DOI: https://doi.org/10.17816/KMJ646818

The Role of the NLRP3 Inflammasome in the Pathogenesis of Bronchial Asthma: Inflammatory Mechanisms and Emerging Therapeutic Perspectives

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ABSTRACT

This article explores the pathophysiological mechanisms and therapeutic potential for treating bronchial asthma, a significant global public health issue. Immune-mediated inflammation is central to asthma pathogenesis and involves the formation of inflammasomes—molecular complexes that regulate inflammatory responses. The NLRP3 inflammasome plays a pivotal role in disease progression by interacting with allergens and triggering signaling cascades that lead to the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and IL-18. These cytokines recruit immune cells, including mast cells, eosinophils, and T lymphocytes, which contribute to airway inflammation, hyperresponsiveness, and bronchial obstruction. The article discusses asthma phenotypes, including infection-induced and atopic asthma, and the link between NLRP3 inflammasome activation and impaired lung function, steroid resistance, and neutrophilic inflammation. Special attention is given to the cellular and molecular pathways involved in the inflammatory response, including interactions between the inflammasome and T helper cells, macrophages, eosinophils, and mast cells. These interactions lead to the release of histamine, heparin, lysosomal enzymes, reactive oxygen species, nitric oxide, prostaglandins, and leukotrienes. Inflammatory mediators such as IL-4, IL-5, and IL-13 contribute to airway remodeling, mucus hypersecretion, and bronchospasm. Additionally, inflammasome activation can impair epithelial barrier integrity, further exacerbating allergic inflammation. The article emphasizes the chronic changes in the bronchial tree caused by sustained inflammation and highlights the importance of regulating inflammasome activity. In particular, the selective NLRP3 inflammasome inhibitor MCC950 has demonstrated efficacy in reducing inflammation and shows promise as a novel therapeutic approach. The article concludes that integrating inflammasome research into clinical practice (particularly through the use of targeted therapies such as MCC950) may transform the approach to asthma treatment. This underscores the importance of transitioning toward personalized medicine in the management of chronic inflammatory diseases such as bronchial asthma.

Keywords: bronchial asthma; inflammasome; proinflammatory interleukins; inflammation; NLRP3 inflammasome inhibitors; review.

To cite this article:
Borukaeva IKh, Edilov KG, Dzueva AS, Labazanova MI, Gidizov Kh-AR. The role of the NLRP3 inflammasome in the pathogenesis of bronchial asthma: inflammatory mechanisms and emerging therapeutic perspectives. *Kazan Medical Journal.* 2025;106(2):287–297. doi: https://doi.org/10.17816/KMJ646818

Submitted: 27.01.2025 **Accepted**: 14.02.2025 **Published online**: 24.03.2025

DOI: https://doi.org/10.17816/KMJ646818
УДК 616-002: 616-092/18: 616.233-008.8

Роль инфламмасомы NLRP3 в патогенезе бронхиальной астмы: механизмы воспаления и новые перспективы терапии

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АННОТАЦИЯ

Статья посвящена патофизиологическим механизмам и терапевтическому потенциалу в лечении бронхиальной астмы, которая представляет собой глобальную проблему здравоохранения. В основе патогенеза бронхиальной астмы лежит иммунное воспаление с образованием инфламмасом, молекулярных комплексов, регулирующих воспалительные реакции. Инфламмасомы, особенно NLRP3, играют ключевую роль в развитии заболевания, взаимодействуя с аллергенами и инициируя сигнальные каскады, которые приводят к выработке провоспалительных цитокинов, таких как интерлейкин-1β (IL-1β) и IL-18. Эти цитокины привлекают иммунные клетки, включая тучные клетки, эозинофилы и Т-лимфоциты, которые способствуют воспалению дыхательных путей, гиперреактивности и обструкции бронхов. Рассмотрены фенотипы бронхиальной астмы, включая инфекционно-зависимую и атопическую астму, а также связь активации инфламмасомы NLRP3 с нарушениями лёгочной функции, стероидорезистентностью и нейтрофильным воспалением. Особое внимание уделено клеточным и молекулярным механизмам, задействованным в формировании воспалительного процесса, включая взаимодействие инфламмасомы с Т-хелперами, макрофагами, эозинофилами и тучными клетками, приводящее к выделению гистамина, гепарина, лизосомальных ферментов, свободных радикалов кислорода, пероксида азота, простагландинов и лейкотриенов. Медиаторы воспаления, такие как IL-4, IL-5, IL-13, вызывают ремоделирование дыхательных путей, гиперсекрецию слизи и бронхоспазм. Кроме того, активация инфламмасом может привести к нарушению барьерной функции эпителия, что ещё более усиливает аллергическое воспаление. В работе акцентируется внимание на хронических изменениях в бронхиальном дереве, вызванных длительным воспалением. Подчёркивается важность регуляции инфламмасом, включая использование селективного ингибитора инфламмасомы NLRP3 — MCC950, который эффективно снижает воспаление, демонстрируя перспективы лечения бронхиальной астмы. В статье делается вывод о важности интеграции исследований инфламмасом в клиническую практику, предполагая, что таргетная терапия (в виде использования MCC950) может преобразовать подход к лечению астмы. Это подчёркивает важность перехода к персонализированной медицине в лечении хронических воспалительных заболеваний, таких как бронхиальная астма.

Ключевые слова: бронхиальная астма; инфламмасома; провоспалительные интерлейкины; воспалительный процесс; ингибиторы инфламмасомы NLRP3; обзор.

Как цитировать:
Борукаева И.Х., Эдилов К.Г., Дзуева А.С., Лабазанова М.И., Гидизов Х.-А.Р. Роль инфламмасомы NLRP3 в патогенезе бронхиальной астмы: механизмы воспаления и новые перспективы терапии // Казанский медицинский журнал. 2025. Т. 106, № 2. С. 287–297. doi: https://doi.org/10.17816/KMJ646818

Рукопись получена: 27.01.2025 **Рукопись одобрена:** 14.02.2025 **Опубликована online:** 24.03.2025

BACKGROUND

Bronchial asthma currently poses a significant public health challenge, as the number of individuals affected by this disease continues to increase annually [1]. According to the World Health Organization, approximately 340 million people worldwide are presently diagnosed with bronchial asthma, and this number is steadily rising [2]. The high prevalence of bronchial asthma is linked to multiple contributing factors, including air pollution, urbanization, and changes in the human microbiome [3]. As a global health issue, bronchial asthma demands comprehensive strategies focused on prevention, early diagnosis, and access to high-quality treatment [4]. Given that immune-mediated inflammation plays a central role in the pathogenesis of atopic asthma [5], understanding the mechanisms underlying the inflammatory process is of critical importance.

This review aims to examine the role of the NLRP3 inflammasome in the pathogenesis of bronchial asthma and to identify new therapeutic targets based on existing research. A total of 106 sources, published between 2011 and 2025, were analyzed. The literature review was conducted using databases such as *PubMed, eLIBRARY.RU*, *Scopus*, and *Google Scholar*, with open access results also retrieved through *Yandex* and *Google*. Search terms included *патогенез бронхиальной астмы* (pathogenesis of bronchial asthma), *роль инфламмасом в развитии воспаления* / role of inflammasome in inflammation, and *новые методы лечения бронхиальной астмы* / novel approaches to the treatment of bronchial asthma. Only studies meeting high methodological standards were included, while abstracts, summaries, and duplicate publications were excluded.

ROLE OF INFLAMMASOMES IN THE PATHOGENESIS OF BRONCHIAL ASTHMA

An *inflammasome* is a macromolecular complex formed by pattern recognition receptors, such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain–like receptors (NLRs), upon interaction with pathogens. This interaction leads to the activation of caspase-1, a cysteine protease that cleaves pro–interleukin (IL)-1β and pro–IL-18 into their active forms, which are released during pyroptosis [6].

Inflammasomes play a central role in initiating inflammatory responses by functioning as molecular sensors of infection, tissue injury, and allergens [7]. TLRs detect extracellular structures such as allergens and microbial agents, while NLRs (e.g., NOD1, NOD2) recognize intracellular pathogens. These interactions initiate signaling cascades that culminate in inflammasome assembly, followed by caspase-1 activation and the subsequent production of IL-1β and IL-18 [8]. Gene polymorphisms encoding these receptors may influence asthma susceptibility and disease severity [9].

Certain damage-associated molecular patterns activate TLRs, thereby amplifying inflammation [10]. TLR2 and TLR4 signaling has been shown to trigger nuclear factor kappa B (NF-κB) activation via high-mobility group box 1 (HMGB1) and S100 calcium-binding protein A8 (S100A8) [11, 12]. These pathways involve multiple signaling intermediates that converge at various points to activate NF-κB, leading to the expression of genes encoding components essential for inflammasome assembly [13].

While inflammasome in myeloid lineage cells have been extensively characterized, their presence and function in bronchial epithelial cells remain poorly understood [14]. Upon entering the bronchial epithelium, the allergen interacts with the NOD-like receptor family pyrin domain-containing protein NLRP3, which is localized in the epithelial cells of the respiratory tract, as well as in dendritic cells and macrophages [15]. NLRP3 (also known as cryopyrin or NALP3) plays a key role in disrupting antigen tolerance and promoting the development of asthma [16].

Following allergen interaction with NLRP3, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain, known as ASC, becomes activated. This adaptor protein functions as a molecular bridge between the NLRP3 receptor and procaspase-1 [17]. The expression, assembly, and activation of the NLRP3 inflammasome lead to the proteolytic cleavage of procaspase-1 into its active form, caspase-1. Activated caspase-1 then cleaves pro–IL-1β and pro–IL-18 into their mature forms, which subsequently recruit and activate immune cells, including mast cells, eosinophils, and T lymphocytes [18, 19]. Ultimately, caspase-1 induces the formation of the pore-forming protein gasdermin D, initiating proptosis and the release of proinflammatory mediators [20].

Eosinophils and *mast cells* play pivotal roles in asthma-related inflammation through the secretion of histamine, heparin, and lysosomal enzymes [21], thereby contributing to edema, bronchospasm, and mucus hypersecretion. IL-1β further stimulates the production of IL-4, IL-5, and IL-13, promoting immediate-type hypersensitivity reactions and airway hyper-responsiveness [22]. The NLRP3 inflammasome can activate mast cells, eosinophils, and T lymphocytes, promoting the release of inflammatory mediators such as nitric oxide, prostaglandins, and leukotrienes, which exacerbate airway edema and obstruction [23]. This process compromises the barrier function of the bronchial epithelium, further amplifying allergic inflammation [24].

Studies by Horvat et al. demonstrated that an increased capacity for inflammasome activation may be a universal characteristic of systemic immune cells in patients with varying asthma severity, regardless of gender, degree of obesity, or granulocyte content in sputum and blood [25]. The release of mediators depends on disease severity [26]. For example, in severe asthma, systemic immune cells release higher levels of IL-1β due to the combined effect of antigen-specific T-helper precursor cell contact with the antigen and the activation of NLRP3 inflammasome, compared to cells from

patients with moderate asthma [27, 28]. These findings reveal significant differences between moderate and severe asthma, indicating that systemic immune cells in severe cases possess an enhanced capacity to respond during the initiation phase induced by pathogen components required for the synthesis of inflammasome components and pro–IL-1β, as well as an increased responsiveness to inflammasome activation required for cleaving and releasing active IL-1β [29].

Microbial infections serve as critical stimuli for both initiating and activating the NLRP3 inflammasome in the lungs during infection-related asthma [30]. Respiratory infections play a major role in triggering immune responses, including IL-1β-mediated reactions facilitated by the NLRP3 inflammasome in asthma patients. These responses contribute to the development of severe, steroid-resistant asthma forms [31]. Such findings highlight that an enhanced inflammasome activation capacity in systemic immune cells may play a key role in the pathogenesis of bronchial asthma. The increased release of interleukin-1 beta (IL-1β), driven by the NLRP3 inflammasome in immune cells of individuals with severe asthma, can be pharmacologically inhibited by MCC950, demonstrating the therapeutic potential of inflammasome blockade in clinical practice [32].

Several studies have also identified the role of the NLRP1 inflammasome in the development of allergic inflammation, as the gene encoding the NOD1 sensor is located within the same chromosomal locus (7q14-p15) as genes associated with allergic disease susceptibility [33, 34]. Multiple genes within this locus have demonstrated a positive correlation with elevated serum immunoglobulin E (IgE) levels—a hallmark of atopic asthma and a key pathogenic factor [35].

PATHOPHYSIOLOGICAL MECHANISMS IN THE DEVELOPMENT OF BRONCHIAL ASTHMA

Inflammasome formation in asthma can be regarded as an early pathophysiological event that precedes immune inflammation. Inhaled allergens are endocytosed by antigen-presenting cells—primarily dendritic cells in the airways—which continuously monitor the environment for pathogens. These dendritic cells migrate to the lymph nodes, where they present antigens via major histocompatibility complex molecules and engage naive $CD4^+$ T lymphocytes bearing antigen-specific receptors [36].

Dendritic cells play a vital role in shaping immune responses in asthma, acting as sentinels of the immune system. Through the secretion of various mediators and the expression of surface molecules, they can either promote immune tolerance or initiate an active immune response [37]. By directing the differentiation of $CD4^+$ T-cells into functionally distinct helper subsets, dendritic cells determine the character of the ensuing immune response. This differentiation is influenced by both the structural features of the allergen and the mediators secreted by the dendritic cells [38]. The production of IL-4, OX40 ligand (OX40L), and CD86 promotes the differentiation into T-helper type 2 (Th2) cells, which are central to asthma pathogenesis. A Th2-dominant immune response activates a humoral pathway marked by increased IgE production and eosinophil activation, culminating in allergic inflammation [39]. Genetic polymorphisms in the IL-4, IL-13, and IgE receptor genes are recognized as risk factors for atopic asthma [40].

Following Th2 cell activation, specific cytokines are released: IL-4 promotes B-cell class switching to IgE, IL-5 activates eosinophils, and IL-13 stimulates mucus hypersecretion and class switching from IgG to IgE in plasma cells. The synthesized IgE binds to high-affinity FcεRI receptors located on the surface of mast cells in interstitial tissues and on basophils via its Fc fragments. This IgE–FcεRI interaction can persist for years, playing a critical role in asthma exacerbations. The free Fab fragment of membrane-bound IgE remains available to bind allergens upon re-exposure, triggering the immediate release of mediators such as histamine, heparin, reactive oxygen species, leukotrienes, and cytokines, initiating early-phase symptoms within minutes [41].

Histamine is a key mediator that induces bronchial smooth muscle contraction (bronchial spasm), coughing, and expiratory dyspnea; increases vascular permeability, and leading to edema; and stimulates nerve endings, causing itching [42].

Arachidonic acid derivatives, including leukotrienes (LTC_4, LTD_4, LTE_4) and prostaglandin D_2 (PGD_2), contribute to bronchial obstruction by inducing bronchial smooth muscle spasm, mucosal edema, and mucus hypersecretion—factors that further exacerbate airway narrowing [43].

Chemoattractants such as IL-5 and eotaxin recruit eosinophils, lymphocytes, and monocytes to the airway mucosa. These cells release inflammatory mediators, including eosinophil cationic protein and major basic protein, which damage the epithelium and result in bronchial obstruction, mucosal edema, and mucus production several hours later— characteristic of the late-phase response [44, 45].

It is important to highlight the process of memory cell formation: as a result of interaction between T-lymphocyte receptors and co-stimulatory molecules on the surface of Th2 cells, sensitized B-lymphocytes are generated. These lymphocytes have the capacity to differentiate into memory cells, which accelerates the onset of allergic reactions upon repeated exposure to the allergen [46].

As the disease progresses, inflammation becomes chronic, leading to structural changes in the airways—commonly referred to as *airway remodeling* [47]. This process includes smooth muscle hyperplasia and thickening of the bronchial walls, which increases susceptibility to bronchial spasm. Goblet cell hypertrophy and hyperplasia result in excessive mucus production and obstruction of the small airways. Fibrosis and thickening of the basement membrane reduce airway elasticity, contributing to fixed airflow limitation. Epithelial damage and desquamation impair the protective barrier, heightening sensory nerve activation and provoking chronic cough [48].

The pathogenesis of asthma involves a complex interplay between immune, inflammatory, and structural mechanisms [49, 50]. Understanding these processes is essential for developing effective treatment strategies that not only at control symptoms but also prevent airway remodeling [51, 52].

Recent studies have identified the role of inflammasome in the pathogenesis of anaphylactic shock, a life-threatening allergic reaction characterized by excessive immune activation. IL-1β increases vascular permeability, leading to edema and vasodilation—both hallmarks of anaphylaxis. IL-18 enhances the inflammatory response by activating additional immune cells, such as T-helper cells. Both IL-1β and IL-18 activate mast cells, promoting degranulation and the release of mediators including histamine, prostaglandins, and leukotrienes [53]. These actions contribute to the clinical features of anaphylaxis, such as bronchial spasm, hypotension, pruritus, and erythema. IL-1β also induces endothelial cell retraction, further increasing vascular permeability, which exacerbates fluid extravasation, lowers arterial pressure, and may result in shock [54]. Excessive inflammasome activation—such as during a systemic inflammatory response—can trigger a cytokine storm (hypercytokinemia), a state of uncontrolled inflammation that amplifies tissue damage [55].

ROLE OF THE RESPIRATORY EPITHELIUM IN THE PATHOGENESIS OF BRONCHIAL ASTHMA

The structural characteristics of allergens can influence the configuration and activity of proteins, lipids, and nucleic acids, thereby affecting intracellular signaling pathways [56]. Proteases present in many allergens activate immune signaling pathways by modifying protease-activated receptors. These stimuli disrupt epithelial cell function and promote the release of mediators that recruit and activate leukocytes, amplifying allergic inflammation [57].

A key cytokine produced by the airway epithelium is *thymic stromal lymphopoietin* (TSLP), which induces significant changes in dendritic cells—antigen-presenting cells that deliver allergens to T-cells during the early phase of the allergic response. TSLP stimulates dendritic cells to release the chemokines CCL17 and CCL22, which facilitate T-cell recruitment to the airways [58]. It also enhances OX40 ligand expression, guiding dendritic cell–mediated T-cell activation toward a Th2-skewed immune response. TSLP, along with epithelial proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and IL-1β, can also activate mast cells [59].

Once thought to function solely as a physical barrier and site for gas exchange, the respiratory epithelium is now recognized as a central regulator in the inflammatory cascade [60]. In addition to serving as the interface between the host and environment, it produces a wide array of mediators in response to stimuli such as allergens, infectious agents, and oxidants, thereby engaging various components of the immune system [61]. As such, the airway epithelium plays an essential role in the innate immune response in asthma.

Following leukocyte infiltration into the airways, these immune cells produce inflammatory cytokines that strongly activate epithelial cells. This activation fosters chronic inflammation, wherein epithelial cells and leukocytes activate one another [62].

The epithelium also secretes growth factors that enhance inflammation and contribute to structural remodeling [63]. *Granulocyte-macrophage colony-stimulating factor* (GM-CSF) extends the survival of eosinophils and neutrophils, while *stem cell factor* supports mast cell survival and activation [64]. *Vascular endothelial growth factor* promotes angiogenesis, increases vascular permeability, and contributes to airway edema [65]. *Transforming growth factor β1* (TGF-β1) stimulates fibroblast and airway smooth muscle proliferation and promotes extracellular matrix deposition in the bronchial epithelium [66]. Along with cytokines, these mediators initiate and sustain chronic inflammation and airway remodeling, characterized by basement membrane thickening, fibrosis, and smooth muscle hypertrophy, which ultimately impairs lung function [67].

Reactive oxygen species (ROS) further maintain chronic airway inflammation by modulating histone acetylation and phosphorylation through mitogen-activated protein kinase pathways. Oxidative stress promotes the activation of AP-1 and NF-κB, leading to the upregulation of genes that encode proinflammatory mediators and antioxidants [68].

ROS also induce lipid peroxidation and generate toxic metabolites that compromise cell membrane integrity [69]. These species stimulate the expression of chemokines such as *macrophage inflammatory protein* 1α (MIP-1α), which recruits monocytes, neutrophils, eosinophils, basophils, and lymphocytes [70]. ROS also influence the synthesis of nitric oxide (NO), produced by inducible NO synthase in airway macrophages during inflammatory responses [71].

Eosinophils are markedly elevated in the airways of most patients with asthma. IL-5 plays a central role in eosinophil proliferation, a function shared by GM-CSF secreted by epithelial and mast cells [72]. Chemokines such as CCL5 and CCL11 mediate eosinophil recruitment to the airways. [73]. They can present antigens to T-cells and secrete growth factors (e.g., TGF-β1), emphasizing their pathogenic role in asthma [74]. Their contribution may differ across asthma phenotypes, with elevated eosinophils counts more commonly observed in severe cases [75].

IL-13, a Th2-derived cytokine, has emerged as a therapeutic target [76, 77]. It induces airway hyperresponsiveness and structural changes, including subepithelial fibrosis, airway smooth muscle proliferation, and goblet cell hyperplasia. IL-13 drives inflammation primarily via epithelial activation and promotes eosinophilia through chemokine induction (e.g., CCL11) [78]. It is also linked to glucocorticoid resistance, with elevated levels detected in patients with steroid-refractory asthma [79].

Asthmatic airways also contain large numbers of macrophages that secrete inflammatory cytokines and chemokines [80]. In severe asthma, neutrophils are often elevated, likely due to secondary bacterial infections, which may contribute to reduced responsiveness to glucocorticoids [81].

Recently, a subset of T-helper cells known as Th17 cells has been implicated in asthma-related inflammation [82]. In murine models, allergen sensitization leads to Th17 migration to the lungs, where they enhance neutrophilic infiltration and amplify Th2-mediated eosinophilic inflammation [83, 84]. IL-17 upregulates the expression of cytokines, chemokines, adhesion molecules, and growth factors. The exact role of IL-17 in asthma, and its interactions with Th2 cells and other leukocytes populations, remains under active investigation and is vital to understanding disease mechanisms and developing new treatments [85].

Although the NLRP3 inflammasome is essential for mounting effective immune responses, its hyperactivation is linked to a range of inflammation-driven conditions, including cardiovascular, metabolic, neurologic, and autoimmune disorders [86–88].

Multiple regulatory pathways act to limit excessive inflammasome activation [89]. Interferons inhibit inflammasome activation by inhibiting caspase-1, which is required to process pro–IL-1β and pro–IL-18 [90]. Interferons also downregulate the expression of NOD1, NOD2, and ASC, thereby impeding inflammasome formation [91]. They enhance IL-10 production, a key anti-inflammatory cytokine that reduces neutrophil and eosinophil infiltration into the airways [92]. Autophagy further mitigates inflammation by degrading inflammasome components. A critical interferon-induced mechanism for suppressing NLRP3 activity involves inducible nitric oxide synthase in T-cells, which leads to leading to nitric oxide–mediated nitrosylation and inhibition of NLRP3 [93].

Ongoing studies on NLRP3 inhibition seeks to reduce airway inflammation in patients with chronic diseases such as asthma, without compromising systemic immune functions [94, 95].

NEW THERAPEUTIC PERSPECTIVES IN BRONCHIAL ASTHMA

MCC950 is a small-molecule inhibitor that selectively blocks NLRP3 inflammasome activation, representing a promising therapeutic strategy for inflammatory diseases [96].

Initially developed by Pfizer in 2008 under the name CP-456,773 (also known as CRID3), the compound's mechanism of the action was unclear, and subsequent clinical trials were halted. In 2015, researchers led by Matt Cooper and Luke O'Neill identified MCC950 as a potent and selective NLRP3 inhibitor [97].

Currently, Novartis is advancing the clinical development of MCC950, having successfully completed phase I trials, which highlights its potential for treating inflammatory conditions [98].

MCC950 (N-[[[1,2,3,5,6,7-hexahydro-s-indacen-4-yl] amino]carbonyl]-4-[1-hydroxy-1-methylethyl]-2-furansulfonamide) inhibits the NLRP3 inflammasome selectively by preventing its assembly and the subsequent activation of caspase-1. This action suppresses the release of IL-1β and IL-18, thereby reducing airway inflammation. MCC950 interferes with the conformational changes in NLRP3 required for inflammasome formation [99], and it limits neutrophil recruitment and activation—key mechanisms in the pathogenesis of severe and glucocorticoid-resistant asthma [100].

Recent preclinical studies have demonstrated MCC950's efficacy in treating inflammatory, autoimmune, and neurodegenerative diseases [101–105], including severe asthma [106].

CONCLUSION

The NLRP3 inflammasome plays a pivotal role in airway inflammation by promoting cytokine release and immune cell activation. Its hyperactivity is associated with severe and steroid-resistant asthma, making it a compelling target for novel therapies. Modulating inflammasome activity may offer a promising approach for precision treatment of asthma. Inhibitors such as MCC950 show potential in reducing inflammation and improving clinical outcomes. However, further research is necessary to evaluate the safety and long-term effects of NLRP3 inhibition. Continued exploration of its regulatory mechanisms will support the development of effective, personalized therapeutic strategies for asthma.

ADDITIONAL INFORMATION

Authors' contribution. B.I.Kh.—conceptualization, formal analysis, writing—review and editing, supervision; E.K.G.—methodology, validation, investigation, writing—original draft; D.A.S.—methodology, validation, investigation, writing—original draft; L.M.I.—methodology, validation, investigation, writing—original draft; G.Kh-A.R.—methodology, validation, investigation, writing—original draft; B.I.Kh.—writing—review and editing, funding acquisition. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией). Наибольший вклад распределён следующим образом: Б.И.Х. — концептуализация, анализ, редактирование рукописи, общее руководство; Э.К.Г. — методология,

валидация, исследование, создание черновика; Д.А.С. — методология, валидация, исследование, создание черновика; Л.М.И. — методология, валидация, исследование, создание черновика; Г.Х-А.Р. — методология, валидация, исследование, создание черновика; Б.И.Х. — редактирование рукописи, общее руководство.

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

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

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