УДК 616.5-002-097:577.112:576.5:576.385.5
https://doi.org/10.20538/1682-0363-2023-2-111-121

Inflammasome as an early pathophysiological phenomenon of inflammation in skin diseases and other pathologies

Klimov V.V.[1], Zagreshenko D.S.[2], Urazova O.I.[1], Klimov A.V.[1], Naidina O.A.[1], Tsyplina E.Yu.[1], Kologrivova E.N.[1], Koshovkina T.V.[1], Koshkarova N.S.[1]

[1] Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation,

[2] Novokuznetsk State Institute for Advanced Training of Doctors – branch of the Russian Medical Academy for Continuing Professional Education
2, Stroiteley Av., Novokuznetsk, 654005, Russian Federation

ABSTRACT

The review considers the molecular structure of inflammasomes, routes of inflammasome activation, appropriate downstream effects, and their association with autoinflammatory, autoimmune, neurodegenerative, and allergic diseases and malignancies with a focus on the involvement of the skin in these pathologies. Inflammasome activation is interpreted as an early pathophysiological event before the onset of inflammation, and, especially, if inflammasome dysregulation occurs. All research aspects related to the NLRP3 inflammasome are described in detail. The review also considers promising directions for therapeutic interventions in NLRP3-associated diseases.

Keywords: inflammasome, NLRP3, AIM2, myeloid cells, keratinocytes, pattern recognition receptors, signaling, caspases, IL-1β, IL-18, IL-33, pyroptosis, inflammaging, skin diseases

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

Для цитирования: Klimov V.V., Zagreshenko D.S., Urazova O.I., Klimov A.V., Naidina O.A., Tsyplina E.Yu., Kologrivova E.N., Koshovkina T.V., Koshkarova N.S. Inflammasome as an early pathophysiological phenomenon of inflammation in skin diseases and other pathologies. *Бюллетень сибирской медицины.* 2023;22(2):111–121. https://doi.org/10.20538/1682-0363-2023-2-111-121.

Инфламмасома как ранний патофизиологический феномен воспалительного процесса при болезнях кожи и других патологиях

Климов В.В.[1], Загрешенко Д.С.[2], Уразова О.И.[1], Климов А.В.[1], Найдина О.А.[1], Цыплина Е.Ю.[1], Кологривова Е.Н.[1], Кошовкина Т.В.[1], Кошкарова Н.С.[1]

[1] Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

✉ *Klimov Vladimir V.,* klimov@mail.tomsknet.ru

[2] *Новокузнецкий государственный институт усовершенствования врачей (НГИУВ) – филиал Российской медицинской академии непрерывного профессионального образования (РМАНПО) Россия, 654005, г. Новокузнецк, пр. Строителей, 5*

РЕЗЮМЕ

В обзоре рассмотрены молекулярная структура, последовательность, пути активации инфламмасом, варианты нисходящих эффектов и их связь с аутовоспалительными, аутоиммунными, нейродегенеративными, аллергическими и злокачественными патологиями, с фокусом на вовлечение кожи в патологический процесс. Дана интерпретация инфламмасом как раннего патофизиологического события перед началом воспалительного процесса и возможные варианты нарушения регуляции их функционирования. Более подробно описаны все аспекты исследований, относящихся к инфламмасоме NLRP3. Приведены данные по имеющимся и перспективным направлениям терапевтических интервенций при NLRP3-ассоциированных болезнях.

Ключевые слова: инфламмасома, NLRP3, AIM2, миелоидные клетки, кератиноциты, паттерн-распознающие рецепторы, сигнальная трансдукция, каспазы, IL-1β, IL-18, IL-33, пироптоз, старение клетки в связи с воспалением, кожные болезни

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Климов В.В., Загрешенко Д.С., Уразова О.И., Климов А.В., Найдина О.А., Цыплина Е.Ю., Кологривова Е.Н., Кошовкина Т.В., Кошкарова Н.С. Инфламмасома как ранний патофизиологический феномен воспалительного процесса при болезнях кожи и других патологиях. *Бюллетень сибирской медицины.* 2023;22(2):111–121. https://doi.org/10.20538/1682-0363-2023-2-111-121.

INTRODUCTION

The skin is the largest barrier organ of the body in the face of environmental microbes, allergens, and multiple dangerous chemical and physical factors [1, 2]. The skin consists of epidermis and dermis, whereas the epidermis is subdivided into cornified, granular, spinous, clear, and basal layers. Some researchers do not differentiate stratum lucidum (a clear layer) as a separate layer of the epidermis. Many skin cells, including keratinocytes, Langerhans cells, intraepithelial CD8αα+ T lymphocytes, NK cells, innate lymphoid cells (ILC), macrophages, mast cells, eosinophils, neutrophils, and memory T cells, are related to the immune system and, in fact, represent its secondary organ [2, 3].

Most of them express pattern recognition receptors, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and AIM2-like receptors (ALRs), to sense pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) [1, 4], and allergens [5]. Keratinocytes undergo differentiation during keratinization, which is an essential innate immunity mechanism. Lymphocytes (90%) along with some other cells (10%) are structured in the skin-associated lymphoid tissue (SALT). The skin also contains melanocytes and fibroblasts [3]. Inflamed skin contains a variety of cells (Fig. 1)., including many cells of the immune system. Keratinocytes, dendritic cells, neutrophils, macrophages, and fibroblasts can serve as container cells for inflammasomes. A new transcriptomic technology, single-cell RNA sequencing, described skin cell landscape in some skin diseases [6, 7].

The inflammasome is an early phenomenon of inflammation under a harmful effect and refers to innate immunity mechanisms. Structurally, any inflammasome represents a high-molecular-weight protein complex located in the cytosol and containing pattern recognition receptors, signaling molecules (including ASC Speck [8, 9]), enzymes (including caspases [10]), and other components [1, 2, 11].

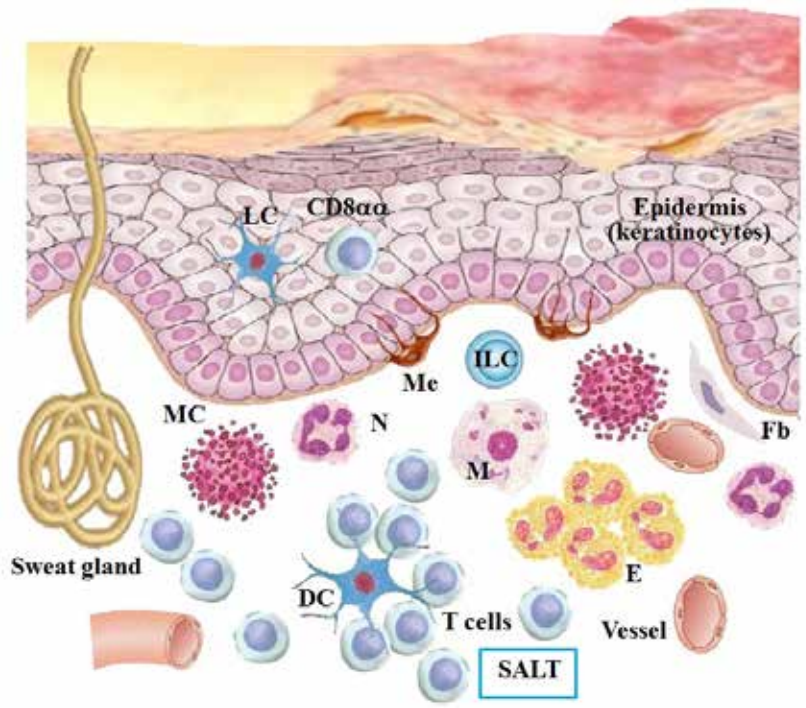

Fig.1. Cells of the inflamed skin: SALT – skin-associated lymphoid tissue, LC – Langerhans cell, CD8αα – γδT cell with CD8αα+ phenotype, ILC – innate lymphoid cell, MC – mast cell, N – neutrophil, Me – melanocyte, M – macrophage, Fb – fibroblast, E – eosinophil, DC – dendritic cell

INFLAMMASOME STRUCTURE, ACTIVATION, FUNCTIONING, AND REGULATION

The inflammasome was first described in 2002 by F. Martinon et al. [12]. Nowadays, about twenty different inflammasomes (NLRP1-NLRP14, NLCR4/NAIP, AIM2, IFI16, CARD8, and PYRIN) have been identified [4, 11]. Their components belong to different families (NLR, ALR, and PYRIN), which recognize different molecular patterns. For example, the NLR family is subdivided into five subfamilies (NLRA, NLRB, NLRC, NLRP, and NLRX) and has up to 23 members in total [4, 13]. In the skin, myeloid cells, keratinocytes, and fibroblasts can serve as main container cells for inflammasomes [4, 14]. Over the past 20 years, inflammasomes in myeloid cells have been characterized in detail, however, inflammasomes contained in non-myeloid cells, such as keratinocytes and fibroblasts, have been described to a lesser extent.

The functioning of inflammasomes implies a downstream effect, such as development of inflammation due to proinflammatory cytokines with or without cell death. For this, an inflammasome has to be activated and assembled. Inflammasome activation proceeds in four key steps [1]:

(1) *priming* – expression of the main inflammasome components and inactive cytokine forms after molecular pattern recognition by TLRs;

(2) *sensing* or recognition of additional activation signals by NLRs or other pattern recognition receptors in the cytosol;

(3) *oligomerization* – assembly of the inflammasome as a high molecular mass multimeric complex;

(4) *final activation* of caspases that results in cytokine secretion through membrane pores and promotion of pyroptosis and possible different types of cell death [15–17].

Depending on the activation route, all inflammasomes are divided into canonical and non-canonical [2, 18–20]. Canonical activation of the LRP3 inflammasome is implemented by two consecutive signal groups. Initially, the first group of impulses go from PAMP / TLR or DAMP / TLR couples and interleukin (IL)-1β, TNF /their receptor couples, which leads to expression of genes encoding inactive pro-IL-1β, pro-IL-18, pro-IL-33, and components of a future inflammasome. After that, the second activation signals arise from many sources and lead to the inflammasome assembly when caspases like caspase-1 enzymatically activate immature forms of IL-1β, IL-

18, and IL-33 before their secretion [11, 20, 21] and promote a cell death mechanism like pyroptosis [18]. A non-canonical activation route is mediated by direct binding of PAMP or DAMP to caspase-4 or caspase-5 [11, 18, 22]. Unfortunately, descriptions of signaling pathways made by various researchers are quite controversial.

In canonical activation, PAMP and DAMP molecular patterns are recognized by TLRs expressed on the cell surfaces or located in endosomes. Next, TLR signaling is triggered which involves adaptor proteins MyD88 and TRIF. Also, external cytokines TNF and IL-1 are sensed by appropriate cytokine receptors to take part in the same pathway. After that, transcription factors AP-1, NF-κB, and IRF-3 stimulate expression of genes encoding components related to a future inflammasome and its proinflammatory cytokines [1, 3, 18, 23].

So, the first step (priming) is over. As a result of the next steps, some upstream signaling events occur, including K+ efflux, Ca++ influx, Cl^- efflux, lysosomal disruption, mitochondrion-derived reactive oxygen species (ROS) generation, and release of oxidized mitochondrial DNA. During oligomerization, the NLRP inflammasome is assembled as a high molecular weight complex. In the fourth step, the formed NLRP inflammasome activates caspase-1 to cleave pro-IL-1β, pro-IL-18, and pro- IL-33, as well as a pore-forming protein gasdermin D that promotes pyroptosis and leads to membrane pore formation. Through the pores, cytokines are released outside [14, 18, 21]. More information about the canonical activation route is presented in Fig. 2.

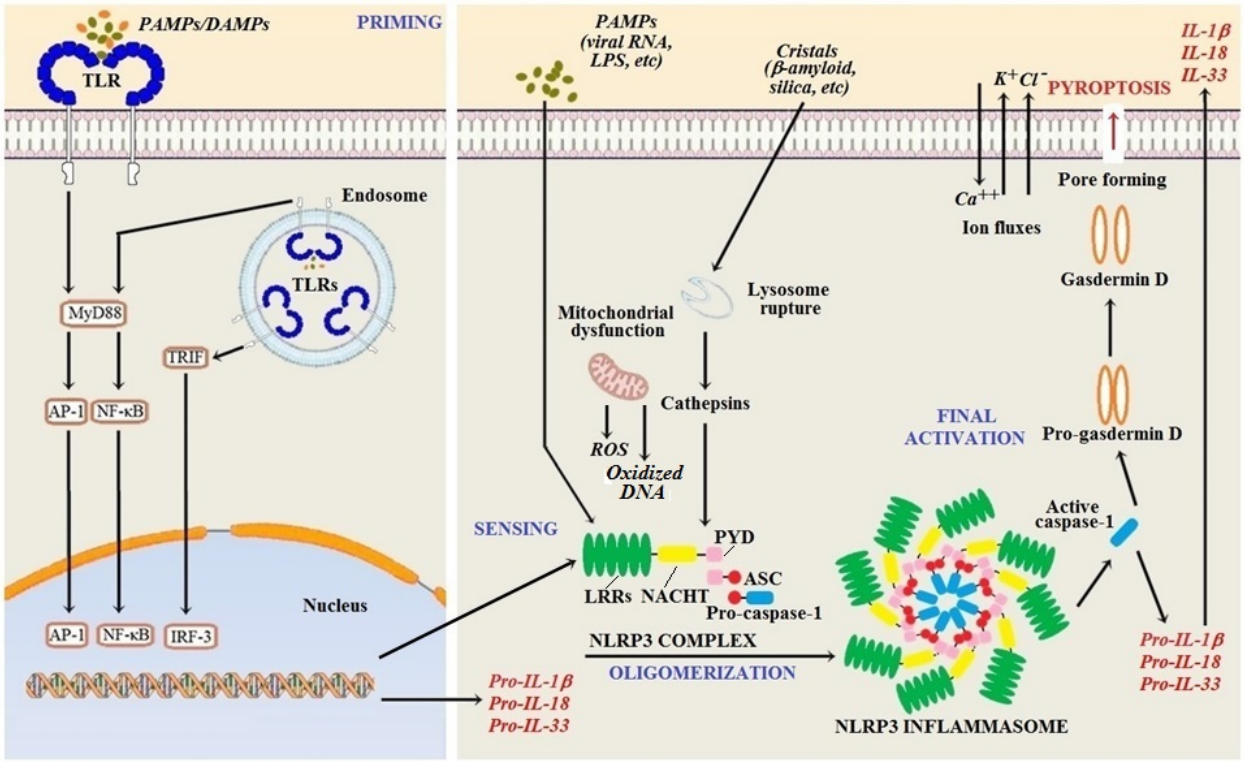

Fig. 2. The canonical inflammasome activation route on the example of NLRP3: TLR – Toll-like receptor, LPS – lipopolysaccharide, MyD88, TRIF, ASC – adaptor proteins, AP-1, NF-κB, IRF-3 – transcription factors, LRR, NACHT, PYD – NLRP3 domains, IL-1β, – interleukin-1β,, IL-18 – interleukin-18, IL-33 – interleukin-33, ROS – reactive oxygen species

Priming, sensing, oligomerization, and final activation are the four steps of the canonical NLRP3 inflammasome activation route. After PAMPs and DAMPs are recognized by TLRs expressed on a container cell, the cell generates immature forms of IL-1β, IL-18, and IL-33, and inactive components of the NLRP3 complex. The NLRP3 complex consists of 1) leucine-rich repeats (LRRs), 2) central NACHT domain, 3) pyrin domain (PYD), 4) apoptosis-associated speck-like (ASC) protein, and 5) pro-caspase-1. The NLRP3 complex is committed to sense signals, including those of PAMPs, cathepsins, ion fluxes, and ROS, required for NLRP3 inflammasome assembly. Eventually, active caspase-1 upregulates the production of membrane pore-forming gasdermin D that leads to pyroptosis. Also, caspase-1 cleaves cyto-

kine pro-forms, which become active secreted IL-1β, IL-18, and IL-33. Here, the early pathophysiological event preceding inflammation completes. Not all the details of the NLRP3 inflammasome activation are presented in Fig. 2.

In non-canonical activation, lipopolysaccharide (LPS) in Gram-negative bacterial infection, is recognized by TLR4 that leads to type I interferon (IFN) upregulation and then expression of GTPases (including IFN-induced GTP-ase IRGB10) and guanylate-binding proteins (GBPs). They destroy intracellular bacteria and promote release of LPS into the cytosol [24]. The cytosolic LPS activates caspase-4 and caspase-5. Subsequently, caspases cleave gasdermin D to induce pyroptosis. In parallel, caspase-1 upregulates the conversion of pro-IL-1β to a secreted IL-1β form [14, 18, 23].

In addition, an alternative inflammasome activation route was described [1, 23, 25] which enables the secretion of cytokines without gasdermin D involvement and pyroptosis induction. In response to LPS that proceeds in the absence of other activation signals, the TRIF-RIPK1-FADD-caspase-8 complex triggers this activation route.

The functioning of any inflammasome is a well-regulated process [4, 18, 20, 26]. It is crucial to establish the optimal balance between inflammasome activation and inhibition. Due to differences in the structures and molecules of inflammasome sensors, different inflammasomes are regulated by different mechanisms [20]. Depending on polarization control, inflammasome can be canonical and non-canonical [11, 18, 20, 23], proinflammatory and anti-inflammatory [4], and protumoral and anti-tumoral [11].

Paradoxically, NLRP10 and NLRP12 inflammasomes downregulate caspase-1, and NLRP6 and NLRP7 inhibit IL-1β, manifesting anti-inflammatory properties. However, NLRP10 and NLRP12 are known to be associated with atopic dermatitis [4]. In cancer, the functioning of various inflammasomes is contradictory. On the one hand, inflammasomes take part in upregulating anti-tumor immunity, but, on the other hand, they can directly contribute to pathological tolerance or promote tumor cell survival, proliferation, and metastasis [11].

Appropriate inflammasome activation is a physiological event for the body to protect against environmental and its own reactivated microbes using innate immunity mechanisms. However, aberrant inflammasome activation can cause uncontrolled cell death and damage to healthy tissues that may contribute to various disorders, particularly autoinflammatory, neurodegenerative, and cardiometabolic diseases, and cancer [20].

PYROPTOSIS, APOPTOSIS, NECROPTOSIS, AND PANOPTOSIS

Nowadays, our understanding of the types and mechanisms of cell death and its effects on the functioning of the whole body has increased significantly; some pathways of programmed cell death have been described in current research: apoptosis [27, 28], pyroptosis [18, 27], necroptosis [16, 27], and PANoptosis [15]. In addition, NETosis and ferroptosis are known [27]. Cell death has both physiological and pathological features. For example, clonal deletion of T lymphocytes in the thymus, selection of B lymphocytes in the bone marrow, and embryonic development are physiological processes required for the body; conversely, death of numerous cells during chronic inflammation and tissue damage is an absolutely pathological event [28].

Apoptosis is commonly a non-inflammatory event, but in case when acute inflammation prolongs and efferocytosis of apoptotic cells is delayed, *late apoptosis*, a lytic form of cell death, occurs [27]. Apoptosis-related conditions and specific features, including wound healing in space and molecular mechanisms of apoptosome assembly in both extrinsic and intrinsic apoptosis, are well-known and described in some review articles [27, 29].

Pyroptosis is described as inflammasome-dependent programmed cell death, which is implemented by gasdermin family members at the last step of inflammasome activation. It is characterized by cell swelling, early cytoplasm membrane rupture, and nuclear condensation. Release of cell content into the extracellular space upregulates both inflammatory and repair processes [18, 27].

Necroptosis is the most unfavorable programmed cell death type for organs and tissues. It contributes to the pathogenesis of many severe disorders (toxic epidermal necrolysis, acute pancreatitis, neurodegenerative diseases, complications of cardiovascular pathologies, etc.). When apoptosis signaling is blocked, necroptotic pathways are activated, and caspase-8, PIP1 / PIP3 kinases, and MLKL pseudokinase are upregulated [16, 28]. So far, the precise mechanism of the necroptosome assembly is not entirely clear.

PANoptosis is a newly described programmed cell death type implemented by a recently identified cytoplasmic multimeric protein complex termed the

PANoptosome. At the same time, the PANoptosome can involve three key modalities of programmed cell death, such as pyroptosis, apoptosis, and necroptosis [15]. Although the PANoptosome incorporates fundamentally distinct mechanisms of cell death, in fact, PANoptosis is a combined inflammatory cell death pathway. Expressed PANoptosome components are associated with autoinflammatory, autoimmune, and neurodegenerative diseases, and many cancer types [15].

INFLAMMAGING

There are many environmental factors affecting the skin and cells of the immune system in the skin and other barrier organs. Some of these factors can be harmful, represent danger signals, and, at least, induce inflammasome formation or skin inflammation.

In an experiment on NLRP1 and NLRP3 inflammasomes, normal human epidermal keratinocytes were exposed to UVB (ultraviolet B) radiation and adenosine triphosphate (ATP), which resulted in release of caspase-1, whereas the bacterial toxin nigericin and urban dust did not exert such an effect [30]. In another experiment, it was described that cigarette smoke extract increased the caspase-1 activity via the NLRP3-independent and TLR4-TRIF-caspase-8-dependent pathway. Simultaneously, it inhibited the expression of the NLRP3 inflammasome and release of IL-1β and IL-18, acting at the transcriptional level [31].

Solar UVB radiation is a major challenge for the skin, which can induce inflammation, cell aging, and even skin cancer. Upon inflammasome activation, the secretion of proinflammatory cytokines and pyroptosis occur. Using the CRISPR / Cas9 protocol with regard to human primary keratinocytes, it was reported that NLRP1 plays a more important role in UVB sensing and subsequent IL-1β and IL-18 secretion than NLRP3 [32]. Other signals apart from pattern recognition receptors are required for NLRP3 formation and caspase-1 activation; they are signals from ATP, nigericin, uric acid crystals, or asbestos. UVB and nigericin are known as inflammasome activators in myeloid cells and keratinocytes, because they both promote IL-1β secretion only in the presence of ASC and NLRP1, whereas knocking out NLRP3 does not impact IL-1β release [33].

In general, the influence of harmful factors on the skin results in development of chronic low-grade subclinical inflammation or *inflammaging* [34]. This phenomenon is associated with a combination of environmental and genetic factors, which can include accumulation of persistent senescent cells and cellular memory formed by epigenetic modifications of the genome [35]. Based on the experiments using cell cultures and laboratory animals, it has been reported that cellular senescence is greatly dependent on the tumor suppressive protein p53 and caspase-4 (caspase-8 in mice) non-canonical pathway triggered by stress and cytoplasmic LPS [22, 36].

If persons already suffer from atopic dermatitis, psoriasis, and acne, exposure to air and contact pollutants and UVB leads to exacerbation of chronic conditions due to an increase in skin inflammation caused by IL-1β and IL-18 [33, 37]. If the exposure lasts for a long time, inflammasome-associated diseases develop. Furthermore, UVB may trigger the development of skin cancer [9, 33].

INFLAMMASOME-ASSOCIATED DISEASES

Inflammation is not a single downstream effect of inflammasomes, since there are other forms of their activity, such as antigen presentation, transcription [4], post-transcriptional and post-translational regulation [18, 19], cell aging and death [37], and tumorigenesis [9]. In case inflammasomes have been overactivated in an uncontrolled manner, their combined downstream effects can result in the development of inflammasome-associated diseases: autoinflammatory [38–40], autoimmune [41, 42], allergic [43, 44] diseases, and cancer [11, 45] (Table). Classical, most common inflammasome-associated disorders are autoinflammatory diseases, such as Familial Mediterranean fever, cryopyrin-associated syndromes, periodic fever, Still's disease, etc. [38, 39].

Table

Association of inflammasomes with pathologies

Inflammasome	Diseases and syndromes	References
NLRP1	Generalized vitiligo, congenital toxoplasmosis, Addison's disease	[2, 4]
	Cutaneous squamous cell carcinoma	[45, 46]
NLRP2	Early-onset childhood atopic dermatitis	[4, 47]
NLRP3	Atopic dermatitis, psoriasis, acne vulgaris, urticaria, bullous pemphigoid, vitiligo	[1, 2, 13, 23, 42, 48–52]
	Allergic contact dermatitis	[53]
	Autoinflammatory, neurodegenerative, and cardiovascular diseases, cancer	[9, 23, 38]
NLRP10, NLRP12	Atopic dermatitis	[4]
	Periodic fever	[38, 39]

Table (continued)

Inflammasome	Diseases and syndromes	References
NAIP-NLRC4	Autoinflammatory syndromes	[1, 38]
NLRC5	Melanoma, fibrous tumors	[4, 54]
AIM-2	Vitiligo, allergic contact dermatitis, aldosterone-induced kidney injury	[1, 2]
IFI16	Cervical cancer	[55]
PYRIN	Autoinflammatory diseases	[1, 38]

The skin is a barrier organ through which invaders enter the body, therefore, it is here that both innate and adaptive immune responses most frequently proceed. Most immune-related skin diseases are affected by genetic and epigenetic mechanisms and environmental factors in different combinations among which inflammasomes occupy a specific place.

As seen from Table, almost all skin diseases were included in the list of inflammasome-associated conditions. In the past 15 years, great progress has been made in identifying new associations of inflammasomes and their components with skin disorders and developing new medications, which enable to regulate inflammasome activity. The canonical NLRP3 and AIM2 inflammasomes were especially well studied [1, 2, 42]. Functional deficiencies in some NLRs and skin colonization with *S. aureus* were observed more frequently in persons with atopic dermatitis than in healthy controls. Higher expression of NLRs was also found in plaque psoriasis [4]. The role of NLRP3 inflammasomes in the pathogenesis and therapy for psoriasis has been demonstrated at different levels, including epigenetic regulation. In particular, researchers reported that miR-155 can trigger psoriasis-like inflammation via activation of the NLRP3 inflammasome [56]. The NLRC5 presence is downregulated in melanoma cells due to a decrease in oncoantigen presentation [54], and, conversely, it is highly upregulated in keloid fibroblasts and skin fibrous tumors [4].

There are new interesting data related to another barrier organ, the unified airway. It has been described that NLRP3 inflammasome activation promotes the development of allergic rhinitis via nasal epitheliocyte and macrophage pyroptosis [57, 58]. It was found that the NLRP3 inflammasome is involved in cytokine shock in a severe course of COVID-19 and acute respiratory distress syndrome due to the fact that SARS-CoV-2 N protein strongly upregulates the binding of NLRP3 to ASC and NLRP3 assembly [59].

PROSPECTS OF THERAPEUTIC INTERVENTIONS

The use of the NLRP3 inflammasome as a target in new therapeutic approaches to disease treatment is rapidly progressing. Some known drugs used in other diseases were tested in NLRP3 inflammasome-associated pathologies [23]. Many new medications, including small molecules, became promising candidates in trials [20]. Depending on inflammasome polarization, current treatment for NLRP3 pathologies focuses on medications with inhibitory or stimulatory effects [18]. More often used inhibitors are directed to NLRP3 activation, signaling molecules, caspases, ASC, and NLRP3-derived proinflammatory cytokines [23]. Approved for clinical use, tranilast, an analog of a tryptophan metabolite, directly binds to the NACHT domain of the NLRP3 complex and downregulates the assembly of the NLRP3 inflammasome by blocking NLRP3 oligomerization step [60].

Over last years, the main approach to treatment for NLRP3-associated pathologies was inhibition of the inflammasome-derived cytokine IL-1β. Three biologicals were approved by the US FDA for many inflammatory (or inflammasome NLRP3-mediated) diseases: canakinumab, an IL-1β inhibitor; anakinra, a recombinant IL-1 receptor antagonist; and rilonacept, a decoy receptor that binds IL-1β and IL-1α [18, 61]. In particular, canakinumab, an anti-IL-1β monoclonal antibody, has been reported to treat a generalized pustular psoriasis patient and resulted in complete remission of skin lesions [62]. Effective anti-TNF therapy by monoclonal antibodies in psoriasis has also been described [49]. However, in some cases, these biologicals displayed side-effects [18].

The second approach directly targeting NLRP3 by small molecules, is specific, cost-effective, and less toxic compared to cytokine blockade [18, 63]. *B. pertussis* bacteria-derived outer membrane vesicles (nanoparticles) are proposed as a new vaccine platform targeted at the NLRP3 inflammasome in macrophages. Bacterial LPS can be delivered by the nanoparticles and transfected into macrophage NLRP3 inflammasome components to trigger the non-canonical activation route and then innate immunity [64].

The novelty of recent years has been the understanding of the association between NLRP3 inflammasome activation and the development of united airway diseases like allergic rhinitis. The NLRP3 inflammasome appears to be a new target in drug therapy to supplement or even replace traditional therapeutic approaches in the future [65].

There are not many medications for the therapy for NLRP3-associated diseases currently approved by the FDA or other agencies. It remains crucial to assess the safety, tolerance, and dose-dependent toxicity of NLRP3 inflammasome modulators to implement them into clinical practice [23]. Nevertheless, novel research data on inflammasome-associated pathogenesis of skin diseases can help to transfer molecular knowledge into clinical therapy in the nearest future.

CONCLUSION

The discovery of the inflammasome as an early event just before the onset of the inflammatory process at the beginning of the XXI century was a starting point for the impressive cellular and molecular research that followed, leading to a new understanding of the mechanisms of inflammation and innate immunity. So far, about 20 inflammasomes have been identified, but only two canonical inflammasomes, NLRP3 and AIM2, have been described in detail. Such container cells for inflammasomes as previously well-known myeloid cells and keratinocytes and fibroblasts, related to the skin have also been studied. Omics technologies made it possible to renew and update our understanding of cell landscape of the skin.

Inflammasome research involved specialists of various specialties: pathologists, histologists, immunologists, molecular biologists, clinicians, etc. As is often the case in science, at the interface of different approaches, new thoughts are born and discoveries are made. At the fundamental level, an understanding of the structure, routes of inflammation activation, signaling pathways, and various downstream effects not limited to the onset of inflammation has been shaped. However, transfer of fundamental knowledge into clinical practice has not yet happened. There is a reason to believe that new therapeutic approaches and drugs with high efficacy and a better adverse effect profile will contribute to modern therapy for autoinflammatory, autoimmune, neurodegenerative, allergic diseases, and cancer in the nearest future.

REFERENCES

1. Lara-Reyna S., Caseley E.A., Topping J., Rodrigues F., Jimenez Macias J., Lawler S.E. et al. Inflammasome activation: from molecular mechanisms to autoinflammation. *Clin. Transl. Immunol*. 2022;11(7):e1404. DOI: 10.1002/cti2.1404.
2. Tang L., Zhou F. Inflammasomes in common immune-related skin diseases. *Front. Immunol*. 2020;11:882. DOI: 10.3389/fimmu.2020.00882.
3. Klimov V.V. Innate immunity. In: From basic to clinical immunology. Cham: Springer, 2019:127–159. DOI: 10.1007/978-3-030-03323-1_3.
4. Danis J., Mellett M. Nod-Like receptors in host defence and disease at the epidermal barrier. *Int. J. Mol. Sci*. 2021;22(9):4677. DOI: 10.3390/ijms22094677.
5. Jacquet A. Characterization of innate immune responses to house dust mite allergens: Pitfalls and limitations. *Front. Allergy*. 2021;2:662378. DOI: 10.3389/falgy.2021.662378.
6. Liu B., Li A., Xu J., Cui Y. Single-cell transcriptional analysis deciphers the inflammatory response of skin-resident stromal cells. *Front. Surg*. 2022;9:935107. DOI: 10.3389/fsurg.2022.935107.
7. Solé-Boldo L., Raddatz G., Schütz S., Mallm J.-P., Rippe K., Lonsdorf A.S. et al. Single-cell transcriptomes of the human skin reveal age-related loss of fibroblast priming. *Commun. Biol*. 2020;3(1):188. DOI: 10.1038/s42003-020-0922-4.
8. Nagar A., Rahman T., Harton J.A. The ASC Speck and NLRP3 inflammasome function are spatially and temporally distinct. *Front. Immunol*. 2021;12:752482. DOI: 10.3389/fimmu.2021.752482.
9. Ciążyńska A., Bednarski I.A., Wódz K., Narbutt J., Lesiak A. NLRP1 and NLRP3 inflammasomes as a new approach to skin carcinogenesis (Review). *Oncol. Letters*. 2020;19(3):1649–1656. DOI: 10.3892/ol.2020.11284.
10. Ross C., Chan A.H., von Pein J.B., Maddugoda M.P., Boucher D., Schroder K. Inflammatory caspases: toward a unified model for caspase activation by inflammasomes. *Annu. Rev. Immunol*. 2022;40:249–269. DOI: 10.1146/annurev-immunol-101220-030653.
11. Lillo S., Saleh M. Inflammasomes in cancer progression and anti-tumor immunity. *Front. Cell Dev. Biol*. 2022;10:839041. DOI: 10.3389/fcell.2022.839041.
12. Martinon F., Burns K., Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspase and processing of proIL-beta. *Mol. Cell*. 2002;10(2):417–426. DOI: 10.1016/s1097-2765(02)00599-3.
13. Tsang M.S.-M., Hou T., Chan B.C.-L., Wong C.K. Immunological roles of NLR in allergic diseases and its underlying mechanisms. *Int. J. Mol. Sci*. 2021;22(4):1507. DOI: 10.3390/ijms22041507.
14. Lachner J., Mlitz V., Tschachler E., Eckhart L. Epidermal cornification is preceded by the expression of a keratinocyte-specific set of pyroptosis-related genes. *Sci. Rep*. 2017;7(1):17446. DOI: 10.1038/s41598-017-17782-4.
15. Samir P., Malireddi R.K.S., Kanneganti T.D. The PANoptosome: A deadly protein complex driving pyroptosis, apoptosis, and necroptosis (PANoptosis). *Front. Cell Infect. Microbiol*. 2020;10:238. DOI: 10.3389/fcimb.2020.00238.
16. Dmitriev Yu.V., Galagudza M.M. Necroptosis and the experience of its targeted modulation in the context of personalized medicine. Rus J Person Med 2022;2(2):33–45 (in Russ.). DOI: 10.18705/2782-3806-2022-2-2-33-45.
17. Li Y., Sun L., Zhang Y. Programmed cell death in the epithelial cells of the nasal mucosa in allergic rhinitis. *Int. Immunopharm*. 2022;112:109252. DOI: 10.1016/j.intimp.2022.109252.

18. Swanson K.V., Deng M., Ting J.P. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat. Rev. Immunol*. 2019;19(8):477–489. DOI: 10.1038/s41577-019-0165-0.
19. Seok J.K., Kang H.C., Cho Y.Y., Lee H.S., Lee J.Y. Regulation of the NLRP3 inflammasome by post-translational modifications and small molecules. *Front. Immunol.* 2020;11:618231. DOI: 10.3389/fimmu.2020.618231.
20. Zheng D., Liwinski T., Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. *Cell Discov*. 2020;6(1):36. DOI: 10.1038/s41421-020-0167-x.
21. Zheng J., Yao L., Zhou Y., Gu X., Wang C., Bao K. et al. A novel function of NLRP3 independent of inflammasome as a key transcription factor of IL-33 in epithelial cells of atopic dermatitis. *Cell Death Dis*. 2021;12(10):871. DOI: 10.1038/s41419-021-04159-9.
22. Fernandez-Duran I., Quintanilla A., Tarrats N., Birch J., Hari P., Millar F.R. et al. Cytoplasmic innate immune sensing by the caspase-4 non-canonical inflammasome promotes cellular senescence. *Cell Death Differ*. 2022;29(6):1267–1282. DOI: 10.1038/s41418-021-00917-6.
23. Seok J.K., Kang H.C., Cho Y.-Y., Lee H.-S., Lee J.Y. Therapeutic regulation of the NLRP3 inflammasome in chronic inflammatory diseases. *Arch. Pharm. Res.* 2021;44(1):16–35. DOI: 10.1007/s12272-021-01307-9.
24. Ha H.J., Chun H.L., Lee S.Y., Park H.H. Molecular basis of IRGB10 oligomerization and membrane association for pathogen membrane disruption. *Commun. Biol.* 2021;4(1):92. DOI: 10.1038/s42003-020-01640-7.
25. Gaidt M.M., Hornung V. Alternative inflammasome activation enables IL-1β release from living cells. *Curr. Opin. Immunol*. 2017;44:7–13. DOI: 10.1016/j.coi.2016.10.007.
26. Christgen S., David E., Place D.E., Kanneganti T.-D. Toward targeting inflammasomes: Insights into their regulation and activation. *Cell Res*. 2020;30(4):315–327. DOI: 10.1038/s41422-020-0295-8.
27. Anderton H., Alqudah S. Cell death in skin function, inflammation, and disease. *Biochem. J*. 2022;479(15):1621–1651. DOI: 10.1042/BCJ20210606.
28. Bertheloot D., Latz E., Franklin B.S. Necroptosis, pyroptosis and apoptosis: An intricate game of cell death. *Cell Mol. Immunol*. 2021;18(5):1106–1121. DOI: 10.1038/s41423-020-00630-3.
29. Riwaldt S., Corydon T.J., Pantalone D., Sahana J., Wise P., Wehland M. et al. Role of apoptosis in wound healing and apoptosis alterations in microgravity. *Front. Bioengin. Biotechnol*. 2021;9:679650. DOI: 10.3389/fbioe.2021.679650.
30. Gruber J.V., Holtz R. *In vitro* expression of NLRP inflammasome-induced active Caspase-1 expression in normal human epidermal keratinocytes (NHEK) by various exogenous threats and subsequent inhibition by naturally derived ingredient blends. *J. Inflam. Res*. 2019;12:219–230. DOI: 10.2147/JIR.S215776.
31. Buscetta M., Di Vincenzo S., Miele M., Badami E., Pace E., Cipollina C. Cigarette smoke inhibits the NLRP3 inflammasome and leads to caspase-1 activation via the TLR4-TRIF-caspase-8 axis in human macrophages. *FASEB J*. 2020;34(1):1819–1832. DOI: 10.1096/fj.201901239R.
32. Fenini G., Grossi S., Contassot E., Biedermann T., Reichmann E., French L.E. et al. Genome editing of human primary keratinocytes by CRISPR/Cas9 reveals an essential role of the NLRP1 inflammasome in UVB sensing. *J. Invest. Dermatol*. 2018;138(12):2644–2652. DOI: 10.1016/j.jid.2018.07.016.
33. Burian M., Yazdi A.S. NLRP1 Is the key inflammasome in primary human keratinocytes. *J. Invest. Dermatol*. 2018;138(12):2507–2510. DOI: 10.1016/j.jid.2018.08.004.
34. Latz E., Duewell P. NLRP3 inflammasome activation in inflammaging. *Sem. Immunol*. 2018;40:61–73. DOI: 10.1016/j.smim.2018.09.001.
35. Nardini C., Moreau J.-F., Gensous N., Ravaioli F., Garagnani P., Bacalini M.G. The epigenetics of inflammaging: The contribution of age-related heterochromatin loss and locus-specific remodelling and the modulation by environmental stimuli. *Sem. Immunol*. 2018;40:49–60. DOI: 10.1016/j.smim.2018.10.009.
36. Cyr B., Hadad R., Keane R.W., Vaccari J.P.R. The role of non-canonical and canonical inflammasomes in inflammaaging. *Front. Mol. Neurosci*. 2022;15:774014. DOI: 10.3389/fnmol.2022.774014.
37. Ferrara F., Prieux R., Woodby B., Valacchi G. Inflammasome activation in pollution-induced skin conditions. *Plast. Reconstr. Surg*. 2021;147(1S-2):15S–24S. DOI: 10.1097/PRS.0000000000007617.
38. Georgin-Lavialle S., Fayand A., Rodrigues F., Bachmeyer C., Savey L., Grateau G. Autoinflammatory diseases: state of the art. *Presse Med*. 2019;48(1Pt2):e25–e48. DOI: 10.1016/j.lpm.2018.12.003.
39. Georgin-Lavialle S., Ducharme-Benard S., Sarrabay G., Savey L., Grateau G., Hentgen V. Systemic autoinflammatory diseases: clinical state of the art. Best practice and research. *Clin. Rheumatology*. 2020;34(4):101529. DOI: ff10.1016/j.berh.2020.101529.Georgin-Lavialle S., Ducharme-Benard S., Sarrabay G., Savey L., Grateau G., Hentgen V. Systemic autoinflammatory diseases: clinical state of the art. Best practice and research. *Clin. Rheumatology*. 2020;34(4):101529. DOI: ff10.1016/j.berh.2020.101529.
40. Pirozhkov S.V., Litvitskiy P.F. Inflammasome-associated diseases. *Immunology*. 2018;39(2-3):158–165 (in Russ.). DOI: 10.18821/0206-4952-2018-39-2-3-158-165.
41. Zhang Y., Yang W., Li W., Zhao Y. NLRP3 inflammasome: Checkpoint connecting innate and adaptive immunity in autoimmune diseases. *Front. Immunol*. 2021;12:732933. DOI: 10.3389/fimmu.2021.732933.
42. Wang D., Duncan B., Li X., Shi J. The role of NLRP3 inflammasome in infection-related, immune-mediated and autoimmune skin diseases. *J. Dermatol. Sci*. 2020;98(3):146–151. DOI: 10.1016/j.jdermsci.2020.03.001.
43. Kazimirsky A.N., Salmasi J.M., Poryadin G.V., Svitich O.A., Bragvadze B.G., Alekseeva A.A., Gankovskaya L.V. The role of epithelial cells in atopy pathogenesis. *Bulletin of Siberian Medicine.* 2019;8(1):201–210 (in Russ.). DOI: 10.20538/1682-0363-2019-1-201–210.
44. Zagreshenko D.S., Klimov V.V., Trofimenko N.A., Dorofeeva M.S. “Skin window” exudate IL-1β and IL-18 in patients

with chronic urticaria. *Medicine in Kuzbass*. 2022;21(3):27–29 (in Russ.). DOI: 10.24412/2687-0053-2022-3-27-29.
45. Di Filippo M., Hennig P., Karakaya T., Slaufova M., Beer H.-D. NLRP1 in cutaneous SCCs: An example of the complex roles of inflammasomes in cancer development. *Int. J. Mol. Sci*. 2022;23(20):12308. DOI: 10.3390/ijms232012308.
46. Zhong F.L., Mamaï O., Sborgi L., Boussofara L., Hopkins R., Robinson K. et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell*. 2016;167(1):187–202.e17. DOI: 10.1016/j.cell.2016.09.001.
47. Thürmann L., Grützmann K., Klös M., Bieg M., Winter M., Polte T. et alEarly-onset childhood atopic dermatitis is related to NLRP2 repression. *J. Allergy Clin. Immunol*. 2018;141(4):1482–1485.e16. DOI: 10.1016/j.jaci.2017.11.018.
48. Li S., Kang P., Zhang W., Jian Z., Zhang Q., Yi X. et al. Activated NLR family pyrin domain containing 3 (NLRP3) inflammasome in keratinocytes promotes cutaneous T-cell response in patients with vitiligo. *J. Allergy Clin. Immunol*. 2020;145(2):632–645. DOI: 10.1016/j.jaci.2019.10.036.
49. Deepti V., Shora Z.F., Gunnthorunn S., Cecilia B.E., Charlotta S., Charlotta E. Enhanced inflammasome activity in patients with psoriasis promotes systemic inflammation. *J. Invest. Dermatol*. 2021;141(3):586–595.e5. DOI: 10.1016/j.jid.2020.07.012.
50. Su F., Xia Y., Huang M., Zhang L., Chen L. Expression of NLPR3 in psoriasis is associated with enhancement of interleukin-1b and caspase-1. *Med. Sci. Monit*. 2018;24:7909–7913. DOI: 10.12659/MSM.911347.
51. Tsuji G., Hashimoto-Hachiya A., Yen V.H., Takemura M., Yumine A., Furue K. et al. Metformin inhibits IL-1β secretion via impairment of NLRP3 inflammasome in keratinocytes: implications for preventing the development of psoriasis. *Cell Death Discovery*. 2020;6:11. DOI: 10.1038/s41420-020-0245-8.
52. Yang B.-Y., Cheng Y.-G., Liu Y., Liu Y., Tan J.-Y., Guan W. et al. *Datura Metel L*. ameliorates imiquimod-induced psoriasis-like dermatitis and inhibits inflammatory cytokines production through TLR7/8–MyD88–NF-kB–NLRP3 inflammasome pathway. *Molecules*. 2019;24(11):2157. DOI: 10.3390/molecules24112157.
53. Bonnekoh H., Vera C., Abad-Perez A., Radetzki S., Neuenschwander M., Specker E. et al. Topical inflammasome inhibition with disulfiram prevents irritant contact dermatitis. *Clin. Transl. Allergy*. 2021;11(5):e12045. DOI: 10.1002/clt2.12045.
54. Luo Q., Zeng J., Li W., Lin L., Zhou X., Tian X. et al. Silencing of miR155 suppresses inflammatory responses in psoriasis through inflammasome NLRP3 regulation. *Int. J. Mol. Med*. 2018;42(2):1086–1095. DOI: 10.3892/ijmm.2018.3677.
55. Cai H., Yan L., Liu N., Xu M., Cai H. IFI16 promotes cervical cancer progression by upregulating PD-L1 in immunomicroenvironment through STING-TBK1-NF-kB pathway. *Biomed. Pharmacother*. 2020;123:109790. DOI: 10.1016/j.biopha.2019.109790.
56. Yang Z., Liang C., Wang T., Zou Q., Zhou M., Cheng Y. et al. *Biochem. Biophys. Res. Commun.* 2020;522(1):61–67. DOI: 10.1016/j.bbrc.2019.11.031.
57. Kim H., Kim H., Feng Y., Li Y., Tamiya H., Tocci S. et al. PRMT5 control of cGAS/STING and NLRC5 pathways defines melanoma response to antitumor immunity. *Sci. Transl. Med*. 2020;12(551):eaaz5683. DOI: 10.1126/scitranslmed.aaz5683.
58. Zhou H., Zhang W., Qin D., Liu P., Fan W., Lv H. et al. Activation of NLRP3 inflammasome contributes to the inflammatory response to allergic rhinitis via macrophage pyroptosis. *Int. Immunopharmacol.* 2022;110:109012. DOI: 10.1016/j.intimp.2022.109012.
59. Pan P., Shen M., Yu Z., Ge W., Chen K., Tian M. et al. SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. *Nat. Commun*. 2021;12(1):4664. DOI: 10.1038/S41467-021-25015-6.
60. Huang Y., Jiang H., Chen Y., Wang X., Yang Y., Tao J. et al. Tranilast directly targets NLRP3 to treat inflammasome-driven diseases. *EMBO Mol. Med*. 2018;10(4):e8689. DOI: 10.15252/emmm.201708689.
61. Nasonov E.L. The role of interleukin 1 in the development of human diseases. *Rheumatology Science and Practice*. 2018;56(Suppl. 4):19–27 (in Russ.). DOI: 10.14412/1995-4484-2018-19-27.
62. Skendros P., Papagoras C., Lefaki I., Giatromanolaki A., Kotsianidis I., Speletas M. et al. Successful response in a case of severe pustular psoriasis after interleukin-1beta inhibition. *Br. J. Dermatol*. 2017;176(1):212–215. DOI: 10.1111/bjd.14685.
63. Sebastian-Valverde M., Wu H., Rahim M.A, Sanchez R., Kumar K., De Vita R.J. et al. Discovery and characterization of small-molecule inhibitors of NLRP3 and NLRC4 inflammasomes. *J. Biol. Chem*. 2021;296:100597. DOI: 10.1016/j.jbc.2021.100597.
64. Elizagaray M.L., Gomes M.T.R., Guimaraes E.S., Rumbo M., Hozbor D.F., Oliveira S.C. et al. Canonical and non-canonical inflammasome activation by outer membrane vesicles derived from Bordetella pertussis. *Front. Immunol*. 2020;11:1879. DOI: 10.3389/fimmu.2020.01879.
65. Leszczyńska K., Jakubczyk D., Górska S. The NLRP3 inflammasome as a new target in respiratory disorders treatment. *Front. Immunol*. 2022;13:1006654. DOI: 10.3389/fimmu.2022.1006654.

Authors' information

Klimov Vladimir V. – Dr. Sci. (Med.), Professor, Head of the Immunology and Allergy Division, Siberian State Medical University, Tomsk, klimov@mail.tomsknet.ru, http://orcid.org/0000-0001-6673-7556

Zagreshenko Denis S. – Cand. Sci. (Med.), Associate Professor, Clinical Lab Diagnostics Division, Novokuznetsk State Institute for Advanced Training of Doctors, Novokuznetsk, zagreshenko@rambler.ru, http://orcid.org/0000-0003-4309- 664X

Urazova Olga I. – Dr. Sci. (Med.), Professor, Corresponding Member of the RAS, Head of the Pathophysiology Division, Siberian State Medical University, Tomsk, http://orcid.org/ 0000-0002-9457-8879

Klimov Andrew V. – Cand. Sci. (Med.), Associate Professor, Immunology and Allergy Division; Teaching Assistant, ENT Division, Siberian State Medical University, Tomsk, klimov.lor@mail.ru, http://orcid.org/0000-0002-2776-5834

Naidina Oxana A. – Cand. Sci. (Med.), Teaching Assistant, Immunology and Allergy Division, Siberian State Medical University, Tomsk, klimov.lor@mail.ru, http://orcid.org/0000-0002-1407-2086

Tsyplina Ekaterina Yu. – Research Lab Assistant, Immunology and Allergy Division, Siberian State Medical University, Tomsk, katyts9917@gmail.com, http://orcid.org/ 0000-0001-9046-6637

Kologrivova Elena N. – Dr. Sci. (Med.), Professor, Immunology and Allergy Division, Siberian State Medical University, Tomsk, enkologrivova@mail.ru, http://orcid.org/0000-0003-1639-4676

Koshovkina Tatiana V. – Cand. Sci. (Med.), Associate Professor, Immunology and Allergy Division, Siberian State Medical University, Tomsk, koshov.tan@yandex.ru, http://orcid.org/0000-0001-7280-1980

Koshkarova Natalia S. – Cand. Sci. (Med.), Associate Professor, Immunology and Allergy Division, Siberian State Medical University, Tomsk, kasy@list.ru, http://orcid.org/0000-0002-6032-2402

(✉) **Klimov Vladimir V.,** klimov@mail.tomsknet.ru

Received 30.12.2022;
approved after peer review 16.01.2023;
accepted 27.02.2023