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The role of purinergic signaling and cytokine network in the inflammatory process

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ABSTRACT

Introduction. Inflammation is a complex biological process essential for host defense against pathogens and tissue repair. This process is regulated by a variety of signaling molecules, among which purines and cytokines play an important role. Purinergic signaling mediated by adenosine triphosphate, adenosine monophosphate, and other nucleotides plays a key role in regulating immune responses and inflammatory processes. The cytokine network, including interleukins, tumor necrosis factor *α* and other molecules, is also an important component of inflammation, providing communication between cells of the immune system and regulating their activity. Understanding the purinergic signaling and the cytokine network interaction mechanisms is crucial for developing innovative treatments for inflammatory diseases.

Objective. To synthesize current research findings on the role of purinergic signaling and the cytokine network in inflammatory processes within animal models.

Materials and methods. 55 scientific publications by Russian and international authors (2000–2021) investigating the effects of nucleotides, nucleosides, and purinergic receptors on immune response development, macrophage activation, and cytokine release mechanisms were analyzed. Source databases included eLIBRARY.RU, CyberLeninka, PubMed, NCBI, ResearchGate, CABI, and Google Scholar.

Results. The analysis explored mechanisms of the inflammatory response, including the role of various cells and molecules – cytokines and receptors – in the regulation of the immune response. The latter plays an important role in activating immune system cells and regulating inflammatory reactions. The process of adenosine triphosphate dephosphorylation by CD39 and CD73 enzymes, which promotes the production of adenosine and the activation of anti-inflammatory mechanisms, is discussed. The functions of pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor *α* and interleukin-6 are analyzed in the context of macrophage activation and neutrophil migration to the site of inflammation. The importance of regulating these processes is emphasized in order to prevent excessive inflammatory response and ensure homeostasis. The mechanisms of transition between the phases of inflammation are examined, including the role of anti-inflammatory cytokines such as interleukin-10 and transforming growth factor *β* in controlling neutrophil activity and resolving the inflammatory process.

Conclusion. Further study of this topic can deepen the modern knowledge of scientists about the mechanisms of inflammation and create the basis for the development of innovative therapeutic strategies aimed at treating diseases caused by disorders of the immune system.

Keywords: review, nucleotides, receptors, purinergic regulation, CD39, CD73, ATP, ADP, AMP, adenosine, macrophages, cytokines, interleukins

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Роль пуринергической сигнализации и цитокиновой сети в воспалительном процессе

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РЕЗЮМЕ

Введение. Воспаление представляет собой сложный биологический процесс, направленный на защиту организма от патогенов и восстановление поврежденных тканей. Этот процесс регулируется множеством сигнальных молекул, среди которых важное значение имеют пурины и цитокины.

Пуринергическая сигнализация, опосредованная аденозинтрифосфатом, аденозинмонофосфатом и другими нуклеотидами, играет ключевую роль в регуляции иммунных реакций и воспалительных процессов. Цитокиновая сеть, включающая интерлейкины, фактор некроза опухоли *α* и другие молекулы, также является важным компонентом воспаления, обеспечивая коммуникацию между клетками иммунной системы и регулируя их активность. Понимание механизмов взаимодействия между пуринергической сигнализацией и цитокиновой сетью имеет важное значение для разработки новых стратегий лечения воспалительных заболеваний.

Цель исследования. Обобщение результатов исследований по значению роли пуринергической сигнализации и цитокиновой сети в воспалительном процессе у животных.

Материалы и методы. Проведен анализ 55 научных публикаций российских и иностранных авторов за период с 2000 по 2021 г., исследующих влияние нуклеотидов, нуклеозидов и пуринергических рецепторов на формирование иммунного ответа, а также механизмы активации макрофагов и выделения цитокинов. Для поиска источников использовались базы данных eLIBRARY.RU, CyberLeninka, PubMed, NCBI, ResearchGate, CABI и Google Scholar.

Результаты. Рассмотрены механизмы воспалительного ответа, включая роль различных клеток и молекул, таких как цитокины и рецепторы, в регуляции иммунной реакции. Последние имеют важное значение в активации клеток иммунной системы и регуляции воспалительных реакций. Обсуждается процесс дефосфорилирования аденозинтрифосфата с участием ферментов CD39 и CD73, что способствует образованию аденозина и активации противовоспалительных механизмов. Проанализированы функции провоспалительных цитокинов, таких как интерлейкин-1, фактор некроза опухоли *α* и интерлейкин-6, в контексте активации макрофагов и миграции нейтрофилов к месту воспаления. Подчеркивается важность регуляции этих процессов для предотвращения чрезмерного воспалительного ответа и обеспечения гомеостаза. Рассмотрены механизмы перехода между фазами воспаления, включающие роль противовоспалительных цитокинов, таких как интерлейкин-10 и трансформирующий фактор роста *β*, в контроле активности нейтрофилов и разрешении воспалительного процесса.

Заключение. Дальнейшее изучение данной темы способно углубить современные знания ученых о механизмах возникновения воспаления и создать основу для разработки инновационных терапевтических стратегий, направленных на лечение болезней, обусловленных нарушениями иммунной системы.

Ключевые слова: обзор, нуклеотиды, рецепторы, пуринергическая регуляция, CD39, CD73, АТФ, АДФ, АМФ, аденозин, макрофаги, цитокины, интерлейкины

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INTRODUCTION

Currently, innovative medicinal products are widely used in human medicine and veterinary medicine. The development of liposome-based medicinal products for targeted delivery of medicinal substance attracts the attention of scientists all over the world. Special attention is paid to the creation of immunomodulating liposomal medicinal products that specifically affect the macrophage component of the immune system. Scientists from the Laboratory of Veterinary Medicine and Biotechnology of the Federal Agricultural Kursk Research Center are working in this field. They proposed and tested a method for obtaining liposomal immunotropic composition for the pre-nosological prevention of pathologies in cattle of different ages in the settings of the Uchkhoz Znamenskoye of the Kursk State Agrarian University.

The immune system is a complex mechanism that helps to protect the body from pathogenic microorganisms. Nucleic acids, purinergic receptors, and cytokines play an important role in regulating immune system functions. These components are involved in a wide range of processes: from cell signaling to providing energy for active immune responses. Nucleotides such as adenosine triphosphate (ATP) act as key mediators in intercellular communication and intracellular signaling. Purinergic receptors that respond to extracellular nucleotides promote the activation of inflammatory processes and regulate the behavior of immune cells. Nucleosides, required for DNA and RNA synthesis, support the division and growth of immunocompetent cells, thus playing a vital role in adaptive immunity [1, 2]. By understanding how these mechanisms function, we can simulate potential inflammatory processes in animal models and develop methods to prevent pathologies.

Inflammation plays a key role in the animal immune response, protecting against infection, injury, and other harmful factors. This process is a complex and well-coordinated reaction that includes the activation of various cells of the immune system, release of cytokines and other mediators, as well as changes in blood circulation and vascular permeability. Inflammation is the body's initial defense against infection. When pathogens like bacteria, viruses, or fungi invade tissues, local immune cells such as macrophages and dendritic cells are triggered to initiate an immune response. When cells recognize a pathogen, they start to release pro-inflammatory cytokines, signaling molecules that attract other white blood cells to the site of infection. The inflammatory process recruits neutrophils and monocytes from the bloodstream to affected tissues. Neutrophils are the first responders to inflammation, phagocytosis of pathogens and releasing antimicrobial substances. Once in the tissues, monocytes differentiate into macrophages, which continue to destroy pathogens and promote tissue repair. Inflammation is not only aimed at fighting infection, but also at eliminating tissue damage [3, 4, 5].

Macrophages play an important role in the healing process by removing dead cells and cellular debris. They also release growth factors involved in tissue regeneration [4, 6, 7, 8, 9]. By presenting antigens to T lymphocytes, inflammation helps activate the adaptive immune response. Dendritic cells capturing pathogens during inflammation migrate to the lymph nodes, where they present antigens to T cells. This leads to the development of a specific immune response against specific pathogens. Although inflammation is necessary to protect the body, but its excessive or prolonged activity can lead to tissue damage and the development of chronic diseases. Therefore, it is important to have mechanisms for regulating the inflammatory response, such as anti-inflammatory cytokines (for example, interleukin IL-10) and other molecules that help resolve inflammation once the threat is eliminated. For veterinary medicine it is important to understanding the mechanisms of inflammation. Chronic inflammation is associated with a number of diseases in animals, including allergies, autoimmune disorders and metabolic diseases [2, 10].

The interaction of purinergic receptors with the cytokine network is an important aspect of the regulation of the immune response and inflammatory processes in the body. Purinergic receptors such as P2X and P2Y are activated by nucleotides such as adenosine and ATP and are important in the immune response in animals. Purinergic receptors regulate macrophage phagocytosis. This leads to the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), which play an important role in initiating and maintaining the inflammatory response. Adenosine signaling through P1 receptors (A2A and A2B) can suppress pro-inflammatory cytokines and promote anti-inflammatory cytokines, notably IL-10. This establishes a balance between pro-inflammatory and anti-inflammatory signals, that is crucial for preventing excessive inflammation and subsequent tissue damage. Purinergic receptors regulate leukocyte migration to inflammatory sites by detecting extracellular nucleotides like ATP released from damaged cells. This activation triggers immune cells to release chemoattractants such as IL-6 and IL-8, which in turn recruit and increase the number of immune cells at the site of inflammation [11]. Purinergic signaling interacts with other cellular pathways, including those associated with Toll-like receptors (TLRs). This interaction can enhance or modulate the response to infection or tissue damage. Purinergic receptors play an important role in maintaining immune homeostasis. They help regulate immune response activation and suppression, which is crucial for preventing autoimmune diseases and chronic inflammation [12, 13, 14, 15].

Thus, the interaction between purinergic receptors and the cytokine network is a complex, dynamic system vital for regulating immune responses and inflammatory processes. Understanding these interactions could facilitate the development of novel therapeutics for inflammatory and autoimmune diseases.

This study aims to systematize data reflecting the importance of purinergic signaling and the cytokine network in the development of inflammatory processes.

MATERIALS AND METHODS

This review is based on an analysis of 55 scientific publications by Russian and international authors, investigating the role of purinergic signaling and cytokine networks in regulating inflammatory responses. The literature search was conducted using major digital repositories, including eLIBRARY.RU, CyberLeninka, PubMed, NCBI, ResearchGate, CABI, and Google Scholar. Key search terms comprised the following: "purinergic regulation", "cytokine network", "CD39", "CD73", "ATP", "ADP", "AMP", "adenosine", "macrophages", "cytokines", "interleukins" and "tumor necrosis factor".

Publications were selected based on the following criteria: relevance to the research topic, scientific significance, methodological clarity, and the inclusion of a robust analytical discussion comparing the results with existing literature.

RESULTS AND DISCUSSION

Purinergic signaling in animals involves the interaction of purines, such as adenosine and ATP, with purine receptors that are located on the surface of cells. These receptors are divided into two main groups: P1 (adenosine) and P2 (ATP receptors) [2, 3, 4]. Adenosine functions as an anti-inflammatory and pro-healing molecule by interacting with P1 receptors, leading to reduced pro-inflammatory signals and enhanced immune cell regulation. Specifically, it suppresses the production of inflammatory cytokines and promotes tissue repair, playing a vital role in healing processes. On the contrary, ATP, particularly through P2 receptors, acts as a "danger signal" that activates immune cells like macrophages, leading to the release of pro-inflammatory cytokines such as IL-1β and TNF-α, thus promoting inflammation even tissue damage. ATP release is triggered by various cellular stress factors, including inflammation, hypoxia, apoptosis, and necrosis [3, 4, 5].

Inflammation and hypoxia (low oxygen) conditions promote the release of ATP and ADP (adenosine diphosphate) from cells, leading to increased extracellular adenosine levels [1, 11]. Hypoxia and HIFs increase extracellular adenosine concentrations by transcriptionally regulated genes involved in its adenosine metabolism and receptor expression [12, 13, 14, 15, 16, 17]. The critical role of extracellular adenosine metabolism is demonstrated in mice. Mice with genetic defects in ectonucleoside triphosphate diphosphohydrolase-1 (CD39) and ecto-5'-nucleotidase (CD73), exhibit reduced extracellular adenosine, leading to impaired adenosine signaling, even when ATP levels are normal or high. Adenosine signaling plays a key role in the lung's response to damage. Adenosine has complex and multifaceted effects on inflammation, repair, and remodeling by binding to G protein-coupled receptors on cell surfaces [18, 19, 20], causing both protective and destructive reactions. Its anti-inflammatory and protective-regenerative roles are primarily mediated through A2A and A2B receptor activation (A2AAR, A2BAR). Conversely, elevated adenosine levels can activate A1 (A1AR), A2BAR, and A3 (A3AR) receptors, promoting a pro-inflammatory state and dysregulated tissue remodeling that exacerbates chronic lung diseases [10, 21].

The role of purine nucleotides, nucleosides and purinergic signaling in acute and chronic inflammation has been extensively studied, particularly with regard to ATP, ADP and adenosine. In health ATP is found in mammalian cells. In disease, such as inflammation or ischemia, ATP is released from intracellular stores due to cellular necrosis [19, 20, 22, 23]. During apoptosis, pannexin hemichannels control ATP release into the extracellular space, where ATP serves as a phagocyte chemotactic signal [24]. Inflammatory cells, like neutrophils, and endothelial cells can release ATP into the extracellular space through connexin hemichannels [25, 26, 27, 28]. ADP can be released from intracellular platelet granules. ATP signals pass through receptors, initially designated as P2 receptors [25], and then reclassified into P2X receptors (ligand-gated ion channels) and P2Y receptors (G protein-coupled receptors). Mice with deleted P2 receptors are viable and they exhibit protection against inflammatory diseases like asthma, vascular inflammation, and "graft-versus-host disease" [18, 29, 30, 31, 32]. Pharmacological antagonism of P2 receptors has been shown to suppress inflammation in various conditions, including inflammatory bowel diseases, lung inflammation and ischemic reperfusion injury [26, 31, 33].

Adenosine's interaction with P1 receptors, which are G-protein coupled receptors, occurs in the extracellular environment. These receptors are categorized into four subtypes: A1, A2A, A2B, and A3. A1 and A2A receptors are known for their high affinity, while A2B and A3 receptors exhibit significantly lower affinity. All subtypes of adenylate cyclase affect the enzyme's function and the subsequent production of cyclic adenosine monophosphate (cAMP). The A2A and A2B receptors activate the process, while the A1 and A3 receptors inhibit it [2, 10, 11, 12].

The ATP molecule interacts with P2-purinergic receptors on the cell surface. These receptors are divided into two main types: P2X and P2Y. The P2X receptors are ion channels. This means that when ATP binds to the P2X receptor, it opens a channel allowing certain ions to enter the cell. Sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) ions pass through these channels. Thus, ATP, binding to the P2X receptor, triggers the process of moving these ions inside the cell (the flow of ions depends on the concentration gradient and electrical potential). This process plays an important role in cell signaling and various cellular functions [4, 5]. P2Y receptors are specialized proteins located on the cell's outer membrane and capable of recognizing ATP and ADP, as well as a number of similar substances. Upon binding a substance, the receptor activates a G protein, which then influences enzymes like adenylate cyclase and phospholipase C, and regulates ion channels, ultimately altering ion movement and thereby affecting degree of ion penetration into the cell. These receptors are present on the surfaces of the immune system cells and the endothelium – a layer of cells lining the walls of blood vessels from the inside [14, 15, 16].

Experiments on genetically modified mice lacking P2X and P2Y receptors have demonstrated that their absence does not impair normal development or reaching adulthood in animals. However, studies focusing on mice deficient in the P2X2 and P2X3 receptor (P2X receptor subtype) revealed immune dysregulation, characterized by an increased number of immune cells and enlarged spleen (that is an important part of the body's immune system). This phenotype indicates that P2X2 and P2X3 receptors play a critical role in modulating immune function; their absence may lead to an overly reactive immune response and immune system hypertrophy. These findings are supported by the work of A. Surprenant et al. [6] and E. Kaniewska et al. [7].

Research demonstrates that P2Y receptors play a complex role in regulating cellular activity and immune responses. Although the absence of P2X/P2Y receptors is not lethal, specific loss of the P2X2 and P2X3 subtypes results in pronounced alterations in immune system function [6, 15].

It has been established that ATP can be actively released from intact cells in response to stimuli like mechanical deformation, hypoxia (low oxygen), and acetylcholine, without causing cell damage [7, 11, 12]. For example, ATP release from intact cells was first observed in neurons secreting ATP into the synaptic cleft [13]. However, it has been shown that the underlying mechanism is very complex and includes stretch-activated channels, potential-dependent anion channels, P2X7 receptors, as well as connexin and pannexin hemichannels [14].

Contrasting to intracellular ATP, primarily utilized as energy, extracellular ATP is considered to be a powerful signaling molecule through the nucleotide-selective P2 receptors. Extracellular ATP is rapidly metabolized to adenosine by ectonucleotidases [25]. The ectonucleotidases consist of four family types including ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) family, ectonucleoside triphosphate diphosphohydrolase (ENTPDase) family, alkaline phosphatases (AP), and CD73 [15, 16]. Extracellular adenosine, an intermediate metabolite of nucleotides, can undergo three processes: conversion to inosine by adenosine deaminase, reconversion to AMP by adenosine kinase, and cellular reuptake through concentrative nucleoside transporters (CNTs) or equilibrative nucleoside transporters (ENTs) [15, 17, 18].

Purinergic receptors have been widely studied in signaling systems in response to extracellular ATP and related nucleotides. Purinergic receptors consist of three major families based on their structural and biological properties [19]. The G-protein-coupled P2Y receptors recognize ATP and several other nucleotides, including ADP, uridine triphosphate (UTP), uridine diphosphate (UDP), and UDP-glucose [20]. P2X receptors function as ATP-gated ion channels that facilitate the influx and efflux of extracellular cations, including calcium ions, which only respond to ATP [20, 22]. To date, P2Y receptors consist of eight subtypes, a family of P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14. P2X receptors have seven subunits that may form six homomeric (P2X1–P2X5 and P2X7R), and at least seven heteromeric (P2X1/2, P2X1/4, P2X1/5, P2X2/3, P2X2/5, P2X2/6, and P2X4/6) [21, 22, 23]. The conversion of ATP/ADP to adenosine by ectonucleotidases terminates P2R signaling within the extracellular compartment. Adenosine can signal through four distinct G-protein-coupled receptors (P1 receptors): A1, A2A, A2B, and A3 [24, 25, 26]. The purinergic receptor subtypes are widely distributed throughout the immune cells and the central nervous system (CNS) [25, 27, 28].

Extracellular ATP and ADP are rapidly converted to AMP, which is then further metabolized to adenosine [30].

Adenosine can signal through four distinct G-protein-coupled receptors: A1AR, A2AAR, A2BAR, and A3AR [1, 34]. The subtypes of adenosine receptors are expressed differently in each target cell. A2AAR is largely expressed in immune cells such as neutrophils [35, 36] and lymphocytes, while A2BAR is largely expressed in vascular endothelial cells [37, 38]. Adenosine receptor knockout mice are viable, and no human pathologies have been attributed to mutations and defects of adenosine receptors. However, adenosine receptors, beyond their basic physiological roles, have been extensively studied in the context of various diseases and pathological conditions. For example, adenosine's chronotropic effects via A1AR is essential in the treatment of supraventricular tachycardia. A2AAR serves anti-inflammatory functions in neutrophils, diminishing inflammatory cell activation at various sites [19, 39, 40, 41]. A2AAR antagonists exert benefits in Parkinson's disease. A2BAR contribute to tissue adaptation in response to inflammation, ischemia, and hypoxia [42, 43, 44]. A3AR functions in aqueous humor production in the eye [45], and agonism of A3AR has proven effective in the treatment of dry eye [46].

Extracellular adenosine can be transported into the cell via concentrative or equilibrative nucleoside transporters known as CNTs and ENTs. Diffusion-limited, these channels allow adenosine to diffuse freely across the cellular membrane, following its concentration gradient [21]. Adenosine movement into intracellular space diminishes adenosine signaling [45]. Adenosine signaling can also be terminated by deamination of extracellular adenosine to inosine by cell surface CD26-conjugated adenosine deaminase (ADA) or via phosphorylation back into AMP via adenosine kinase [22]. Genetic deficiency of ENTs is not lethal. ENT-deficient mice exhibit elevated adenosine levels that provide protection during disease states like organ ischemia [41]. Pharmacologic blockade of ENT with dipyridamole, resulting in accumulation of extracellular adenosine causing coronary artery vasodilation, is employed in stress echocardiography to identify coronary atherosclerotic lesions. ENT antagonism is also used to inhibit platelet aggregation and prevent recurrence of stroke and to preserve the patency of hemodialysis grafts. ADA-deficient mice exhibit elevated extracellular adenosine levels, which result in severe pulmonary inflammation and fibrosis. In human, a defect in the ADA gene causes severe combined immunodeficiency (SCID) resulting from metabolites of adenosine exerting cytotoxic effects on lymphocytes. ADA-deficient associated SCID has been successfully treated with ADA gene therapy [39]. The anti-inflammatory effects of cyclosporine may be partially due to inhibition of adenosine kinase, resulting in elevated adenosine levels [40].

Extracellular nucleotides, which activate purinergic receptors, are regulated by enzymes like CD39 and ENPP. CD39 breaks down ATP to AMP and phosphates, influencing hydroxyapatite formation (calcification), while the inorganic pyrophosphate (PPi) formed by ENPP can inhibit calcification. However, the activity of tissue alkaline phosphatase can convert PPi to phosphate, which initiates calcification [44, 47].

Experiments show that the purinergic signaling system, including CD39 and CD73, is actively involved in aortic valve calcification. In particular, studies on porcine aortic valves have shown high expression of CD39 and CD73 in both endothelial and interstitial cells. Adding extracellular nucleotides to cell cultures reveals distinct activity levels for CD39 and CD73, suggesting their different roles in processes like calcification.

In vitro experiments using vascular smooth muscle cells have demonstrated that β-glycerophosphate and uridine adenosine tetraphosphate (Up4A) promote calcification by activating P2X and P2Y receptors. Conversely, inhibition of specific purinergic receptors, such as P2Y, has been shown to reduce valve calcification, highlighting their potential as therapeutic targets.

It has been shown that P2Y2 receptor, activated in various tissues by stress or damage, promotes tissue regeneration by activating multiple signaling pathways. Many studies show that ATP and P2Y2 receptor-mediated signaling influence diverse biological processes, including chemotactic signal production and immune cell activation, thereby promoting migration, proliferation, differentiation, and inflammatory mediator release [48].

Adenosine triphosphate has also been implicated to induce chemotaxis of neutrophils via actin polymerization and direct cell orientation by feedback signaling involving P2Y2R [49]. The subsequent P2Y2 receptor activation will amplify gradient sensing of chemotactic signals (e.g., N-formyl peptides and IL-8) by stimulating F-actin to the leading edge. Chemotaxis of neutrophils to sites of infection is critical for immune defense and for the physiological downregulation of neutrophil-driven inflammation [50].

Therefore, the ATP-P2Y2 receptor signaling system exerts a dual effect. It protects the host from infection, promotes the repair of damaged tissues, and enhances pulmonary clearance of harmful substances. However, if dysregulated, this same healing response can drive chronic inflammation and pathological fibrosis [19, 34].

The P2Y6 receptor also plays an ambivalent role in inflammatory diseases. The receptor is crucial for innate immune responses against bacterial infection any studies show that P2Y6 receptor activation is involved in the release of chemokines from immune cells, such as monocytes, dendritic cells, eosinophils, and recruiting monocytes/macrophages during inflammation or infection [48].

In neurodegenerative diseases, microglia are engaged in the clearance of dead cells or dangerous debris, which is crucial for the maintenance of brain functions. Extracellular ATP regulates microglial motility dynamics in the intact brain, and its release from the damaged tissues mediates a rapid microglial response toward injury [43]. Moreover, UTP and UDP released from injured neurons have been shown to enhance microglial phagocytic capacity for dying cells via activation of P2Y6 receptor, serving as an "eat-me" signal for microglia. This signal is considered to be an important initiator of the clearance of dying cells or debris in the CNS [48].

When the endothelium or epithelium is inflamed, the signaling pathway mediated by the P2Y6 receptor exert a negative effect. Idiopathic inflammatory bowel diseases include, in particular, Crohn's disease and ulcerative colitis. These chronic conditions arise from a dysregulated inflammatory response to intestinal microbiota in genetically susceptible individuals. Experimental studies of colitis have shown an increase in the expression of both P2Y2 and P2Y6 receptors in intestinal epithelial cells [41, 45, 46].

Similarly, P2Y6 receptor plays an important role in acute and chronic allergic airway inflammation, and selective blocking of P2Y6 receptor or P2Y6 receptor deficiency in structural cells reduces symptoms of experimental asthma. Recently, P2Y6 receptors have not only been found to be up-regulated in murine atherosclerotic plaques, but also to play a key role in inflammatory diseases.

Thus, P2Y6 receptor activation plays a role in innate immunity against infection whereas P2Y6 receptor over-activation can result in harmful immune responses and chronic inflammation [48].

P2X7 receptor is highly expressed in immune cells, in particular, mast cells, macrophages, microglia cells and dendritic cells. The best-investigated and most widely accepted P2X7 functions are it role in inflammation and immune signaling. The P2X7 receptor plays a central role in the immune system's response to bacterial and parasitic infections by acting as a crucial link in the signaling pathways involved in inflammation and pathogen control. It has been shown to be involved in the killing of intracellular pathogens such as *Mycobacterium tuberculosis, Chlamydia trachomatis,* and *Leishmania amazonensis*, either by killing the microorganism or by inducing apoptosis of infected macrophages [19]. In addition, this receptor is involved in the development of fever by stimulating the production of prostaglandin E2 (PGE2) and IL-1β [20].

The P2X7 receptor is widely recognized to mediate the pro-inflammatory effects of extracellular ATP. However, as a recent study has shown, this receptor can function as one of the scavenger receptors involved in the recognition and removal of apoptotic cells in the absence of extracellular ATP and the P2X7 receptor a promising target for the development of new drugs [30, 44].

In the CNS, P2X7 receptor activation promotes neuroinflammation by causing the release of proinflammatory cytokines, such as IL-1*β* and TNF-*α* as well as activation of mitogen-activated protein kinases and nuclear factor kappa-light-chain-enhancer of activated B cells, resulting in upregulation of proinflammatory gene products, including cyclooxygenase-2 and the P2Y2 receptor. In P2X7 receptor knock-out mice, amyloid *β* (A*β*) triggered increase of intracellular Ca^{2+}, ATP release, IL-1*β* secretion, and plasma membrane permeabilization in microglia [25]. In fact, *in vivo* inhibition of P2X7 receptor in mice transgenic for mutant human amyloid precursor protein indicated a significant decrease of the number of hippocampal amyloid plaques [48]. Thus, the identification of extracellular ATP and P2X7 receptor as key factors in A*β*-dependent microglia activation unveils a non-conventional mechanism in neuroinflammation and suggests new possible pharmacological targets.

Extracellular ATP and P2X7 receptor signaling also contributes to the development of smoking-induced lung inflammation and emphysema. P2X7 receptor knock-out mice exhibit decreased inflammatory responses, including a reduction in pulmonary fibrosis in a mouse model of lung inflammation. Inhibition of this receptor may be a new possible therapeutic target for the treatment of chronic obstructive pulmonary disease [29, 30].

The purinergic P2X7 receptor is associated with activation and release of IL-1 and IL-18, which is strongly implicated in the multiple inflammatory pathways involved in the pathogenesis of rheumatoid arthritis (RA). P2X7 receptor has also been shown to be expressed by synoviocytes from RA joints and contributes to modulation of IL-6 release. P2X7 receptor activation also plays a novel and direct role in tissue damage through release of cathepsins in joint diseases. Although, AZD9056, a P2X7 receptor antagonist, has been shown to reduce articular inflammation and erosive progression [38], clinical trials with the P2X7 receptor antagonist in patients with RA failed to inhibit disease progression [19, 39]. Similarly, the effect and safety of AZD9056 in Crohn's disease is still under clinical trial.

Taken together, P2X7 receptor signaling not only plays a critical role in mediating appropriate inflammatory and immunological responses against invading pathogens, but also contributes to a wide range of chronic inflammatory diseases when activated inappropriately.

Studies have also shown that pathological dysregulation of purinergic signaling can lead to serious diseases such as autoimmune disorders, cardiovascular problems, and cancers [51]. Elucidating the molecular mechanisms underlying this dysregulation will enable the development of novel diagnostic and therapeutic strategies. Consequently, further research into the purinergic regulation of inflammation is paramount, as it opens avenues for innovative treatments aimed at improving patient quality of life and reducing the population-level disease burden.

In addition, it was found that adenosine, formed as a result of ATP metabolism, has an anti-inflammatory effect, suppressing the activity of immune cells and reducing the severity of the inflammatory process. Adenosine signalling has long been a target for drug development.

Thus, the study of the mechanisms of purinergic regulation of inflammation is an important aspect of modern medicine and biology. It has been established that ATP and ADP play a significant role in activating immune cells and initiating inflammatory responses. These nucleotides activate P2X and P2Y receptors, which initiates a series of signaling pathways that lead to the release of cytokines and chemokines.

Cytokines are a diverse group of small signaling proteins that produced by a wide variety of cells, including immune cells, endothelial cells, and fibroblasts. They perform multiple functions, including attracting and activating immune cells, stimulating cell proliferation and differentiation, and inducing the synthesis of other inflammatory mediators.

It is important to note that the purinergic system closely interacts with the cytokine network. For example, ATP and ADP can stimulate the production of cytokines such as IL-1*β*, TNF-*α* as well as interferon-*γ* through activation of the corresponding receptors. In their turn, cytokines can modulate the expression of purinergic receptors and influence the metabolism of ATP and adenosine. Thus, the interaction between these two systems is a key factor in determining the nature and intensity of the inflammatory response. Cytokines are key players in orchestrating cellular interactions during inflammation, both promoting and suppressing the cooperation between different cell types [4]. Acting as a chemoattractant, ATP stimulates phagocytes to produce reactive oxygen species and macrophages to produce pro-inflammatory cytokines [1, 2, 3, 4].

Pro-inflammatory cytokines are small protein molecules produced by cells of the body's immune system, mainly by macrophages, T cells, and dendritic cells. They are pivotal in initiating and sustaining inflammation, orchestrating interactions among immune components, and stimulating protective responses to infections and tissue damage. These cytokines, acting together in a cascade, aim to eliminate pathogens and repair damaged tissues. Excessive production of pro-inflammatory cytokines can lead to harmful consequences if not properly regulated. This overproduction can damage tissues and contribute to the development of chronic inflammatory diseases, autoimmune disorders, and even sepsis.

Pro-inflammatory cytokines include IL-1, TNF-*α*, and IL-6. These substances cause local and systemic changes characteristic of acute inflammation

[9, 10]. IL-1 plays a pivotal role in the immune response by orchestrating key defense mechanisms and initiating tissue repair [2]. Following antigen exposure, secretion of mature interleukins begins after approximately 2 hours, peaks between 24 and 48 hours, and subsequently declines rapidly [9, 11].

The chain of inflammatory processes is triggered by the activation of endothelial cells [11, 12, 13, 14, 15]. Cytokines released at the inflammatory site act on the endothelium (the inner blood vessel lining), triggering the recruitment of specific immune cells to form an infiltrate tailored to the stimulus. The appearance and accumulation of leukocytes at an inflammatory site is a process involving changes in the activity of adhesion molecules both on the surface of leukocytes and endothelial cells, as well as variations in the inflammatory substances produced by these cells [16, 17]. Tissue damage triggers a cascade of events leading to acute inflammation, characterized by neutrophil migration from blood vessels [17, 18, 19]. Specific interleukins (IL-1, IL-6, IL-8, IL-12) activate endothelial cells to produce adhesion molecules (E-selectin, P-selectin, ICAM1, VCAM1), these adhesion molecules then facilitate the movement and passage of white blood cells (leukocytes) from the bloodstream into inflamed tissues, a process essential for immune response and tissue repair [11, 18, 19, 20]. This process is further enhanced by endothelial cell contraction and widening of intercellular space. In an inflammatory response, activated endothelial cells are essential by releasing chemokines like MCP1 and IL-8, and cytokines such as IL-1, IL-6, and GM-CSF, which attract and activate immune cells like neutrophils and monocytes to the site of injury [18]. Endothelial cell stimulation also leads to the expression of phospholipids on their surface [11, 12, 13].

Cytokines IL-1, IL-6, GM-CSF, and TNF-*α* increase circulating neutrophil counts by stimulating their production in the bone marrow, promoting their release, and enhancing their survival [21, 22, 23].

Neutrophils are the initial responders to injury and are later replaced by monocyte-derived macrophages, a process driven by chemokines secreted by the neutrophils themselves that attract these subsequent immune cells to the site of inflammation [21, 23]. Neutrophils play a crucial role in the inflammatory process by migrating from the bone marrow into the bloodstream, adhering to blood vessel walls, and ultimately penetrating the tissue to reach the site of inflammation. Once at the site, they form a leukocyte "shaft", engage in phagocytosis, release destructive lysosomal enzymes, and ultimately undergo self-destruction [23]. Chemokines, secreted by neutrophils, act as signaling molecules that trigger the release of neutrophils from the bloodstream and guide their migration towards the site of infection. IL-8 plays an important role in attracting white blood cells [21, 24, 25].

The first effect of IL-8 on neutrophils is to trigger their activation, specifically by activating their contractile cytoskeleton and causing the formation of broad cytoplasmic extensions. These changes are noticeable after 20–30 seconds and they reach their highest intensity after about 1.52 minutes [26]. Neutrophils use constitutively expressed L-selectin on their membrane to initiate rolling and slow down within capillaries. IL-8, released in the affected area, binds to receptors on neutrophils, prompting them to rearrange their surface molecules to better adhere to the blood vessel lining (endothelium) and to activate expression of integrins LFA-1 and Integrin-1 on the surface of macrophages (Mac1). The interaction of specific adhesive molecules on neutrophils and endothelial cells causes rolling neutrophils to stop their movement, allowing them to penetrate the tissue and migrate towards a chemoattractant source [27]. IL-8 stimulates the release of neutrophils from postcapillary venules [2], leading to their migration into acute inflamed areas [28]. IL-8 also increases calcium levels within neutrophils, prompting their migration and activating the pentose phosphate pathway, which, in turn, boosts the production of reactive oxygen species, which are involved in fighting off pathogens. Furthermore, IL-8 causes the release of enzymes from neutrophils through degranulation. IL-8 production is increased by the paracrine action of TNF-*α* and IL-1 on nearby macrophages [2, 9, 10].

Anti-inflammatory cytokines are small signaling molecules secreted by immunocompetent cells, including regulatory T cells, macrophages and others, to limit inflammation and prevent excessive immune responses. By doing so, they help restore immunological homeostasis and mitigate the risk of damage to healthy tissues [49, 50, 52].

Anti-inflammatory cytokines are vital components of the immunoregulatory system, preventing excessive immune responses (hyperinflammation) and mitigating damage from chronic inflammation. For instance, transforming growth factor *β* (TGF-*β*) and IL-10 are key cytokines that protect the gastrointestinal tract's mucous membranes from the aggressive effects of the intestinal microflora [40, 53].

An imbalance between pro-inflammatory and anti-inflammatory cytokines can disrupt the body's ability to regulate the immune response, leading to a range of diseases, such as chronic inflammation, autoimmune diseases, and allergies.

Some anti-inflammatory cytokines exert an inhibitory effect on neutrophils, significantly suppressing their production of pro-inflammatory cytokines [54]. TGF-*β* further inhibits inflammation by preventing leukocyte adhesion to the endothelium and reducing the secretion of superoxide radicals and monokines (IL-1, IL-6, TNF-*α*) [2, 4, 18, 21, 29]. IL-10 and TGF-*β* suppress both monocyte and neutrophil-mediated inflammation by blocking the transcription of genes responsible for producing inflammatory cytokines in neutrophils [18]. IL-6 inhibits the synthesis of IL-1 and TNF-*α* [2, 4, 18, 21]. Furthermore, it stimulates the production of the IL-1 receptor antagonist and promotes neutrophil apoptosis. Thus, IL-6 acts as a negative regulator in the complex network of cytokines, it helps to reduce inflammation by controlling neutrophil activity and shaping their functional phenotype during the resolution of an inflammatory response [4, 30]. Furthermore, neutrophils can modify their response to monokines by altering their receptor expression, specifically, they can reset their receptors into a state of increased activity, which potentially alters their susceptibility to monokine signaling. Additionally, detached neutrophil receptors act as "traps", reducing the availability of cytokines and thus diminishing their effect on other cells.

Neutrophil recruitment is a tightly controlled process essential for shifting inflammation from its acute phase to the resolution and repair phase carried out by monocytes and macrophages. Excessive neutrophil activity, however, can be harmful, leading to impaired function and undesirable immune reactions [4]. In mammals, the leukocytic stage of inflammation – spanning from the initial insult to the peak of neutrophil death in the affected tissue – typically lasts 12 to 24 hours [23]. Cytokines thus play a central role in orchestrating an effective inflammatory response. They ensure balance through bidirectional regulation – both enhancing and suppressing signals – and by determining the precise sequence of the process' stages.

The interaction between purinergic signaling and the cytokine network is a critical regulatory mechanism for inflammation. For instance, ATP activation of P2 receptors stimulates pro-inflammatory cytokine release. These cytokines then elevate ATP levels, further activating purinergic signaling and creating a self-amplifying, pro-inflammatory cycle that can contribute to various diseases.

Conversely, adenosine counteracts this by activating P1 receptors, which suppresses pro-inflammatory cytokines and promotes anti-inflammatory ones [43, 55].

CONCLUSION

The investigation of purinergic signaling and cytokine networks is a rapidly growing field in modern medicine and biology. A review of extensive literature reveals a remarkable diversity of molecular mechanisms regulating inflammation, confirming the pivotal role of purinergic receptors and cytokines in both maintaining homeostasis and driving pathology.

A key aspect of this regulation is the crosstalk between purinergic signaling and cytokines, which fine-tunes macrophage and T cell activity. This interaction determines outcomes in infectious diseases, autoimmunity, and cancer. Critically, an imbalance between pro-inflammatory and anti-inflammatory signals can lead to chronic inflammation, a key precursor to serious conditions like cardiovascular disease, diabetes, arthritis, and cancer.

The data obtained indicate that drugs modulating purinergic receptors and cytokine levels could effectively treat inflammatory diseases of various origins. For instance, compounds stimulating the synthesis of anti-inflammatory metabolites like adenosine may suppress excessive immune activation and mitigate tissue damage in autoimmune pathologies. Conversely, blocking receptors for pro-inflammatory agents can help prevent both acute and chronic inflammation.

Consequently, elucidating the interactions between purinergic systems and cytokine networks is vital for creating innovative medicinal products to treat immune regulatory disorders and mitigate the complications of excessive inflammation. Progress in this field promises to enhance quality of life and reduce the societal burden of common diseases driven by pronounced inflammatory processes.

REFERENCES

1. Golovkin A. S., Asadullina I. A., Kudryavtsev I. V. Purinergic regulation of basic physiological and pathological processes. *Medical Immunology (Russia)*. 2018; 20 (4): 463–476. https://doi.org/10.15789/1563-0625-2018-4-463-476 (in Russ.)

2. Coutinho-Silva R., Knight G. E., Burnstock G. Impairment of the splenic immune system in $P2X_2/P2X_3$ knockout mice. *Immunobiology*. 2005; 209 (9): 661–668. https://doi.org/10.1016/j.imbio.2004.09.007

3. Eltzschig H. K., Sitkovsky M. V., Robson S. C. Purinergic signaling during inflammation. *New England Journal of Medicine.* 2012; 367 (24): 2322–2333. https://doi.org/10.1056/NEJMra1205750

4. Lazarowski E. R. Vesicular and conductive mechanisms of nucleotide release. *Purinergic Signalling*. 2012; 8 (3): 359–373. https://doi.org/10.1007/s11302-012-9304-9

5. Faas M. M., Sáez T., de Vos P. Extracellular ATP and adenosine: The Yin and Yang in immune responses? *Molecular Aspects of Medicine*. 2017; 55: 9–19. https://doi.org/10.1016/j.mam.2017.01.002

6. Surprenant A., North R. A. Signaling at purinergic P2X receptors. *Annual Review of Physiology.* 2009; 71: 333–359. https://doi.org/10.1146/annurev.physiol.70.113006.100630

7. Kaniewska E., Sielicka A., Sarathchandra P., Pelikant-Małecka I., Olkowicz M., Słomińska E. M., et al. Immunohistochemical and functional analysis of ectonucleoside triphosphate diphosphohydrolase 1 (CD39) and ecto-5′-nucleotidase (CD73) in pig aortic valves. *Nucleosides, Nucleotides & Nucleic Acids*. 2014; 33 (4–6): 305–312. https://doi.org/10.1080/15257770.2014.885985

8. Orriss I., Syberg S., Wang N., Robaye B., Gartland A., Jorgensen N., Arnett T., Boeynaems J. M. Bone phenotypes of P2 receptor knockout mice. *Frontiers in Bioscience-Scholar*. 2011; 3 (3): 1038–1046. https://doi.org/10.2741/208

9. Ledderose C., Bao Y., Kondo Y., Fakhari M., Slubowski C., Zhang J., Junger W. G. Purinergic signaling and the immune response in sepsis: a review. *Clinical Therapeutics*. 2016; 38 (5): 1054–1065. https://doi.org/10.1016/j.clinthera.2016.04.002

10. Ledderose C., Bao Y., Ledderose S., Woehrle T., Heinisch M., Yip L., et al. Mitochondrial dysfunction, depleted purinergic signaling, and defective T cell vigilance and immune defense. *The Journal of Infectious Diseases.* 2016; 213 (3): 456–464. https://doi.org/10.1093/infdis/jiv373

11. Colgan S. P., Eltzschig H. K., Eckle T., Thompson L. F. Physiological roles for ecto-5′-nucleotidase (CD73). *Purinergic Signalling*. 2006; 2: 351–360. https://doi.org/10.1007/s11302-005-5302-5

12. Bynoe M. S., Waickman A. T., Mahamed D. A., Mueller C., Mills J. H., Czopik A. CD73 is critical for the resolution of murine colonic inflammation. *BioMed Research International.* 2012; 2012:260983. https://doi.org/10.1155/2012/260983

13. Muller-Haegele S., Muller L., Whiteside T. L. Immunoregulatory activity of adenosine and its role in human cancer progression. *Expert Review of Clinical Immunology*. 2014; 10 (7): 897–914. https://doi.org/10.1586/1744666x.2014.915739

14. Chen J.-F., Eltzschig H. K., Fredholm B. B. Adenosine receptors as drug targets – what are the challenges? *Nature Reviews. Drug Discovery*. 2013; 12 (4): 265–286. https://doi.org/10.1038/nrd3955

15. Chrobak P., Charlebois R., Rejtar P., El Bikai R., Allard B., Stagg J. CD73 plays a protective role in collagen-induced arthritis. *The Journal of Immunology*. 2015; 194 (6): 2487–2492. https://doi.org/10.4049/jimmunol.1401416

16. Deaglio S., Dwyer K. M., Gao W., Friedman D., Usheva A., Erat A., et al. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *Journal of Experimental Medicine*. 2007; 204 (6): 1257–1265. https://doi.org/10.1084/jem.20062512

17. Dwyer K. M., Deaglio S., Gao W., Friedman D., Strom T. B., Robson S. C. CD39 and control of cellular immune responses. *Purinergic Signalling*. 2007; 3: 171–180. https://doi.org/10.1007/s11302-006-9050-y

18. Titov V. N. The significance of macrophages in the onset of inflammation; the effects of interleukin-1, interleukin-6 and the activity of hypothalamo-hypophysis system (a survey). *Russian Clinical Laboratory Diagnostics*. 2003; (12): 3–10. https://elibrary.ru/ojcjtb (in Russ.)

19. Choy E. H. S., Panayi G. S. Cytokine pathways and joint inflammation in rheumatoid arthritis. *New England Journal of Medicine*. 2001; 344 (12): 907–916. https://doi.org/10.1056/nejm200103223441207

20. Danilov L. N., Lebedeva E. S., Dvorakovskaya I. V., Simbirtsev A. S., Ilcovich M. M. Effect of interleukin 1 receptor antagonist on the development of oxidative stress in lungs. *Cytokines and Inflammation*. 2003; 2 (4): 14–20. https://elibrary.ru/gxsgmp (in Russ.)

21. Starikova E. A., Amtchislavsky E. I., Sokolov D. I., Freidlin I. S., Polosukhina E. R., Baryshnikov A. Yu. Deviations of endothelial cells surface phenotype under the influence of pro-inflammatory and anti-inflammatory cytokines. *Medical Immunology (Russia)*. 2003; 5 (1-2): 39–48. https://elibrary.ru/jtymrn (in Russ.)

22. Serebrennikova S. N., Seminsky I. Zh. The role of cytokines in the inflammatory process (part 1). *Sibirskii meditsinskii zhurnal*. 2008; (6): 5–8. https://elibrary.ru/jwbssl (in Russ.)

23. Lysikova M., Wald M., Masinovsky Z. Mechanisms of inflammatory reaction and proteolytic enzymes influence upon them. *Cytokines and Inflammation*. 2004; 3 (3): 48–53. https://elibrary.ru/hrrkot (in Russ.)

24. Totolyan A. A. Rol' khemokinov I ikh retseptorov v immunoregulyatsii = The role of chemokines and their receptors in immunoregulation. *Immunologiya*. 2001; 22 (5): 7–15. (in Russ.)

25. Shaimova V. A. The role of inflammatory cytokines in eye diseases. *Cytokines and Inflammation*. 2005; 4 (2): 13–15. https://elibrary.ru/hrrled (in Russ.)

26. Jersmann H. P. A., Hii C. S. T., Ferrante J. V., Ferrante A. Bacterial lipopolysaccharide and tumor necrosis factor alpha synergistically increase expression of human endothelial adhesion molecules through activation of NF-κB and p38 mitogen-activated protein kinase signaling pathways. *Infection and Immunity*. 2001; 69 (3): 1273–1279. https://doi.org/10.1128/iai.69.3.1273-1279.2001

27. Lum H., Roebuck K. A. Oxidant stress and endothelial cell dysfunction. *American Journal of Physiology. Cell Physiology.* 2001; 280 (4): C719–C741. https://doi.org/10.1152/ajpcell.2001.280.4.c719

28. Starikova E. A., Freidlin I. S., Sokolov D. I., Selkov S. A. Changes of properties of endothelial cells, line EA.hy 926, caused by TNFα, IFNγ and IL-4. *Immunologiya*. 2005; 26 (2): 83–87. https://elibrary.ru/hrwxyb (in Russ.)

29. Belova O. V., Arion V. Y., Sergienko V. I. Role of cytokines in immunological function of the skin. *Immunopathology, allergology, infectology*. 2008; (1): 41–55. https://elibrary.ru/jvvrav (in Russ.)

30. Sarlos P., Kovesdi E., Magyari L., Banfai Z., Szabo A., Javorhazy A., Melegh B. Genetic update on inflammatory factors in ulcerative colitis: Review of the current literature. *World Journal of Gastrointestinal Pathophysiology*. 2014; 5 (3): 304–321. https://doi.org/10.4291/wjgp.v5.i3.304

31. Vasileva G. I., Ivanova I. A., Tyukavkina S. Yu. Kooperativnoe vzaimodeistvie mono- i polinuklearnykh fagotsitov, oposredovannoe mono- i neitrofilokinami = Cooperative interaction of mono- and polynuclear phagocytes mediated by mono- and neutrophilokines. *Immunologiya*. 2000; 21 (5): 11–17. (in Russ.)

32. Heydtmann M., Adams D. H. Chemokines in the immunopathogenesis of hepatitis C infection. *Hepatology*. 2009; 49 (2): 676–688. https://doi.org/10.1002/hep.22763

33. Sysoyev K. A., Tchukhlovin A. B., Totolyan A. A. The diagnostic role of chemokines and their receptors under chronic hepatitis C. *Clinical Laboratory Diagnostics.* 2013; (2): 23–29. https://elibrary.ru/pycuoj (in Russ.)

34. Simbirtsev A. S. Cytokines – classification and biologic functions. *Cytokines and Inflammation*. 2004; 3 (2): 16–22. https://www.elibrary.ru/hrrmzv (in Russ.)

35. Ketlinskiy S. A., Simbirtsev A. S. Cytokines: monograph. Saint Petersburg: Foliant; 2008. 552 p. (in Russ.)

36. Immunology: practicum. Ed. by L. V. Kovalchuk, G. A. Ignatieva, L. V. Gankovskaya. Moscow: GEOTAR-Media; 2014. 174 p. (in Russ.)

37. Tengvall S., Che K. F., Lindén A. Interleukin-26: an emerging player in host defense and inflammation. *Journal of Innate Immunity*. 2016; 8 (1): 15–22. https://doi.org/10.1159/000434646

38. Glotov A. V., Potudanskaya M. G. Fundamentals of immunology, immunogenetics and immunobiotechnology: Part 1. General immunology: a textbook. Omsk: Omsk State University; 2009. 119 p. (in Russ.)

39. Ryabov V. V., Gombozhapova A. E., Rogovskaya Yu. V., Ivanyuk E. E., Kzhyshkowska J. G., Karpov R. S. Functional plasticity of monocytes/macrophages in post-infarction cardiac regeneration and remodeling. *Immunologiya*. 2016; 37 (6): 305–311. https://elibrary.ru/xipgjd (in Russ.)

40. Potapnev M. P. Immune mechanisms of sterile inflammation. *Immunologiya*. 2015; 36 (5): 312–318. https://elibrary.ru/umtevn (in Russ.)

41. Nesterova I. V., Balmasova I. P., Kozlov V. A., Malova E. S., Sepiashvili R. I. Chronic fatigue syndrome and immune dysfunction in patients with recurrent viral infections: clinical immunologic characteristic and features of serotonin regulation. *Cytokines and Inflammation*. 2006; 5 (2): 3–14. https://elibrary.ru/tfvgux (in Russ.)

42. Yurova K. A., Khaziakhmatova O. G., Malashchenko V. V., Norkin I. K., Ivanov P. A., Khlusov I. A., et al. Cellular-molecular aspects of inflammation, angiogenesis and osteogenesis. A short review. *Tsitologiya*. 2020; 62 (5): 305–315. https://doi.org/10.31857/S0041377120050090 (in Russ.)

43. Zubova S. G., Bykova T. V. Regulation of the mTOR signaling pathway in macrophages in various pathologies. *Tsitologiya*. 2015; 57 (11): 755–760. https://elibrary.ru/uteazl (in Russ.)

44. Chesnokova N. P., Morrison V. V., Bizenkova M. N., Polutova N. V. Lektsiya 9. Vospalenie – kak tipovoi patologicheskii protsess, lezhashchii v osnove razvitiya razlichnykh nozologicheskikh form patologii = Lecture 9. Inflammation is a typical pathological process underlying the development of various nosological forms of pathology. *Scientific Review. Abstract Journal*. 2018; (1): 124–128. https://abstract.science-review.ru/ru/article/view?id=1877 (in Russ.)

45. Yarilin D. A. Role of tumor necrosis factor in the regulation of the inflammatory response of monocytes and macrophages. *Immunologiya.* 2014; 36 (4): 195–201. https://elibrary.ru/sjzplv (in Russ.)

46. Donina Zh. A., Baranova E. V., Aleksandrova N. P. A comparative assessment of effects of major mediators of acute phase response (IL-1, TNF-α, IL-6) on breathing pattern and survival rate in rats with acute progressive hypoxia. *Journal of Evolutionary Biochemistry and Physiology.* 2021; 57 (4): 936–944. https://doi.org/10.1134/S0022093021040177

47. Litvitsky P. F. Inflammation. *Current Pediatrics*. 2006; 5 (4): 75–81. https://elibrary.ru/hyvrrn (in Russ.)

48. Chen J., Zhao Y., Liu Y. The role of nucleotides and purinergic signaling in apoptotic cell clearance – implications for chronic inflammatory diseases. *Frontiers in Immunology*. 2014; 5:656. https://doi.org/10.3389/fimmu.2014.00656

49. Eshmolov S. N., Sitnikov I. G., Melnikova I. M. The role of cytokines TNF-α, IFN-γ, IL-1, IL-4, IL-8 in the immune response in infectious lesions of CNS in children. *Children Infections*. 2018; 17 (1): 17–22. https://doi.org/10.22627/2072-8107-2018-17-1-17-22 (in Russ.)

50. Krenev I. A., Berlov M. N., Umnyakova E. S. Antimicrobial proteins and peptides of neutrophilic granulocytes as modulators of complement system. *Immunologiya.* 2021; 42 (4): 426–433. https://doi.org/10.33029/0206-4952-2021-42-4-426-433 (in Russ.)

51. Belokrinitskaya T. Ye., Vitkovsky Yu. A., Ponomaryova Yu. N., Mochalova M. N., Lomneva G. M. TNFα and TGFβ in regulation of apoptosis and cell proliferation in cervical intra-epithelial neoplasia and carcinoma of uterine cervix. *Cytokines and Inflammation.* 2006; 5 (1): 31–33. https://elibrary.ru/tfvglh (in Russ.)

52. Zheleznikova G. F. The role of cytokines in pathogenesis and diagnosing of infectious diseases. *Infektsionnye Bolezni (Infectious Diseases)*. 2008; 6 (3): 70–76. https://elibrary.ru/juigfv (in Russ.)

53. Sibiryak S. V. Cytokines as cytochrome P450-dependent monooxygenases regulators. Theoretical and applied aspects. *Cytokines and Inflammation.* 2003; 2 (2): 12–22. https://elibrary.ru/hrrjut (in Russ.)

54. Berezhnaya N. M. Cytokine network regulation in pathology: rapid progress in knowledge and inevitable questions. *Cytokines and Inflammation.* 2007; 6 (2): 26–34. https://elibrary.ru/rzmyrj (in Russ.)

55. Vasileva G. I., Ivanova I. A., Tyukavkina S. Yu. Tsitokiny – obshchaya sistema gomeostaticheskoi regulyatsii kletochnykh funktsii = Cytokines – a general system of homeostatic regulation of cell functions. *Tsitologiya.* 2001; 43 (12): 1101–1111. https://elibrary.ru/cvdbkn (in Russ.)

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