ISSN 2079-0864, Biology Bulletin Reviews, 2019, Vol. 9, No. 4, pp. 358–372. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Uspekhi Sovremennoi Biologii, 2019, Vol. 139, No. 1, pp. 59–74.

Correlation of the Evolution of Immunity and Inflammation in Vertebrates

E. Yu. Gusev[a], *, Yu. A. Zhuravleva[a], **, and N. V. Zotova[a, b], ***

[a] *Institute of Immunology and Physiology, Ural Branch, Russian Academy of Sciences, Yekaterinburg, Russia*
[b] *Ural Federal University Named after the First President of Russia B.N. Yeltsin, Yekaterinburg, Russia*
**e-mail: gusev36@mail.ru*
***e-mail: jazhur@mail.ru*
****e-mail: zotovanat@mail.ru*

Received April 27, 2018; revised July 10, 2018; accepted November 6, 2018

Abstract—The paper discusses the sequence of the developmental stages in the immune system and inflammation in vertebrates: the formation of classic forms of adaptive immunity and inflammation for vertebral species, the origin of cytotoxic T lymphocytes and T cell–dependent variants of productive inflammation in fish; the appearance of new antibody classes in tetrapods, and the origin of exudative–destructive inflammation in higher vertebrates and suppurative inflammation in mammals. Each evolutionary stage in the development of immunity and inflammation was determined by the need to organize the immune system to conform to the level of the general organization of vertebrate species. At the same time, each stage predetermined the appearance of "windows of vulnerability" in the form of the possible development of autoimmune, allergic diseases, and systemic complications of the inflammatory process.

Keywords: evolution, immunity, inflammation, vertebrates
DOI: 10.1134/S2079086419040029

INTRODUCTION

Inflammation is a common type of pathological process that formed evolutionarily as a protective–adaptive reaction to noxious stimuli or extrinsic/intrinsic damage. The goal of the inflammatory response is to eliminate the pathogenic initiator, followed by complex tissue repair to the preinflammation phenotype. Immune mechanisms play a central role in inflammation. In terms of an evolutionary perspective, it is reasonable to consider the mechanisms of inflammation, innate immunity, and adaptive immunity as a whole and to identify the most significant stages in their interrelated development from the most primitive forms of vertebrates, i.e., fishlike cyclostomes ("round mouths," which comprise lamprey and hagfishes) to mammals, including humans. An understanding of these patterns is important not only for evolutionary biology but also for the integral characterization of inflammation in general pathology, which constitutes the theoretical basis of modern medicine. This single system of inflammatory, innate, and adaptive immunity mechanisms should be adequate for the levels of species organization and the levels of biological aggression affecting these species. Several qualitative changes can be identified in the evolution of this single system of inflammation and innate and adaptive immune defenses. The goal of this paper is to characterize and determine the relationships between these components.

EVOLUTIONARY ORIGINS OF IMMUNITY AND INFLAMMATION IN INVERTEBRATES

During evolution, invertebrates were exposed to biological aggression, including allogeneic parasitic invasion in colonial animals, infection, and tumor growth. In response, invertebrates evolved a range of changes in their innate immune system and developed proinflammatory reactions in the form of local phagocytic clusters that can encapsulate parasites (Williams, 2007; Krautz et al., 2014). As a safe-guard against allogeneic parasitism, some invertebrates (for example, sponges) recognize histocompatibility proteins on cytotoxic cells, analogs of mammal normal (natural) killers (NK) (Müller et al., 2002). Invertebrate phagocytes have all the main effector mechanisms present in mammals: hydrolases, free radicals, cationic proteins, and extracellular DNA traps (formed during programmed necrosis of phagocytes) (Krautz et al., 2014). Target recognition by invertebrate phagocytes is mediated by pattern-recognizing receptors (PRRs). These receptors bind to highly conserved pathogen regions, which are termed pathogen-associated molecular patterns (PAMPs) or endogenous danger-

associated molecular patterns (DAMP) (Williams, 2007; Ivasaki et al., 2010). Invertebrate phagocytes carry a wide repertoire of PRR. For example, the diversity of external and intracellular PRRs of two major families, i.e., TLR (Toll-like receptors) and NLR (NOD-like receptors) in some species of echinoderms exceeds that in mammals by more than an order of magnitude (Hibino et al., 2006). Thus, it is probable that the PAMP recognition system by PRRs reaches the maximum of its development in invertebrates.

Invertebrates possess a closed or open hemolymph circulatory system in which they can trigger the systemic inflammatory response via the accumulation of hemocytes, acute phase proteins, and stress hormones in hemolymph (Lacoste et al., 2001; Ottaviani et al., 2010). Upon vascular injury, invertebrate hemocytes, together with plasma adhesion proteins, form hemostatic clots (Krautz et al., 2014). However, these mechanisms are qualitatively different from the vertebrate hemostatic system, which comprises platelets and a complex system of fibrin formation. The acute-phase hemolymph proteins include antibiotic-like factors, soluble cell adhesion molecules, and opsonins, such as tridacnin in molluscs, a counterpart of the mammalian C-reactive protein, or limulin in arthropods, certain factors of the complement system (for example, in echinoderms) or prophenoloxidase cascade, a complement-like pathway in arthropods (Krautz et al., 2014).

Meanwhile, invertebrates do not possess the blood microcirculation system inherent to all known vertebrates, including the relatively primitive capillary network in cyclostomes (which is absent in the intestine and gill apparatus) (Welsch and Potter, 1998; Russell et al., 2008). The fundamental basis of the vertebrate microcirculatory bed is made up of separate microcirculatory units, including vascular (precapillary arterioles, capillaries, and postcapillary venules) and extravascular transport networks that provide metabolic processes between blood and a certain tissue region (Tyagi et al., 2009). The branched system of blood microcirculation not only ensures metabolic processes; it is also involved in the development of inflammatory edema, hyperemia, local temperature rise, and the selective migration of leukocytes into the area of inflammation. Due to the lack of these phenomena during invertebrate response to injury, invertebrate inflammatory processes cannot be attributed to the category of canonical (classic) inflammation.

Another principal difference between invertebrate and vertebrate immunity is that invertebrates lack the classic (lymphocytic) system of adaptive immunity characteristic of vertebrates. However, invertebrates, such as insects, can exploit adaptive immune processes that drive acquired resistance against viral and extracellular infections (Cooper and Eleftherianos, 2017; Rowley and Powell, 2007; Tassetto et al., 2017). Indeed, prokaryotes can also possess antiviral immunity based on the CRISPR-Cas system (Koonin and Makarova, 2013). These mechanisms can be regarded as nonclassic forms of adaptive immunity.

Clones of the antigen-specific lymphocytes formed by the lymphoid organs constitute a classic system of adaptive immunity. When a lymphocyte encounters its antigen, naive lymphocytes undergo clonal expansion and differentiation and become mature cells of the immune response, including immune memory cells (Abbas et al., 2017). The system of adaptive immunity is a superstructure over the innate immune system and qualitatively expands its functions on an antigen-specific basis. Only highly organized animals could afford the classic system of adaptive immunity, wherein the systems of innate and possibly nonclassic acquired immunity were unable to maintain genetic homeostasis.

The cytokine network plays a key role in the integration of innate and adaptive immune cells in lymphoid organs and the inflammatory focus. More than 100 cytokine genes have been identified in humans (Dinarello, 2007).

APPEARANCE OF CLASSIC ADAPTIVE IMMUNITY AND CLASSIC INFLAMMATION

All modern vertebrates inherited adaptive immunity and the possibility of developing classic inflammation. Meanwhile, the levels of morphological and functional organization of mechanisms involved in inflammation and innate and acquired immunity in the evolutionary range of round-mouths to mammals are characterized by qualitative differences.

Inflammation is associated with leukocyte migration through microvessels into injured tissue. The leukocyte count of the round-mouths and jawed fish is dominated by mononuclear cells (up to 90–99%), mainly lymphocytes (Claver and Quaglia, 2009; Finstad and Good, 1964). A few granulocytes in bony fish were differentiated into populations also typical of mammals, while they are not clearly differentiated in the round-mouths (Claver and Quaglia, 2009). Cyclostomes have the productive (cellular) type of inflammation, and lymphocyte-like cells predominate in infiltration (Finstad and Good, 1964). Bony fish can induce exudative inflammation in some cases, i.e., the presence of tissue edema and fibrin deposition in the inflammatory focus (Loch and Faisal, 2015; Sudheesh et al., 2012). In general, the exudative reactions involved in the rapid response to injury are weakly developed in fish.

The lymphoid system of round-mouths includes cell clusters around the gill apparatus and the intestinal tube (Finstad and Good, 1964). The lymphocyte-like cells of lampreys can secrete into an inflamed area cytokines important for productive inflammation, such as interleukin IL-17, macrophage migration

inhibitory factor (MIF), pleiotropic proinflammatory cytokines IL-1 and IL-6, and chemokines from the CXC and CC sub-families (including IL-8), meaning that lampreys form a primitive cytokine network (Herrin and Cooper, 2010).

Cyclostomes have a system of adaptive immunity based on other genetic structures than jawed fish. The most probable evolutionary pathways in the formation of antigen-recognizing structures can be identified. According to these concepts (Shilov and Kuprash, 2016), the first stage was associated with the incorporation of a certain number of transposons in the ancestral receptor genes. The second stage involved recombination between these segments, followed by the consolidation of each variant of chaotic rearrangements into separate clones of lymphocytes specialized to recognize particular antigenic determinants (epitopes).

Cyclostomes were found to possess three types of molecular structures, i.e., single-chain variable lymphocyte receptors (VLRs), which belong to the acquired immunity system (Herrin and Cooper, 2010; Das et al., 2015). Two VLRs (VLRA and VLRC) are cell receptors, and VLRBs are soluble, antibody-like proteins. All of these proteins belong to the super-family of molecules with leucine-rich repeats. Rearrangements in the VLR genes occur due to gene conversion without RAG recombinases, in contrast to all jawed animals. Cellular and humoral VLRs are released by various lymphocyte-like cells that interact with each other. For example, activated VLRA cells of lampreys secrete IL-17 and carry the IL-8R receptor; conversely, VLRB cells have IL-17R and secrete IL-8 (Herrin and Cooper, 2010). No proteins of the major histocompatibility complex MHC and no mechanisms for the negative selection of potentially autoreactive clones of VLR cells have been detected yet in round-mouths (Shilov and Kuprash, 2016). Nonetheless, cyclostomes have an immune memory to xenoantigen exposure (e.g., sheep erythrocytes), and they are also capable of allograft rejection (Finstad and Good, 1964; Das et al., 2015).

The mammalian $CD5^+$ B_1 lymphocytes probablu perform a similar function to the VLR system (Sidorova, 2009; Zhu et al., 2014). In contrast to B_2 lymphocytes, the primary pool for antibody production, the generation of $CD5^+$ B_1 lymphocytes, is independent of T cells. B_1 cells secrete low-affinity IgM immunoglobulins, which make up the majority of normal (natural) serum antibodies. Furthermore, mammalian T lymphocytes of the TCRγδ cell line composed of γ- and δ-TCR chains can interact with various antigens and stress proteins without the involvement of classic MHC proteins (Kreslavsky et al., 2010). These factors are associated with barrier tissues and belong to a transitional zone between innate and adaptive immunity.

In general, the ability to trigger inflammation and the organizational level of adaptive immunity in round-mouth animals as compared to jawed vertebrates have not been completely developed.

In jawed vertebrates, adaptive immunity formed on the basis of protein molecules related to the immunoglobulin superfamily, i.e., MHC proteins, TCR, and immunoglobulins (Ig). The V-domain (VJ-type) of the NKp30 receptor on normal killers is genetically closest to the V-domains of variable receptors of adaptive immunity; however, this domain cannot rearrange its segments (Ohta and Flajnik, 2015). This receptor recognizes a stress-inducible ligand B7H6 on target cells.

The formation of antigen-recognition structures (paratopes) in jawed animals was associated with the function of RAG-1 and RAG-2 recombinases of viral origin; the genes of these recombinases were probably present in the genome, not only from ancestral chordates but also in echinoderms, another type of secondary invertebrate (Fugmann et al., 2006). However, the function of RAG-1/2 in invertebrates is not clear. A probable mechanism involved in the formation of the first genes for adaptive immunity was the insertion of RAG-dependent transposons into the V-domain gene of the ancestral receptor in NK or NK-like cells, which can bind histocompatibility proteins (Shilov and Kuprash, 2016; Fugmann et al., 2006). This resulted in the formation of structures that include a multitude (n) of two- or three-type segments: Vn-Jn or Vn-Dn-Jn. At the initial stage of lymphocyte clonal differentiation, recombination leads to the maintenance of only a certain isotype, i.e., V-(D)-J, in the V-gene structure; the rest are removed from the genome. V-(D)-J is then integrated into the gene encoding constant domains (C) of the receptor chain. With consideration of the two chains that form the paratope in TCRαβ or TCRγδ and two chains of Ig (L-light and H-heavy), two isoforms of L-chains (κ, λ), multiple point mutations, and recombination at end segments of V-genes (Flajnik and Kasahara, 2010), the total number of diverse paratopes in most vertebrate species can exceed 10^8 variants. Apparently, this amount of paratopes is enough to recognize almost any antigen by a particular lymphocyte clone. This principle in the formation of antigen-recognition structures has been preserved in evolution, from bony fish to mammals.

All jawed animals have a thymus involved in the negative selection of T lymphocytes, which recognize the autoantigens displayed by MHC molecules (Flajnik and Kasahara, 2010). The spleen and kidneys also belong to the lymphoid organs in bony fish and represent an analog to bone marrow in mammals (Uribe et al., 2011).

IgM is the main antibody class in all fish; IgD have some significance in bony fish and IgT is significant in some species (Flajnik and Kasahara, 2010; Uribe et al., 2011). In addition to IgM, cartilaginous fish have IgHAR (primitive single-chain antibodies), IgR

(IgX), and IgW. All of these fish have an archaic clustered-type of V-gene organization, since their segments are already combined in the embryonic genome (Dooley and Flajnik, 2006; Litman et al., 1999). Monomer IgM contains four chains (2L and 2H) and, hence, two paratopes. Several IgM monomers form multidimensional tetrameric Ig (in most fish) or pentameric Ig (in mammals), which can activate a classic complement pathway after interaction with the antigen (Nonaka and Yoshizaki, 2004). Exudative inflammation and phagocytosis effectiveness can be enhanced in fish via complement activation. Immune complex pathology is possible in bony fish: deposition of the antigen–IgM–complement complex in the microvessels (Sami et al., 1992).

The fish B-lymphocytes that secret antibodies represent phagocytes, which recognize phagocytosis targets via transmembrane Ig (the antigen-recognizing part of the B-cell receptor) and complement receptors (CRs). They have a certain grade of functional similarity with mammalian B_1 cells, including the ability to present antigens to T helpers (Th) (Zhuet al., 2014). B-cells became specialized only upon the secretory function (B_2-lymphocytes) in mammals (Zimmerman et al., 2010). In terms of other vertebrate classes, one can speak only of nonclassic variants of B_1 and B_2 cells.

In general, IgM allowed jawed fish to more effectively recognize viruses and other parasites with a low PAMP density on their surface and to bind soluble toxins and other infectious pathogenicity factors in the extracellular environment. However, this efficacy is relatively low; thus, more highly organized vertebrates, tetrapods, evolved radical advancement of the components involved in antibody generation.

Meanwhile, jawed fishes had an apparent evolutionary success in the development of T-cell mechanisms of immune response and inflammation associated with MHC-restricted TCRαβ.

APPEARANCE OF $CD8^+$ CYTOTOXIC LYMPHOCYTES

Recognition of their own infected cells is a major problem for all vertebrates. In the cells of jawed vertebrates, a certain amount of any protein synthesized on ribosomes is partially hydrolyzed. The resulting oligopeptide fragments are then combined inside the cell with two chains of class 1 MHC proteins (MHC I), and this complex is seen on the cytoplasmic membrane (Wieczorek et al., 2017). MHC I proteins are expressed on most nucleated cells of jawed animals. These proteins are controlled by cytotoxic T lymphocytes (CTLs). They recognize the antigen–MHC I complex not only by TCRαβ but also by the CD8 contact receptor (Abbas et al., 2017). This receptor binds to one of the constant MHC I domains and transmits an additional activation signal inside CTLs. The activated CTLs then trigger an apoptosis program in the infected cell or lyses the cell with cytotoxic factors, including the perforin protein, which is an analog of the membrane attack complex of the complement (Nakanishi et al., 2015). In an area of inflammation, CTLs cooperate with NK; CTLs act as regulatory cells and secrete interferon IFN-γ, which enhances the activity of macrophages for the destruction of intracellular parasites (Abbas et al., 2017). To a lesser extent, CTLs secrete tumor necrosis factor TNF-α, which has a wider range of proinflammatory effects (Buchholz et al., 2012). In turn, CTL generation is triggered by macrophage IL-15, which upregulates the expression of Runx3 and STAT5 transcription factors (Yamaguchi et al., 2015). These CTL mechanisms are found in all jawed animals, starting with the most primitive species of cartilaginous fish (Venkatesh et al., 2014). They retained their relative stability and biological significance throughout vertebrate evolution up to humans (Nakanishi et al., 2015; Yamaguchi et al., 2015).

FORMATION OF MHC CLASS II-RESTRICTED $CD4^+$ T HELPER CELLS

During inflammation, certain populations of white blood cells are selectively attracted to the inflammatory focus by different types of chemoattractants; these lymphocytes then release proinflammatory regulatory factors, primarily cytokines (Abbas et al., 2017). Macrophages and T cells in the inflammatory focus can be divided into subpopulations that exert selective activity against a particular damaging factor (Hodgkinson et al., 2015). As early as at beginning of vertebrate evolution, vertebrates needed to regulate inflammatory cells. In jawed vertebrates, $CD4^+$ T helpers (THs) began to orchestrate the cytokine network and recognized an antigen displayed by MHC II molecules (Jiang and Chess, 2006). In addition, CD4 is a coreceptor of TCR and assists in TCR binding with MHC II.

In contrast to MHC I, MHC II products usually present to T cells as fragments of external proteins absorbed by phagocytosis or pinocytosis (Wieczorek et al., 2017). Therefore, MHC II–dependent mechanisms of immunity have become a weapon against extracellular pathogens.

MHC II can be expressed by cells directly involved in TH induction (B_1-cells, dendritic cells in lymphoid organs) and inflammatory effector cells: phagocytic leukocytes, macrophages, platelets, mastocytes, postcapillary venule endothelial cells, and B_2-cells during antibody production (Pan-Yun Ting and Trowsdale, 2002). These interactions are needed both to generate THs from low-differentiated precursors and to implement the effector and regulatory functions of THs (Abbas et al., 2017). In contrast to MHC I, the expression of MHC II proteins on the cell membrane

Table 1. Variants in the development of cell-mediated immunoresponse in productive inflammation in mammals (homologs of the presented genes encoding transcription factor, cytokines, and their receptors were revealed in bony fish, Yamaguchi et al., 2015; Zou and Secombes, 2016)

i	THs (transcription factors), production (→) and sensing (←) of key cytokines	M (transcription factors), production (→) and sensing (←) of key cytokines and enzymes
i1	Th1 (T-bet, STAT4, STAT1) → IFN-γ; Th1 ← IL-12, IFN-γ, **IL-4***, **IL-10*** CTL (Runx3, STAT5) → IFN-γ; CTL ← IL-15, **IL-10*, TGF-β***	M1 (STAT1, NF-κB) → TNF-α, IL-1β, IL-6, IL-10 (↓), IL-12 (↑), IL-15, IL-23; M1 ← IFN-γ, TNF-α, **IL-10***, **TGF-β***; iNOS
i2	Th2 (GATA3, STAT6, STAT3) → IL-4, IL-5, IL-13; Th2 ← IL-4, IL-33, **IFN-γ***, **TGF-β***	M2a (STAT6, STAT1, GATA3) → IL-6, IL-10; M2a ← IL-4, IL-13, IL-33; ARG-1
i3	Th17 (RORγt, STAT3, STAT4, FOXP3, SMAD2, SMAD3) → IL-17A/F, IL-21, IL-22; Th17 ← IL-1β, IL-6, IL-23, **IL-10***	M2b → TNF-α, IL-1β, IL-6, IL-10, IL-12 (↓); iNOS; M2b ← IL-17A/F, TNF-α, IL-1, IL-6, IL-23, **IL-10***
i-reg	Treg (FOXP3, STAT3/5, SMAD2/3, GATA3, RORγt) → IL-10, TGF-β; Treg ← IL-2, IL-10, TGF-β	M2c (SMAD2, SMAD3, STAT3) → IL-10 (↑), TGF-β; ARG-1; M2c ← IL-10, TGF-β

Marker enzymes of M characterizing their individual subpopulations: iNOS—inducible NO-synthase, ARG-1—arginase-1 (involved in the synthesis of extracellular matrix proteins). Key cytokines released by cells or affecting their differentiation are shown (see direction of arrows): ↑—high level of cytokine production, ↓—low level of cytokine production. Cytokines that act as suppressor factors in a particular case are highlighted in bold and *. The transcription factors involved in the formation and differentiation of the corresponding THs and M subpopulations are presented in parentheses; the most important are underlined.

depends more strongly on the functional state of cells and their maturation status.

Different $CD4^+$ TH subpopulations are differentiated from their precursors (naive $CD4^+$ T cells) under the effect of various cytokines upon contact with antigen-presenting cells. Further, mature THs migrate from lymphoid organs to an inflammation area and interact with effector cells by means of MHC-II molecules and cytokines. The interaction between THs and macrophages (M) is most critical. Thus, monocytes migrating to the inflammatory focus give rise to inflammatory macrophages, which can differentiate into several subsets in response to the action of various cytokines. There are two main competitive variants of TH and M differentiation: (1) the classic pathway with the first type of TH and M generation (Th1 and M1); (2) an alternative pathway with the formation of the second type of TH and M (Th2 and M2) (Yamaguchi et al., 2015).

The presence of a dominant pathway of the TH ↔ M relationship determines the nature of cellular inflammation. The TH and M interactions have been quite well determined for mammals (human, mouse). Meanwhile, even for these species, the classification of TH and M subsets is primarily based on in vitro studies, whereas these interactions in vivo are more sophisticated and less studied. The latter is especially true for other classes of jawed animals. Therefore, there is a need for at least a general distinguishing of the most basic vectors in the polarization of immune reactivity (i) associated with a particular pathway of TH ↔ M interaction (Table 1) (Yamaguchi et al., 2015).

Next, the characteristics of vectors in mammalian immune reactivity are briefly described, since they have been better studied (Banchereau et al., 2012; Olson et al., 2013; Yamaguchi et al., 2015; Abbas et al., 2017).

Response i1 is driven by Th1 ↔ M1 interaction; NK and CTLs are also involved in this response. This vector of immune response competes with i2. Thus, i1 cytokines (primarily, the Th1 cytokine IFN-γ) restricts i2, and cytokines i2 (mainly the Th2 cytokine IL-4) restrict i1 (Table 1). Indeed, an alternative use of arginine by macrophages is observed in these two responses: either for the production of NO radical (M1), which has an expressed bactericidal activity, or the biosynthesis of extracellular matrix proteins (M2a) (Zenkov et al., 2007). Vector i1 is particularly effective against intracellular parasitic infection and for antitumor immunity. It is activated during allograft rejection, classic mononuclear delayed-type hypersensitivity reaction, and some autoimmune processes. Nevertheless, this response can damage the organism's own tissues due to the secretion of free radicals and hydrolases by M1.

Response i2 is driven by the Th2 ↔ M2a interaction (Table 1). Eosinophils, basophils, and mast cells are also involved in this response. It is most appropriate against metazoic infection, in some types of chronic inflammation, postinflammatory regenera-

tion and tissue repair, and inflammatory processes in tissues sensitive to damage, such as the uterus, but this response can also contribute to fibrosis in the internal organs (Yamaguchi et al., 2015). Response i2 is characteristic of a delayed-type, hypersensitivity, allergic reaction mediated by basophils and eosinophils. In addition, the dominant i2 response can contribute to the development of intracellular infection and tumor growth (Abbas et al., 2017). Pleotropic Th9, as the main producer of IL-9, similar to Th2, is involved not only in the development of allergic diseases and response to metazoic infection (i2); they also take part in antitumor immunity (i1) (Kaplan et al., 2015). In fish, an IL-9 homolog has not yet been identified.

Response i3 is driven by Th17 ↔ M2b interaction and linked to neutrophils. The i3 vector conflicts less with other variants of TH responses (Table 1) and is mainly triggered against extracellular bacterial and fungal infections (Yamaguchi et al., 2015). In mammals, Th17 (IL-17A and IL-17F producers) are involved in autoimmune inflammation, some types of delayed-type hypersensitivity, graft rejection, and antitumor immunity (Onishi and Gaffen, 2009). The i3 vector also includes Th22; they more actively produce IL-22. These THs are more related to the processes of the postinflammatory regeneration of cover tissues (Lanfranca et al., 2016). Upon activation by immune complexes, complement, and PAMP, inflammatory macrophages that are functionally close to M2b and M1 may form (Murray et al., 2014; Yamaguchi et al., 2015).

Response i-reg is triggered in parallel with other variants of immune response as a restriction mechanism to prevent the pathological development of proinflammatory mechanisms. Natural $CD4^+$ T-regulatory cells (Tregs) are cells involved in the immunosuppressive response; they secrete IL-10 and TGF-β and interact with M2c (Table 1) (Banchereau et al., 2012; Yamaguchi et al., 2015). Other cells involved in the immunosuppressive response are antigen-specific Tr1, which releases IL-10, and Th3 (Tr2), which predominantly secretes TGF-β (Zheleznikova, 2011). The TGF-β cytokine is involved in the sclerosing of damaged tissues and Th17 differentiation, but less actively than IL-10; it restricts bactericidal and cytotoxic phenomena induced by i1 and i3. Excessive activation of i-reg suppresses i1- and i3-dependent inflammation, and a low activity of this pathway causes autoimmune diseases.

Meanwhile, M1–M2 macrophage polarization in mammals can include a more complex array of macrophage subpopulations (Murray et al., 2014). Innate lymphoid cells (ILC) can also participate in the polarization of i1 (ILC-1), i2 (ILC-2), and i3 (ILC-3) (Yamaguchi et al., 2015). Different immune reactivity vectors can have functional overlap zones (Yamaguchi et al., 2015). TH differentiation is adaptive and occurs in response to a certain spectrum of cytokines: Treg can be differentiated into Th17 or Th2, and Th17 can be differentiated into Th1 and Th2 into $CD4^+$ T cells, which simultaneously produce IL-4 (i2) and IFN-γ (i3) (Wang et al., 2010; Olson et al., 2013). Inflammation can involve different variants of the immunoresponse. All of these factors affect the dynamics of inflammation and its adaptation to the damaging factor, and they also complicate the assessment of inflammation in vivo.

A multitude of facts have suggested that bony fish possess all four vectors of immune reactivity. Thus, homologs corresponding to those in mammals were revealed at the genetic level for most key transcription factors, cytokines, and the receptors of all four immune response vectors in bony fish (Table 1). This conclusion is based on numerous studies of fish genomes presented in a range of reviews (Yamaguchi et al., 2015; Zou and Secombes, 2016). Next, bony fish were found to have $CD4^+$ T cells, counterparts of mammalian Th1 and Th2, by the gene expression of cytokines and transcription factors (Maisey et al., 2016). Macrophage polarization toward M1 and M2 phenotypes was revealed in bony fish (Forlenza et al., 2011; Wiegertjes et al., 2016). These fish are also characterized by a dominant i2 gene expression in the gill apparatus, which is an organ susceptible to damage (Yamaguchi et al., 2015). Bony fish can develop the classic, mononuclear, delayed-type, hypersensitivity reaction (i1) to infectious antigens (Feng and Woo, 1996). They can effectively (in less than 14 days) trigger secondary allograft rejection via productive inflammation (i1 and i3) (Romano et al., 2005). In addition, $CD4^+$ and $CD8^+$ T cells (more likely i1) (Shibasaki et al., 2015) accumulate in the inflammatory focus during transplant rejection. In bony fish, experimental autoimmune encephalitis (probably i1 and i3) can be induced (Quintana et al., 2010). Focal fibrosis (i2, i-reg) of parenchymal organs was observed during chronic inflammation (Feist and Longshaw, 2008). Mast cells and eosinophils in bony fish are involved in antimetazoan immunity (i2) (Reite and Evensen, 2006). At the same time, mainly granulocyte recruitment, granuloma formation (i2, i3), and fibrosis of the injured epidermis (i2, i3, i-reg) have been detected only in tetrapods, whereas delayed-type recruitment of hypersensitivity eosinophil (i2) has been revealed in birds and mammals (Montali, 1988; Hill et al., 2010; Abbas et al., 2017).

The development of the $CD4^+$ Th response during fish evolution was probably not as discrete as the appearance of $CD8^+$ CTLs. To illustrate, there are two examples.

First, genome mapping of *Callorhinchus milii*, a cartilaginous fish (Chondrichthyes) belonging to the subclass Holocephali (chimaera) that evolved from sharks and skates 400 million years ago, showed that their genome is characterized by a slow rate of evolutionary changes. This species has all of the characteris-

tic features of i1 and polymorphic MHC II genes, but it lacks the genes for CD4, cytokines i2 (IL-4, IL-5, IL-13), some cytokines i3 (IL-21, IL-23), and i-reg (IL-2), as well as important transcription factors RORγt (i3) and FOXP3 (i-reg) (Venkatesh et al., 2014).

Second, a reduction of MHC II genes (probably due to influence of the habitat) occurred during the evolution of the Atlantic cod *Gadus morhua*, a bony fish species belonging to the group of ray-finned fishes (class Actinopterygii), but they trigger productive inflammation and the generation of $CD8^+$ CTLs and IgM (Nederbragt et al.,2011). Apparently, some functions of $CD4^+$ TH are redistributed between other mechanisms of adaptive and innate immunity in these fish.

In general, the majority of productive-inflammation phenomena that depend on THs in mammals were detected to some extent in bony fish.

FORMATION OF NEW CLASSES OF IMMUNOGLOBULINS IgG, IgA, IgE, AND IgY IN TETRAPODA

Compared to the progress in the development of different variants of productive inflammation, the cytokine network, and the irreplaceable function of CTLs, the evolutionary success of antibody generation in fish seems modest. IgM antibodies have a limited functional potential, including an increased affinity to an antigen during antibody generation, as well as the ability to effectively bind soluble antigens and penetrate the inflammatory focus and various tissue compartments from bloodstream. Due to the relatively high avidity provided by several centers of antigen binding, IgM can effectively activate the complement system. However, an alternative pathway of complement activation in fish plays no less an important role than the classic one. The alternative pathway can function successfully at a relatively low body temperature (Nonaka and Yoshizaki, 2004).

The situation changed dramatically with the appearance of new classes of antibodies in tetrapods. This evolutionary acquisition led to the emergence of new functions in B-lymphocytes and additional regulatory function in $CD4^+$ TH for an increase Ig affinity, the formation of long-lived immune memory B-cells and, finally, a switch of antibody generation in plasma cells from IgM to other classes of light (mainly monomer) antibodies (Zimmerman et al., 2010). Thus, in addition to IgM, amphibians, reptiles, and birds have a new main class of serum antibodies, i.e., IgY (Litman et al., 1999). In mammals, duplications and mutations of the heavy chain genes of IgY resulted in the formation of several other antibody classes: IgG, IgA (present in reptiles and birds), and IgE (Flajnik, 2002). In addition, tetrapods exhibited a gradual evolution in antibodies. Thus, due to their relatively slow and less stable adaptive humoral reactions, reptiles rely substantially on natural IgM antibodies (Zimmerman et al., 2010).

The main classes of antibodies are IgG in mammals and IgY in birds; they are differentiated into several subclasses with different functions, e.g., IgG_1, IgG_2, IgG_3, and IgG_4 in humans (Abbas et al., 2017). In mammals, the main THs involved in antibody generation are $CD4^+$ follicular THs (Tfh) (Zou and Secombes, 2016), which actively secrete IL-21 and a range of Th1- and Th2-dependent cytokines. They promote a switch in IgM synthesis to IgG and IgA in B cells. The Tfh homologs have not yet been identified in other classes of vertebrates. The class of secretory antibodies IgA (which enhance the barrier properties of mucus) has been detected in humans, but not in all species of mammals and birds. IgE generation occurs in response to low levels of soluble antigens without preliminary IgM synthesis and requires the participation of Th2 rather than Tfh cells (Abbas et al., 2017).

Different cells recognize antigen–antibody complexes via receptors to the heavy chain Fc-fragment of the immunoglobulin. Different types of phagocytes interact mainly with aggregated IgG associated with the corpuscular antigen by several types of FcγR: FcγRI, FcγRII, and FcγRIII (Bournazos et al., 2016). FcγRI can also bind free IgG. In turn, free IgE binds to the high affinity FcεRI on mastocytes. The interaction of the IgE–FcεRI complex with the antigen initiates rapid degranulation of mast cells, leading to an enhanced immediate-type hypersensitivity reaction (EIHR) (Beghdadi et al., 2011). Mammals were also revealed to carry the FcαR receptors (to IgA) and the low-affinity receptor FcεRII (Abbas et al., 2017). Birds have several types of FcR to IgY (FcυR), including the high-affinity receptor CHIR-AB1 (Viertlboeck et al., 2007).

IgG is the main class of antibodies in mammalian blood plasma. This immunoglobulin penetrates various bodily fluids well via the placental barrier, as well as the inflammatory focus, and it has a wide range of proinflammatory functions: opsonization (IgG_1 is more involved), the binding of toxins and bacterial capsular antigens (IgG_2), complement activation (IgG_3), and the regulation of mast cell functions (IgG_4) (Vidarrson et al., 2014). Upon incomplete hydrolysis in an inflammation area, IgG is cleaved into tuftsin (Thr-Lys-Pro-Arg tetrapeptide) and some other activators of phagocytosis (Fridkin and Najjar, 1989). IgG and IgM antibodies play a role in the pathogenesis of many autoimmune diseases, including immune-complex-mediated pathology (Weissmann, 2009). Adaptive IgG and IgY (at least, in birds), along with the complement, are the main factors involved in opsonization of extracellular bacteria; in addition, granulocytes (neutrophils in mammals and heterophils (pseudoeosinophils) in reptiles and birds) are the main populations of leukocytes mediat-

ing phagocytosis of opsonized bacteria (Bournazos et al., 2016).

IgE can effectively recognize soluble molecules, including toxins and helminth antigens. IgE-dependent EIHR is involved in rapid exudative reaction, mucosal secretion, and the contraction of smooth muscles in the bronchi and intestine (Abbas et al., 2017). EIHR is important for immediate-type allergic reactions, including anaphylactic shock in mammals. A similar reaction but with a slower developmental dynamics in response to bovine serum albumin is observed in chickens (Chand and Eyre, 1978). Systemic anaphylactic reactions have not been described for amphibians and reptiles. Anaphylactic shock in mammals is characterized by not only an expressed and rapid reaction; it also has distinctive species-related characteristics, e.g., in dogs, rabbits and Guinea pigs (Abbas et al., 2017).

In general, mammalian IgG and IgE are homologous in function but more perfect than IgY in birds and, especially, amphibians and reptiles. In reptiles, immunoglobulins of new classes exert their protective functions in a less contrasting way as compared to more archaic forms of antibody generation. The mentioned progress in the system of antibody generation has given new opportunities for all areas of the immunoresponse: virus binding in the extracellular medium (i1); EIHR (i2); pathogen opsonization and the hormone-like effects of IgG cleavage products, which activate phagocytosis (i3); expression of the suppressor FcγR (for example, FcγRIIB) and FcυR on phagocytes (i-reg) (Viertlboeck et al., 2007; Windau et al., 2013).

EVOLUTION OF MECHANISMS INVOLVED IN EXUDATIVE AND EXUDATIVE–DESTRUCTIVE INFLAMMATION IN VERTEBRATES

Exudative–destructive inflammation was an evolutionary response to the invasion of extracellular bacteria (Montali, 1988). It is triggered in the case of the failure of other types of inflammation that are less harmful to the organism's own tissues. The exudative–destructive type of inflammation is commonly initiated in response to a high load of extracellular pathogenic bacteria in the inflammatory focus; it is characterized by an increased microvascular permeability, exudation of plasma proteins (including the complement proteins, antibodies, and acute-phase proteins), granulocyte recruitment into inflammation areas, and the release of inflammatory factors by granulocytes. Heterophils/neutrophils, the complement system, and IgY/IgG (IgM probably also plays a significant role in reptiles) are the driving force of this type of inflammation. Neutrophils and heterophils, along with lymphocytes, dominate the leukocyte count in higher vertebrates (Claver and Quaglia, 2009; Montali, 1988). In addition, in acute inflammation, heterophils in birds and neutrophils in mammals are recruited into the circulation system from the bone marrow and vascular depot in response to the action of glucocorticoids and cytokines (Harmon, 1998).

Exudative–destructive inflammation can be triggered only in the higher vertebrates: in the form of caseous necrosis in reptiles and birds and in the form of suppurative tissue dissolution in mammals (Montali, 1988; Harmon, 1998). Secondary tissue destruction at the inflammation focus is related to the phenomenon of "unfulfilled phagocytosis" (the situation in which a phagocyte encounters a large object and fails to engulf the object because the size of the object is much larger than the phagocyte size), with a significant release of free radicals, hydrolases, cationic proteins, and extracellular DNA traps (Abbas et al., 2017). At the same time, free radicals not only damage their own tissues but also inactivate antiproteinases (MacNee and Tuder, 2009), contributing to tissue decay. Suppurative inflammation has a significant advantage over caseous necrosis, i.e., it can remove irreversibly damaged tissue from the body. However, reptiles and birds have evolutionarily abandoned this progressive variant of inflammation and have a lower level of proteinase activity and free radical production in heterophils than in neutrophils, including that due to the myeloperoxidase gene reduction, which is already detected in bony fish (Claver and Quaglia, 2009; Harmon, 1998). The probable cause of this abandonment is the inability to control this process due to the vascular barrier, i.e., the mechanisms of the exudative vascular complex (EVC). It is a morphofunctional complex of microvessels, mastocytes, the hemostatic system, the complement, and the kinin-kallikrein system. Suppurative inflammation is also impossible without the effective removal of directly or indirectly damaging factors (including PAMP and DAMP) from the bloodstream, the effective purification of lymph flowing out of the inflammation area, and the systemic adaptive reactions of the neuroendocrine, immune, and other systems. In addition, suppurative inflammation involves to some extent the immune mechanisms employed by other types of inflammation: the formation of the barrier cell infiltrates in granulation tissue during chronic pathology (for example, abscess), postinflammatory regeneration and repair (Abbas et al., 2017).

Thus, suppurative inflammation in mammals is not associated with the presence of a particular, fundamentally new immune mechanism, but it is a synthetic product resulting from the evolution of the many mechanisms involved in immunity and inflammation, particularly individual EVC components. Next, evolutionary changes of EVC are discussed in more detail.

Lymphatic system. Lymph hearts, a system of lymphatic slits and cavities have been documented in all jawed fish, some species of bony fish, and amphibians have primitive lymphatic vessels; reptiles possess a

lymphatic vascular network with smooth muscular and valve components, some species of birds have lymph nodes, and mammals contain a more developed network of lymphatic vessels and more advanced lymph nodes (Hedrick et al., 2013). Regional lymph nodes located close to an inflammation area provide local immunity and filter the lymph flowing from the inflammatory focus (which is particularly important in suppurative inflammation). In addition, the vertebrate lymphatic system has undergone significant evolutionary changes and corresponds well to the organizational level of species, their immune system, and programed mechanisms of inflammation.

Complement system. Like other plasma systems involved in inflammation, the complement system has undergone significant advancement during vertebrate evolution (Nonaka and Kimura, 2006). Cyclostomes have the alternative and lectin pathway for complement activation. The jawed fish additionally acquired the membrane attack complex (C5–C9), the ability to form anaphylaxines (C3a, C4a, C5a), a diverse repertoire of CR on phagocytes and mastocytes, and the classic activation pathway via C1q,r,s and C2C4 factors (which is primarily activated by IgM and C-reactive protein) (Nonaka and Yoshizaki, 2004). The cellular CR that bind C3b and C3bi and complement activation products are actively involved in phagocytosis. In bony fish, a multitude of complement inhibitors that prevent complement aggression against an organism's own cells appeared (Nonaka and Kimura, 2006). In mammals, anaphylaxines (C3a and C5a) form in the blood plasma, e.g., in response to the action of hemostasis factors: activated Hageman factor (XIIa), plasmin and thrombin (Nonaka and Yoshizaki, 2004). In turn, hormone-like anaphylaxines of the complement activate endothelial cells, platelets, and mastocytes and act as chemoattractants for neutrophils (Abbas et al., 2017). As noted, immune complex pathology related to the microvascular effects of the complement is already possible in bony fish. In mammals, an Arthus reaction is a pathology caused by the deposition of immune complexes containing not only IgM but also IgG. Intravascular activation of the complement systems In mammals with formation of anaphylaxines has an apparent role in pathogenesis of various allergic and autoimmune diseases and septic, traumatic, and anaphylactic shock (Klos et al., 2009; Zotova et al., 2016). In inflammation, complement activation is closely linked to the activation of other EVC components, including the hemostatic system and the kinin-kallikrein system.

System of hemostasis and kininogenesis. The hemostatic system probably appeared in the first vertebrates and initially performed two related functions: the cessation of bleeding and inflammation (Davidson et al., 2003). Cyclostomes have factor XIII and intrinsic pathway factors of blood coagulation in a simplified form: they do not have amplification of the clot-initiating signal gained form f. VIII + f. IX (Doolittle, 2011). The jawed fish evolved all of the major components of this pathway: factors X, IX, and VII; proteins C and S; tissue factor (TF); f. V and f. VIII; thrombomodulin, antithrombin III, and a complex system of plasminogen activation and its conversion to plasmin (fibrinolysin), including urokinase, tissue plasminogen activator, and α_2-antiplasmin (Davidson et al., 2003; Doolittle, 2011). In general, the activity of factors involved in thrombus formation increases in the order fish < amphibians < reptiles < birds < mammals. In particular, the ablood plasma of birds compared to mammals contains significantly fewer triggering factors, V and VII, and the birds do not trigger the formation of soluble TF or a lack of intravascular activation pathway via the Hageman factor in the case of damage (Doolittle, 2011).

EVC formation requires the mutual activation of the hemostatic system and endothelial cells. In roundmouths and cartilaginous fish, the endothelium can apparently be activated by fibrin degradation products. A constitutive receptor for thrombin, i.e., the proteinase-activated receptor 1 (PAR_1), appears on endothelial cells, mastocytes, and platelets in bony fish (Ellertsdottir et al., 2012). This receptor is activated by thrombin, as well as by platelet metalloproteinases in mammals. In mammals, the action on PAR_1 may trigger the contraction of actin cytoskeletal microfilaments, changes in the shape of endothelial cells in postcapillary venules, and the formation of small spaces between these cells (Bogatcheva et al., 2002). Only mammals have anuclear platelets (Levin, 2013), which allow effective microthrombus formation in postcapillary venules during inflammation. Mammalian platelets have a large repertoire of receptors, including TLR and other PRR, various CRs, PAR_1, FcγRII and FcεRI, receptors for biogenic amines, and various cytokines and eicosanoids. Upon activation they secrete numerous inflammatory mediators, including NO, chemokines, and other cytokines (Vieira-de-Abreu, 2012).

Cyclostomes, jawed fish, and amphibians have kininogen in the blood (Doolittle, 2011). It is cleaved by proteinases to form bradykinin, which dilates arterioles and increases microvascular permeability. The kinin-kallikrein system appears in reptiles, including kallikreinogen/kallikrein and high molecular kininogens, which act as precursors for a wide spectrum of kinins; the Hageman factor (f. XII) appears simultaneously in reptiles (Doolittle, 2011). It is activated (XII→XIIa) by a foreign surface and several endogenous factors and, along with some other serine proteases, catalyzes kallikrein formation from kallikreinogen; kallikrein effectively cleaves high-molecular kininogens to kinins. The internal pathway of hemostatic system activation was formed only in mammals with the appearance of factor XI, which is activated by f. XIIa. At the same time, f. XII and plasmin activate one another and the complement system with the for-

mation of C3a and C5a. The presence of f. XII is not a determinant condition for thrombosis, thrombolysis, or kininogenesis, since its gene is reduced in birds and marine mammals (Doolittle, 2011). More likely, the f. Hageman in mammals increases the degree of redundancy of the mechanisms that link the hemostatic system and antihemostasis with inflammation.

Thus, the system of plasma hemostatic factors was almost completely formed in the jawed fish, and the kallikrein-kinin system was in a fairly complete form in reptiles. Mammals evolved additional factors for the activation and integration of these systems, which act as EVC components. Furthermore, mammals possess more progressive anuclear platelets and postcapillary endothelial cells, which can trigger expressed microthrombosis and exudative reactions of the microcirculatory bed during inflammation.

Mast cells are a component of the APUD system of EVC. In mammals, mast cell degranulation is induced in response to myriad stimuli, including signals mediated by IgE and high-affine FcεRI (most strongly), via PRR, CRs and receptors to various inflammatory mediators, as well as in response to mechanical, thermal, and chemical damage (Abbas et al., 2017). The main functional goal of mastocytes is the rapid initiation of the exudative–vascular reaction, as well as the stimulation of mucus secretion and increased smooth muscle contractility (most quickly due to the effects of histamine) for the eradication of parasites and toxic substances from cavernous organs making contact with the external environment. Mammalian mast cells can release numerous cytokines, including IL-1β, TNF-α, and many Th2-dependent cytokines, cysteinyl leukotrienes, and other mediators, and they regulate inflammation without degranulation (Masuda et al., 2002; Theoharides et al., 2012).

Mast cells are found as early as in the roundmouths and are located mainly around skin microvessels and mucous membranes, as in other vertebrates (Crivellato and Ribatti, 2010). Mastocyte granules in fish mainly contain lysozyme, serotonin, heparin, glycosidases, bactericidal peptides, nucleosidases, phosphatases, and individual serine proteases, which facilitate changes in the extracellular matrix and cell migration from vessels (Crivellato and Ribatti, 2010). In bony fish, mastocytes upon activation secrete tryptase, a marker enzyme, that mediates a wide range of proteolytic and regulatory effects, including via kinin formation and binding to PAR_2, action on endothelial cells, various types of epithelial cells, and autocrine action on mast cells (Mulero et al., 2007). Only certain fish species contain histamine in mastocyte granules, in particular, the order Perciformes (Mulero et al., 2007). However, histamine in fish can participate in various neuroendocrine interactions that are not directly associated with inflammation and mastocytes. In amphibians, the presence of histamine in mast cells is not common, but they can secrete histamine-releasing factor as a component of skin poison that triggers the degranulation of mast cells and mucosal edema of the oral cavity in predators (Chen et al., 2005). Undoubtedly, the actions of histamine as a factor of exudative reactions are manifested in reptiles, birds, and, at, maximally, in mammals (Mulero et al., 2007; Beghdadi et al., 2011). As noted, mammals developed the most robust mechanism of mastocyte degranulation, which is associated with FcεRI and IgE (Beghdadi et al., 2011).

Thus, vertebrates had a relatively gradual development of individual EVC components, which reached maximal efficiency in mammals. This has accelerated and optimized the development of local manifestations of inflammation, particularly in the case of suppurative inflammation and EIHR. Meanwhile, mammals faced the problem of microcirculatory disorders due to systemic effects of damaging factors, including PAMP and DAMP accumulation in the bloodstream (Zotova et al., 2016), and IgE effects constitute a basis for systemic allergic EIHR reactions in the form of anaphylactic shock (Abbas et al., 2017).

RELATIONSHIP BETWEEN INFLAMMATION AND IMMUNITY WITH REGARD TO COMPARATIVE PATHOLOGY

The ability to combat infection and tumor growth in mammals is determined by a balanced relationship between the innate and adaptive mechanisms of immunity. These mechanisms, with the participation of neuroendocrine and cardiovascular systems, are involved in inflammation development. Disruption of this balance can be linked to many causes: environmental adverse effects, age-related changes, and genetic disorders. Congenital and acquired defects in these mechanisms lead to allergic and autoimmune diseases. A new class of monogenetic autoinflammatory diseases has been characterized recently in humans. It is associated with disorders in the genes of innate immune factors that control inflammation (Ciccarelli et al., 2013).

The diversity of pathologies associated with inflammation and immunity determines the need to select and characterize the most common patterns in their pathogenesis. In turn, inflammation as a typical pathological process is present not only in mammals but also in other classes of vertebrates, and many of its mechanisms are detected in invertebrates. In other words, inflammation is not only a general pathological phenomenon, but also a general biological one.

As shown above, bony fish exhibit significant similarities with mammals in their implementation of the main directions in the development of the immunoresponse and productive inflammation, even though the functions of individual subpopulations of THs and inflammatory macrophages in vertebrates, except for some mammal species, have been little studied. Like

mammals, bony fish suffer from the same classes of infectious diseases and tumor growth. They can trigger autoimmune processes, mononuclear delayed-type hypersensitivity, and immune complex disease.

Tetrapods evolved more progressive forms of antibody generation; the role of granulocytes and exudative reactions increased in inflammation. Higher vertebrates can trigger exudative–destructive inflammation: in the form of caseous necrosis for reptiles and birds and in the form of suppurative inflammation in mammals. These processes are a more effective form of protection against rapidly reproducing extracellular pathogens, but, at the same time their mechanisms can injure the organism's own tissues. Warm-blooded animals, especially mammals, have a more progressive neuroendocrine system, as well as a microcirculatory bed system and EVC. Therefore, birds and mammals can exert apparent manifestations of the general adaptation syndrome (Selye, 1950) and shock in the case of infections and injuries (Maloney and Gray, 1998). In addition, birds and mammals trigger local and systemic anaphylactic reactions by EIHR type. However, individual examples of such reactions in other classes of vertebrates need to be reverified in order to clarify the mechanisms of their pathogenesis (Gushchin, 2015).

The ability to respond to the systemic effect of damaging factors with a systemic reaction of all EVC components, shock, and multiorgan dysfunction is the hallmark of many mammalian species and, partially, birds. Most clearly, these distinctive features manifest in sepsis. Thus, systemic bacterial infections in fish and amphibians are characterized by microbial colonization of the gill apparatus, skin, muscles, internal organs, their erosion, ulceration, necrosis, vascular damage, and hemorrhage (Loch and Faisal, 2015; Hill et al., 2010; Sudheesh et al., 2012; Parto et al., 2014). A more expressed exudative reaction in the internal organs with fibrin deposition is observed in amphibians (Hill et al., 2010). It is associated in reptiles with multiple granulomas in the internal organs and, in the case of extracellular bacterial infections with high percentages of heterophils, injury to the heart, central nervous system (CNS), impaired breathing, disorders in movement coordination, and seizures (Montali, 1988; Woo et al., 2014). In birds, generalized infection is also manifested by secondary microbial colonization, often affecting the endocardium and myocardium, fibrin depositions in tissues, and granulocyte infiltrates; the main causes of lethal outcome are thromboembolism in vital organs and septic endocarditis (Montali, 1988; Lemon et al., 2012; Saumya et al., 2014). Meanwhile, birds, as well as mammals, can experience a CNS distress reaction, fever, profound acute-phase liver response, and in some cases, vascular shock developed by a type of septic shock in mammals (Maloney and Gray, 1998).

In humans, however, secondary microbial colonization of the internal organs, even bacteremia, is not a determinant for lethal outcome in sepsis (Munford, 2006; Rhee et al., 2015). In dogs, cats, and several other species of domestic mammals, infectious and aseptic critical conditions are characterized by an accumulation of cytokines and other phlogogenic factors in the blood, systemic microthrombosis, and microvascular activation during shock and multiorgan dysfunction (Osterbur et al., 2014). In humans, th administration of bacterial endotoxin (LPS) changes the expression of more than 3600 genes in leukocytes (Calvano et al., 2005). It was shown that the expression of numerous innate immunity genes changes at the systemic level, not only in blood but also in other tissues, in clinical sepsis and in mammalian models of experimental sepsis (Schulte et al., 2013; Maslove and Wong, 2014). Meanwhile, these processes in various mammalian species also have species-related distinctive features. For example, in an experimental septic shock model, cats and dogs exhibited greater resistance to LPS administration than primates, rabbits, and sheep (Garrido et al., 2004). In general, the complex of these changes can be defined as systemic inflammation (Zotova et al., 2016). The core in the pathogenesis of this process (a variant of nonclassic inflammation) is the systemic reaction of microvessels and other EVC components, as well as intravascular leukocyte activation in response to the generalized action of damaging factors (Tyagi et al., 2009; Zotova et al., 2016).

Thus, it is established that there is an evolutionary relationship between mammals and other classes of vertebrates based on common mechanisms of immunity, inflammation, and mediated pathologies. The progress of these mechanisms causes the occurrence of not only general regularities but also distinctive features in certain classes and species of vertebrates.

CONCLUSIONS

More progressive and adaptive evolutionary changes in morphological organization and functions were termed "aromorphosis" by A.N. Severtsov. In some cases, a sequence of several such changes, i.e., connected evolutionary stages, e.g., in CNS development in vertebrates, can be distinguished. In addition to the CNS, at least one other system in which these changes are most expressed can be distinguished, i.e., the immune system (innate and acquired). First of all, it triggers a particular variant of the inflammatory process. Common properties between the nervous and immune systems in vertebrates include the occurrence of acquired memory, the high-priority relationship in adaptation to environmental changes, and the complexity of these reactions in form of multilevel functional systems, including inflammation, which involves both of these systems. Evolutionary changes in these two systems reflect a general organizational level of vertebrate species.

Five qualitative evolutionary acquisitions can be identified in the development of the immune system and inflammatory process in vertebrates:

—the formation of classic adaptive immunity and classic inflammation in round-mouths (defective) and jawed vertebrates;

—the occurrence of the MHC I-mediated function of cytotoxic T lymphocytes and the exudative component of inflammation in jawed fish;

—the appearance of the MHC II-mediated function in T helpers and various forms of productive inflammation in most fish species;

—the formation of new classes (IgY, IgA, IgG, IgE) and subclasses of immunoglobulins with a wide range of proinflammatory functions in tetrapods, the appearance of exudative–destructive inflammation in higher vertebrates;

—the possibility of the development of suppurative inflammation in mammals as a result of a more progressive level of integration between innate and acquired mechanisms of the immune system, neuroendocrine regulation, and microvascular reaction.

Each evolutionary stage in the development of immunity and inflammation was associated with the need to correspond to the general organizational level of the species. In general, this process ensured the progressive development of vertebrates and their adaptation to changes in the environment. At the same time, there were "windows of vulnerability," including the development of an autoimmune process, fibrous changes in vital organs, thromboembolism, allergic diseases (at least in birds and mammals), and a life-threatening systemic inflammation, possibly in birds.

FUNDING

This study was performed within the framework of the State Task of the Institute of Immunology and Physiology, Ural Branch, Russian Academy of Sciences (registration no. NIOKTR AAAA-A18-118020590108-7) and the Complex Program of Ural Branch, Russian Academy of Sciences, no. 18-7-8-16 (registration no. NIOKTR AAAA-A18-118020590109-4).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflict of interest.

Statement of the welfare of animals. This article does not contain any studies involving animals or human participants performed by any of the authors.

REFERENCES

Abbas, A.K., Lichtman, A.H., and Pillai, S., *Cellular and Molecular Immunology*, Amsterdam: Elsevier, 2018.

Banchereau, J., Pascual, V., and O'Garra, A., From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines, *Nat. Immunol.*, 2012, vol. 13, no. 10, pp. 925–931.

Beghdadi, W., Majene, L.C., Benhamou, M., et al., Mast cells as cellular sensors in inflammation and immunity, *Front. Immunol.*, 2011, vol. 2, art. ID 37.

Bogatcheva, N.V., Garcia, J.G.N., and Verin, A.D., Molecular mechanisms of thrombin-induced endothelial cell permeability, *Biochemistry*, 2002, vol. 67, no. 1, pp. 75–84.

Bournazos, S., Wang, T.T., and Ravetch, J.V., The role and function of Fcγ receptors on myeloid cells, *Microbiol. Spectrosc.*, 2016, vol. 4, no. 6, pp. 1–29.

Buchholz, V.R., Gräf, P., and Busch, D.H., The origin of diversity: studying the evolution of multi-faceted CD8+ T cell responses, *Cell. Mol. Life Sci.*, 2012, vol. 69, pp. 1585–1595.

Calvano, S.E., Xiao, W., Richards, D.R., et al., A network-based analysis of systemic inflammation in humans, *Nature,* 2005, vol. 437, pp. 1032–1037.

Claver, J.A. and Quaglia, I.E., Comparative morphology, development and function of blood cells in nonmammalian vertebrates, *J. Exot. Pet Med.*, 2009, vol. 18, no. 2, pp. 87–97.

Chand, N. and Eyre, P., Acute systemic anaphylaxis in adult domestic fowl—possible role of vasoactive lipids and peptides, *Arch. Int. Pharmacodyn. Ther.*, 1978, vol. 236, pp. 164–176.

Chen, T., Reid, C.N., Walker, B., et al., Kassinakinin S: a novel histamine-releasing heptadecapeptide from frog (*Kassina senegalensis*) skin secretion, *Biochem. Biophys. Res. Commun.,* 2005, vol. 337, no. 2, pp. 474–480.

Ciccarelli, F., De Martinis, M., and Ginaldi, L., An update on autoinflammatory diseases, *Curr. Med. Chem.*, 2013, vol. 21, no. 3, pp. 261–269.

Cooper, D. and Eleftherianos, I., Memory and specificity in the insect immune system: current perspectives and future challenges front, *Immunology*, 2017. https://doi.org/10.3389/fimmu.2017.00539

Crivellato, E. and Ribatti, D., The mast cell: an evolutionary perspective, *Biol. Rev. Cambridge Philos. Soc.*, 2010, vol. 85, no. 2, pp. 347–360.

Das, S., Li, J., Hirano, M., et al., Evolution of two prototypic T cell lineages, *Cell Immunol.*, 2015, vol. 296, no. 1, pp. 87–94.

Davidson, C.J., Tuddenham, E.G., and McVey, J.H., 450 million years of hemostasis, *J. Thromb. Haemostasis,* 2003, vol. 1, no. 7, pp. 1487–1494.

Dinarello, C.A., Historical insights into cytokines, *Eur. J. Immunol.,* 2007, vol. 37, pp. 534–545.

Dooley, H. and Flajnik, M.F., Antibody repertoire development in cartilaginous fish, *Dev. Comp. Immunol.,* 2006, vol. 30, nos. 1–2, pp. 43–56.

Doolittle, R.F., Coagulation in vertebrates with a focus on evolution and inflammation, *J. Innate Immunol.*, 2011, vol. 3, pp. 9–16.

Ellertsdottir, E., Berthold, P.R., Bouzaffour, M., et al., Developmental role of zebrafish protease-activated receptor 1 (PAR1) in the cardio-vascular system, *PLoS One,* 2012, vol. 7, p. e42131.

Feist, S.W. and Longshaw, M., Histopathology of fish parasite infections—importance for populations, *J. Fish Biol.*, 2008, vol. 73, no. 9, pp. 2143–2160.

Feng, S. and Woo, P.T.K., Cell-mediated immune response and T-like cells in thymectomized *Oncorhynchus mykiss* (Walbaum) infected with or vaccinated against the pathogenic haemoflagellate *Cryptobia salmositica, Parasitol. Res.*, 1996, vol. 82, no. 7, pp. 604–611.

Finstad, J. and Good, R.A., The evolution of the immune response. III. Immunologic responses in the lamprey, *J. Exp. Med.*, 1964, vol. 120, no. 6, pp. 1151–1168.

Flajnik, M.F., Comparative analyses of immunoglobulin genes: surprises and portents, *Nat. Rev. Immunol.,* 2002, vol. 2, pp. 688–698.

Flajnik, M.F. and Kasahara, M., Origin and evolution of the adaptive immune system: genetic events and selective pressures, *Nat. Rev. Genet.*, 2010, vol. 11, no. 1, pp. 47–59.

Forlenza, M., Fink, I.R., Raes, G., and Wiegertjes, G.F., Heterogeneity of macrophage activation in fish, *Dev. Comp. Immunol.*, 2011, vol. 35, no. 12, pp. 1246–1255.

Fridkin, M. and Najjar, V.A., Tuftsin: its chemistry, biology, and clinical potential, *Crit. Rev. Biochem. Mol. Biol.,* 1989, vol. 24, no. 1, pp. 1–40.

Fugmann, S.D., Messier, C., Novack, L.A., et al., An ancient evolutionary origin of the *Rag1/2* gene locus, *Proc. Natl. Acad. Sci. U.S.A.*, 2006, vol. 103, pp. 3728–3733.

Garrido, A.G., De Figueiredo, L.F.P., and Silva, M.R., Experimental models of sepsis and septic shock: an overview, *Acta Circ. Bras.,* 2004, vol. 19, no. 2, pp. 82–88.

Gushchin, I.S., IgE-associated hypersensitivity as a response on the failure of barrier function of tissue, *Immunologiya,* 2015, vol. 36, no. 1, pp. 45–52.

Harmon, B.G., Avian heterophils in inflammation and disease resistance, *Poult. Sci.*, 1998, vol. 77, pp. 972–977.

Hedrick, M.S., Hillman, S.S., Drewes, R.C., and Withers, P.C., Lymphatic regulation in nonmammalian vertebrates, *J. Appl. Physiol.*, 2013, vol. 115, pp. 297–308.

Herrin, B.R. and Cooper, M.D., Alternative adaptive immunity in jawless vertebrates, *J. Immunol.*, 2010, vol. 185, no. 3, pp. 1367–1374.

Hibino, T., Loza-Coll, M., Messier, C., et al., The immune gene repertoire encoded in the purple sea urchin genome, *Dev. Biol.*, 2006, vol. 300, no. 1, pp. 349–365.

Hill, W.A., Newman, S.J., Craig, L., et al., Diagnosis of *Aeromonas hydrophilia, Mycobacterium species*, and *Batrachochytrium dendrobatidis* in an African clawed frog (*Xenopus laevis*), *J. Am. Assoc. Lab. Anim. Sci.*, 2010, vol. 49, no. 2, pp. 215–220.

Hodgkinson, J.W., Grayfer, L., and Belosevic, M., Biology of bony fish macrophages, *Biology,* 2015, vol. 4, pp. 881–906.

Ivasaki, A. and Medzhitov, R., Regulation of adaptive immunity by the innate immune system, *Science,* 2010, vol. 327, no. 5963, pp. 291–295.

Jiang, H. and Chess, L., Regulation of immune responses by T cells, *N. Engl. J. Med.*, 2006, vol. 354, pp. 1166–1176.

Kaplan, M.H., Hufford, M.M., and Olson, M.R., The development and in vivo function of T helper 9 cells, *Nat. Rev. Immunol.,* 2015, vol. 15, pp. 295–307.

Klos, A., Tenner, A.J., Johswich, K.-O., et al., The role of the anaphylatoxins in health and disease, *Mol. Immunol.,* 2009, vol. 46, no. 14, pp. 2753–2766.

Koonin, E.V. and Makarova, K.S., CRISPR-Cas: evolution of an RNA-based adaptive immunity system in prokaryotes, *RNA Biol.,* 2013, vol. 10, no. 5, pp. 679–686.

Krautz, R., Arefin, B., and Theopold, U., Damage signals in the insect immune response, *Front. Plant Sci.*, 2014, vol. 5, no. 342.
https://doi.org/10.3389/fpls.2014.00342

Kreslavsky, T., Gleimer, M., and von Boehmer, H., $\alpha\beta$ *versus* $\gamma\delta$ lineage choice at the first TCR-controlled checkpoint, *Curr. Opin. Immunol.*, 2010, vol. 22, no. 2, pp. 185–192.

Lacoste, A., Jalabert, F., Malham, S.R., et al., Stress and stress-induced neuroendocrine changes increase the susceptibility of juvenile oysters (*Crassostrea gigas*) to *Vibrio splendidus, Appl. Environ. Microbiol.,* 2001, vol. 67, no. 5, pp. 2304–2309.

Lanfranca, M.P., Lin, Y., Fang, J., et al., Biological and pathological activities of interleukin-22, *J. Mol. Med.*, 2016, vol. 94, no. 5, pp. 523–534.

Lemon, M.J., Pack, L.A., and Forzan, M.J., Valvular endocarditis and septic thrombosis associated with a radial fracture in a red-tailed hawk (*Buteo jamaicensis*), *Can. Vet. J.*, 2012, vol. 53, no. 1, pp. 79–82.

Levin, J., The evolution of mammalian platelets, in *Platelets*, Michelson A., Ed., San Diego: Academic, 2013, ch. 1, pp. 3–25.

Litman, G.W., Anderson, M.K., and Rast, J.P., Evolution of antigen binding receptors, *Ann. Rev. Immunol.*, 1999, vol. 17, pp. 109–147.

Loch, T.P. and Faisal, M., Emerging flavobacterial infections in fish: a review, *J. Adv. Res.*, 2015, vol. 6, no. 3, pp. 283–300.

MacNee, W. and Tuder, R.M., New paradigms in the pathogenesis of chronic obstructive pulmonary disease, *Proc. Am. Thorac. Soc.*, 2009, vol. 6, no. 6, pp. 527–531.

Maisey, K., Montero, R., Corripio-Miyar, Y., et al., Isolation and characterization of salmonid $CD4^+$ T cells, *J. Immunol.*, 2016, vol. 196, no. 10, pp. 4150–4163.

Maloney, S.K. and Gray, D.A., Characteristics of the febrile response in Pekin ducks, *J. Comp. Physiol. B,* 1998, vol. 168, no. 3, pp. 177–182.

Maslove, D.M. and Wong, H.R., Gene expression profiling in sepsis: timing, tissue, and translational considerations, *Trends Mol. Med.*, 2014, vol. 20, no. 4, pp. 204–213.

Masuda, A., Yoshikai, Y., Aiba, K., and Matsuguchi, T., Th2 cytokine production from mast cells is directly induced by lipopolysaccharide and distinctly regulated by c-Jun N-terminal kinase and p38 pathways, *J. Immunol.*, 2002, vol. 169, pp. 3801–3810.

Montali, R.J., Comparative pathology of inflammation in the higher vertebrates (reptiles, birds and mammals), *J. Comp. Pathol.*, 1988, vol. 99, no. 1, pp. 1–26.

Mulero, I., Sepulkre, M.P., Meseguer, J., et al., Histamine is stored in mast cells of most evolutionarily advanced fish and regulates the fish inflammatory response, *Proc. Natl. Acad. Sci. U.S.A.*, 2007, vol. 104, no. 49, pp. 19434–19439.

Müller, W.E., Krasko, A., Skorokhod, A., et al., Histocompatibility reaction in tissue and cells of the marine sponge *Suberites domuncula* in vitro and in vivo: central role of the allograft inflammatory factor 1, *Immunogenetics*, 2002, vol. 54, no. 1, pp. 48–58.

Munford, R.S., Severe sepsis and septic shock: the role of gram-negative bacteremia, *Ann. Rev. Pathol. Mech. Dis.*, 2006, vol. 1, pp. 467–496.

Murray, P.J., Allen, J.E., Biswas, S.K., et al., Macrophage activation and polarization: nomenclature and experimental guidelines, *Immunity,* 2014, vol. 41, no. 1, pp. 14–20.

Nakanishi, T., Shibasaki, Y., and Matsuura, Y., T cells in fish, *Biology*, 2015, vol. 4, pp. 640–663.

Nederbragt, A.J., Jentoft, S., Grimholt, U., et al., The genome sequence of Atlantic cod reveals a unique immune system, *Nature,* 2011, vol. 477, no. 7363, pp. 207–210.

Nonaka, M. and Kimura, A., Genomic view of the evolution of the complement system, *Immunogenetics,* 2006, vol. 58, pp. 701–713.

Nonaka, M. and Yoshizaki, F., Evolution of the complement system, *Mol. Immunol.*, 2004, vol. 40, no. 12, pp. 897–902.

Ohta, Y. and Flajnik, M.F., Coevolution of MHC genes (LMP/TAP/class Ia, NKT-class Ib, NKp30-B7H6): lessons from cold-blooded vertebrates, *Immunol. Rev.,* 2015, vol. 267, no. 1, pp. 6–15.

Olson, N.C., Sallam, R., Doyle, M.F., et al., T helper cell polarization in healthy people: implications for cardiovascular disease, *J. Cardiovasc. Transl. Res.*, 2013, vol. 6, no. 5, pp. 772–786.

Onishi, R.M. and Gaffen, S.L., Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease, *Immunology*, 2010, vol. 129, no. 3, pp. 311–321.

Osterbur, K., Mann, F.A., Kuroki, K., and De Clue, A., Multiple organ dysfunction syndrome in humans and animals, *J. Vet. Int. Med.*, 2014, vol. 28, pp. 1141–1151.

Ottaviani, E., Franchini, A., and Malagoli, D., Inflammatory response in mollusks: cross-taxa and evolutionary considerations, *Curr. Pharm. Des.*, 2010, vol. 16, pp. 4160–4165.

Pan-Yun Ting, J. and Trowsdale, J., Genetic control of MHC class II expression, *Cell,* 2002, vol. 109, pp. S21–S33.

Parto, P., Haghighi, Z.M.S., Vaissi, S., and Sharifi, M., Microbiological and histological examinations of endangered *Neurergus kaiseri* tissues displaying red-leg syndrome, *Asiat. Herpetol. Res.,* 2014, vol. 5, no. 3, pp. 204–208.

Quintana, F.J., Iglesias, A.H., Farez, M.F., et al., Adaptive autoimmunity and Foxp3-based immunoregulation in zebrafish, *PLoS One*, 2010, vol. 5, no. 3, p. e9478.

Reite, O.B. and Evensen, O., Inflammatory cells of teleostean fish: A review focusing on mast cells/eosinophilic granule cells and rodlet cells, *Fish Shellfish Immunol.,* 2006, vol. 20, no. 2, pp. 192–208.

Rhee, C., Murphy, M.V., Li L., and Platt, R., Comparison of trends in sepsis incidence and coding using administrative claims *versus* objective clinical data, *Clin. Infect. Dis.,* 2015, vol. 60, no. 1, pp. 88–95.

Romano, N., Baldassini, M.R., Buonocore, F., et al., In vivo allograft rejection in a bony fish *Dicentrarchus labrax* (L.): characterization of effector lymphocytes, *Cell Tissue Res.,* 2005, vol. 321, pp. 353–363.

Rowley, A.F. and Powell, A., Invertebrate immune systems—specific, quasi-specific, or nonspecific? *J. Immunol.*, 2007, vol. 179, no. 11, pp. 7209–7214.

Russell, M.J., Dombkowski, R.A., and Olson, K.R., Effects of hypoxia on vertebrate blood vessels, *J. Exp. Zool. A*, 2008, vol. 309, no. 2, pp. 55–63.

Sami, S., Fisher-Scherl, T., Hoffman, R.W., and Pfeil-Putzien, C., Immune complex-mediated glomerulonephritis associated with bacterial kidney disease in the rainbow trout (*Oncorhynchus mykiss*), *Vet. Patol.,* 1992, vol. 29, no. 2, pp. 169–174.

Saumya, D., Wijetunge, S., Dunn, P., et al., Acute septicemia caused by *Streptococcus gallolyticus* subsp. *pasteurianus* in turkey poults, *Avian Dis.,* 2014, vol. 58, no. 2, pp. 318–322.

Schulte, W., Bernhagen, J., and Bucala, R., Cytokines in sepsis: potent immunoregulators and potential therapeutic targets—an updated view, *Mediators Inflammation,* 2013, art. ID 16597.

Selye, H., Stress and the general adaptation syndrome, *Br. J. Med.,* 1950, vol. 1, no. 4667, pp. 1383–1392.

Shibasaki, Y., Matsuura, Y., Toda, H., et al., Kinetics of lymphocyte subpopulations in allogeneic grafted scales of ginbuna crucian carp, *Dev. Comp. Immunol.,* 2015, vol. 52, no. 1, pp. 75–80.

Shilov, E.S. and Kuprash, D.V., Genetic mechanisms of adaptive immunity emergence in vertebrates, *Russ. J. Genet.*, 2016, vol. 52, no. 7, pp. 664–675.

Sidorova, E.V., B-1 lymphocytes: origin, differentiation, and functions, *Usp. Sovrem. Biol.,* 2009, vol. 129, no. 1, pp. 27–38.

Sudheesh, P.S., Al-Ghabshi, A., Al-Mazrooei, N., and Al-Habsi, S., Comparative pathogenomics of bacteria causing infectious diseases in fish, *Int. J. Evol. Biol.,* 2012, art. ID 457264.

Tassetto, M., Kunitomi, M., and Andino, R., Circulating immune cells mediate a systemic RNAi-based adaptive antiviral response in *Drosophila, Cell*, 2017, vol. 169, no. 2, pp. 314–325.

Theoharides, T.C., Alysandratos, K.-D., Angelidou, A., et al., Mast cells and inflammation, *Biochim. Biophys. Acta, Mol. Basis Dis.,* 2012, vol. 1822, no. 1, pp. 21–33.

Tyagi, A., Sethi, A.K., Girota, G., and Mohta, M., The microcirculation in sepsis, *Indian J. Anaesth.,* 2009, vol. 53, no. 3, pp. 281–293.

Uribe, C., Folch, H., Enriquez, R., and Moran, G., Innate and adaptive immunity in teleost fish: a review, *Vet. Med.,* 2011, vol. 56, no. 10, pp. 486–503.

Venkatesh, B., Lee, A.P., Ravi, V., et al., Elephant shark genome provides unique insights into gnathostome evolution, *Nature,* 2014, vol. 505, pp. 174–179.

Vidarrson, G., Dekkers, G., and Rispens, T., IgG subclasses and allotypes: from structure to effector func-

tions, *Front. Immunol.,* 2014, vol. 5, no. 520. https://doi.org/10.3389/fimmu.2014.00520

Vieira-de-Abreu A., Platelets: versatile effector cells in hemostasis, inflammation, and the immune continuum, *Semin. Immunopathol.,* 2012, vol. 34, no. 1, pp. 5–30.

Viertlboeck, B.C., Schweinsberg, S., Hanczaruk, M.A., et al., The chicken leukocyte receptor complex encodes a primordial, activating, high-affinity IgY Fc receptor, *Proc. Natl. Acad. Sci. U.S.A.,* 2007, vol. 104, pp. 11718–11723.

Wang, Y., Souabni, A., Flavell, R.A., and Wan, Y.Y., An intrinsic mechanism predisposes Foxp3-expressing regulatory T cells to Th2 conversion in vivo, *J. Immunol.*, 2010, vol. 185, pp. 5983–5992.

Weissmann, G., Rheumatoid arthritis and systemic lupus erythematosus as immune complex diseases, *Bull. Hosp. Jt. Dis.,* 2009, vol. 67, no. 3, pp. 251–253.

Welsch, U. and Potter, I.C., Dermal capillaries, in *The Biology of Hagfishes,* Dordrecht: Springer-Verlag, 1998, pp. 273–283.

Wieczorek, M., Abualrous, E.T., Sticht, J., et al., Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation, *Front. Immunol.,* 2017, vol. 8, no. 292. https://doi.org/10.3389/fimmu.2017.00292

Wiegertjes, G.F., Wentzel, A.S., Spaink, H.P., et al., Polarization of immune responses in fish: the macrophages first point of view, *Mol. Immunol.,* 2016, vol. 69, pp. 146–156.

Williams, M.J., *Drosophila hemopoiesis* and cellular immunity, *J. Immunol.,* 2007, vol. 178, no. 8, pp. 4711–4716.

Windau, K., Viertlboeck, B.C., and Gobel, T.W., The turkey Ig-like receptor family: identification, expression and function, *PLoS One,* 2013, vol. 8, p. e59577.

Woo, P.C.Y., Lau, S.K.P., Martelli, P., et al., Fatal systemic necrotizing infections associated with a novel paramyxovirus, anaconda paramyxovirus, in green anaconda juveniles, *J. Clin. Microbiol.,* 2014, vol. 52, no. 10, pp. 3614–3623.

Yamaguchi, T., Takizawa, F., Fisher, U., and Dijkstra, J.M., Along the axis between type 1 and type 2 immunity; principles conserved in evolution from fish to mammals, *Biology*, 2015, vol. 4, pp. 814–859.

Zenkov, N.K., Men'shchikova, E.B., and Shkurupii, V.A., Macrophage activation mechanisms, *Usp. Sovrem. Biol.,* 2007, vol. 127, no. 3, pp. 243–256.

Zheleznikova, G.F., Regulatory T-cells in immune response to infection, *Zh. Infektol.,* 2011, vol. 3, no. 1, pp. 6–13.

Zhu, L., Lin, A., Shao, T., et al., B cells in teleost fish act as pivotal initiating APCs in priming adaptive immunity: an evolutionary perspective on the origin of the B-1 cell subset and B7 molecules, *J. Immunol.,* 2014, vol. 192, no. 6, pp. 2699–2714.

Zimmerman, L.M., Vogel, L.A., and Bowden, R.M., Understanding the vertebrate immune system: insights from the reptilian perspective, *J. Exp. Biol.,* 2010, vol. 213, pp. 661–671.

Zotova, N.V., Chereshnev, V.A., and Gusev, E.Yu., Systemic inflammation: methodological approaches to identification of the common pathological process, *PLoS One,* 2016, vol. 11, p. e0155138.

Zou, J. and Secombes, C.J., The function of fish cytokines, *Biology,* 2016, vol. 5, no. 2, p. e23.

Translated by M. Novikova