit Care 2015; 19: 175.
[687] Jeschke MG. Post-burn hypermetabolism: past, present and future. J Burn Care Res 2016; 37(2): 86-96.
[688] Williams FN, Jeschke MG, Chinkes DL, *et al*. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. J Am Coll Surg 2009; 208(4): 489-502.
[689] Vincent JL. Metabolic support in sepsis and multiple organ failure: more questions than answers ...Crit Care Med 2007; 35(9 Suppl): S436-40.
[690] Al-Banna N, Lehmann C. Oxidized LDL and LOX-1 in experimental sepsis. Mediators Inflamm. 2013;2013: 761789.
[691] Askim A, Moser F, Gustad LT, *et al*. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med 2017; 25: 56
[692] Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and Septic Shock: Current Treatment Strategies and New Approaches. Eurasian J Med 2017; 49: 53-8.
[693] Pockley AG, Muthana M, Calderwood SK. The dual immunoregulatory roles of stress proteins. Trends Biochem Sci 2008; 33: 71-9.
[694] Pierrakos C, Vincent JL. Sepsis biomarkers: A review. Crit Care 2010; 14: R15.
[695] De Backer D, Donadello K, Taccone FS, *et al*. Microcirculatory alterations: potential mechanisms and implications for therapy. Ann Intensive Care 2011; 1: 27.
[696] Bezemer R, Bartels SA, Bakker J, Ince C. Clinical review: Clinical imaging of the sublingual microcirculation in the critically ill--where do we stand? Crit Care 2012; 16: 224.
[697] Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care 2014; 2: 15.
[698] Bossi F, Peerschke EI, Ghebrehiwet B, Tedesco F. Cross-talk between the complement and the kinin system in vascular permeability. Immunology letters 2011; 140: 7-13.
[699] Ricklin D, Reis ES, Lambris JD. Complement in disease: A defence system turning offensive. Nat Rev Nephrol 2016; 12: 383-401.
[700] Metcalfe DD, Baram D, Mekori YA. Mast cells. Physiol Rev 1997; 77(4): 1033-79.
[701] Guilarte M, Sala-Cunill A, Luengo O, *et al*. The Mast Cell, Contact, and Coagulation System Connection in Anaphylaxis. Front Immunol 2017; 8: 846.
[702] Metcalfe DD. Mast cells and mastocytosis. Blood 2008; 112(4) : 946-56.
[703] Ramos L, Pena G, Cai B, *et al*. Mast cell stabilization improves survival by preventing apoptosis in sepsis. J Immunol 2010; 185(1): 709-16.
[704] Guo L, Song Z, Li M, Wu Q, *et al*. Scavenger receptor bi protects against septic death through its role in modulating inflammatory response. J Biol Chem 2009; 284 (30): 19826-34.
[705] Guo L, Zheng Z, Ai J, Huang B, Li XA. Hepatic scavenger receptor BI protects against polymicrobial-induced sepsis through promoting LPS clearance in mice. J Biol Chem. 2014; 289 (21): 14666-73.
[706] Hoffmeister KM, Falet H. Platelet clearance by the hepatic Ashwell-Morrell receptor: mechanisms and biological significance. Thromb Res 2016; 141(2): S68-72.
[707] Cho J, Kim H, Song J, *et al*. Platelet storage induces accelerated desialylation of platelets and increases hepatic thrombopoietin production. J Transl Med. 2018; 16 (1): 199.
[708] Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol Rev. 2012; 249 (1): 158-75.
[709] Lillis AP, Van Duyn LB, Murphy-Ullrich JE, Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol Rev 2008; 88 (3): 887-918.

[710] Vincent JL, Beumier M. Diagnostic and prognostic markers in sepsis. Expert Rev Anti Infect Ther 2013; 11: 265-75.
[711] Das U. HLA-DR expression, cytokines and bioactive lipids in sepsis. Archive Medical Science 2014; 10: 325-35.
[712] Wu J-F, Ma J, Chen J, *et al*. Changes of monocyte human leukocyte antigen-DR expression as a reliable predictor of mortality in severe sepsis. Critical Care 2011; 15: R220.
[713] Sharma D, Kanneganti TD. The cell biology of inflammasomes: Mechanisms of inflammasome activation and regulation. J Cell Biol 2016; 213: 617-29.
[714] Karlsson S, Pettilä, V, Tenhunen J, *et al*. Vascular Endothelial Growth Factor in Severe Sepsis and Septic Shock. Anesthesia & Analgesia 2008; 106: 1820-26.
[715] Valenzuela-Sánchez F, Valenzuela-Méndez B, Rodríguez-Gutiérrez JF, Estella-García Á, González-García MÁ. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. Ann Transl Med. 2016 Sep;4(17): 329.
[716] Rødgaard-Hansen S, Rafique A, Christensen PA, *et al*. A soluble form of the macrophage-related mannose receptor (MR/CD206) is present in human serum and elevated in critical illness. Clin Chem Lab Med. 2014, 52 (3): 453-61.
[717] Dunne WM. Laboratory Diagnosis of Sepsis? No SIRS, Not Just Yet. J Clin Microbiol 2015; 53: 2404-09.
[718] Kiral E, Dinleyici, EC, Bozkurt-Turhan A, *et al*. Serum endocan levels in children with febrile neutropenia. Hematology Reports 2016; 8: 6110.
[719] Huang W, Tang, Y, Li L. HMGB1, a powerful pro-inflammatory cytokines in sepsis. Cytokine 2010; 51: 119-26.
[720] Mat-Nor MB, Md Ralib A, Abdulah NZ, Pickering JW. The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality. J Crit Care 2016; 33: 245-51.
[721] Dalli J, Colas RA, Quintana, C, *et al*. Human sepsis eicosanoid and proresolving lipid mediator temporal profiles: correlations with survival and clinical outcomes. Crit Care Med 2017; 45: 58-68.
[722] Ayala A, Chaudra IH. Platelet activating factor and its role in trauma, shock, and sepsis. New Horiz 1996; 4: 265-75.
[723] Clodfelter WH, Basu S, Bolden C, *et al*. The relationship between plasma and salivary NOx. Nitric Oxide 2015; 47: 85-90.
[724] Borgen L. Total parenteral nutrition in adults. Am J Nurs 1978; 78(2): 224-8.
[725] Houston MC. Pathophysiology of shock. Crit Care Nurs Clin North Am 1990; 2(2): 143-9.
[726] Kreimeier U. Pathophysiology of fluid imbalance. Crit Care 2000; 4(2): S3-7.
[727] Haljamae H. Rationale for the use of colloids in the treatment of shock and hypovolemia. Acta Anaesthesiol Scand Suppl 1985; 82: 48-54.
[728] Kyttaris VC. Systemic lupus erythematosus: from genes to organ damage. Methods Mol Biol 2010; 662: 265-83.
[729] Wright SA, O Prey FM, Rea DJ, *et al*. Microcirculatory hemodynamics and endothelial dysfunction in systemic lupus erythematosus. Arterioscler Thromb Vasc Biol 2006; 26(10): 2281-7.
[730] Inoh M, Tokuda M, Kiuchi H, *et al*. Evaluating systemic lupus erythematosus disease activity using molecular markers of hemostasis. Arthritis Rheum 1996; 39(2): 287-91.
[731] Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: An update. Ann Rheum Dis 2014; 73(9): 1601-6.
[732] Ponticelli C, Meroni PL. Kallikreins and lupus nephritis. J Clin Invest 2009; 119(4): 768-71.