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Review

Inflammasome-mediated mechanisms of systemic inflammation in COVID-19 and asthma

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Abstract: The review examines the formation of inflammasome-mediated mechanisms of systemic inflammation in asthma after COVID-19. It provides insight into the clinical and pathophysiological relationship between asthma and COVID-19. The review summarizes information about the role of the NLRP3 inflammasome in the pathogenesis of asthma and describes in detail its manifestations in various asthma phenotypes. Emphasizing the significance of the inflammatory-mediated immune response during coronavirus infection in patients with bronchopulmonary pathology, the review outlines the consequences of hyperactivation of the NLRP3 pathway, leading to increased production of cytokines, the appearance of neutrophil and monocyte-derived traps, induction of pyroptosis and the development of complications.

Keywords: asthma, COVID-19, inflammasome.

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Introduction

Currently, the problems of developing symptoms caused by a new coronavirus infection, as well as their persistence occasionally leading to severe progression and long-term recovery, remain relevant. Patients with asthma are at risk. According to the World Health Organization (WHO), as of 2022, there were approximately 339 million people with asthma worldwide, and nearly 400,000 individuals die each year from the disease and its complications [1]. Respiratory viral infections play a critical role in exacerbating asthma. With the high prevalence of the new coronavirus infection, which often leads to damage to the respiratory system, the likelihood of asthma exacerbation is significant.

Asthma is a heterogeneous disease with multiple phenotypes characterized by specific triggers and variations in the development of the inflammatory response. New clinical data shed light on the significant role of inflammasome activation of NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) in the pathogenesis of asthma. Activation of this mechanism for regulating the systemic inflammatory response is also characteristic of COVID-19. Currently, there is a need to detail the mechanisms of inflammasome-mediated inflammatory processes in various asthma phenotypes and highlight the features of the influence of previous COVID-19 infection on the course of asthma.

This review is the first to systematize information about the following issues:

(1) The features of the inflammasome-mediated mechanisms of the systemic inflammatory process in patients with bronchial asthma who previously suffered from COVID-19;

(2) The specific ways of forming an immune response in patients with bronchial asthma of various origins;

(3) The markers that create the prerequisites for the formation of post-COVID syndrome in this pathology.

The results of published studies characterizing the involvement of inflammasome-mediated mechanisms in the formation of long-term consequences after coronavirus infection in patients with bronchial asthma are presented.

Association of asthma with coronavirus infection

The relationship between asthma and viral infections has been extensively studied. However, the emergence of the new coronavirus infection over the past four years has given rise to new considerations. SARS-CoV-2 is a new coronavirus first identified in Wuhan, China, on December 31, 2019 [2]. The infection quickly spread throughout China, and within a month the World Health Organization (WHO) recognized the outbreak [1]. Due to its rapid global spread and high number of deaths, WHO declared coronavirus disease 2019 (COVID-19) a global pandemic [3]. Towards the end of 2020, there was an increasing number of reports of weakness, shortness of breath, decreased quality of life and psychosocial distress increased. Several studies have stated that 87% of patients discharged from hospital continued experiencing symptoms such as weakness (53%), shortness of breath (43%), arthralgia (27%), and chest pain (22%) [4-6].

In the context of the global spread of the new coronavirus infection, asthma patients were of particular concern [7]. The

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established role of respiratory viral infections as triggers and inducers of asthma has raised concerns about the increased susceptibility of asthma patients to coronavirus infection and its possible complications. Given the involvement of the respiratory system in the development of COVID-19, it is logical to assume that patients with asthma are particularly vulnerable to COVID-19. Some publications suggested a possible exacerbation of asthma among patients with confirmed COVID-19 [8, 9]. How asthma affects recovery from SARS-CoV-2 infection remains unclear.

According to clinical recommendations during the COVID-19 pandemic, patients with bronchopulmonary pathology were classified as a high-risk group. Consequently, even in cases of mild COVID-19, patients with asthma require hospitalization. An important characteristic of the immune response during the progression of COVID-19 is the cytokine storm, which is a systemic inflammatory response characterized by the production of large amounts of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α). In atopic asthma, a type 2 T helper (Th2) immune response is more typical, leading to the production of appropriate cytokines (IL-4, IL-5, IL-13, etc.) [10]. Several studies have demonstrated that activation of the Th2 pathway in patients with comorbid asthma and COVID-19 plays an important role: some type 2 cytokines can inhibit the production of proinflammatory cytokines. In addition, the mucus lining the epithelium may act as a physical barrier to block viral entry, while ribonucleases released by activated eosinophils may act on the viral genome [10, 11]. In addition, regular use of low-dose inhaled corticosteroids may attenuate airway inflammation caused by SARS-CoV-2 [12]. However, an increasing number of studies indicate that bronchial asthma contributes to severe and prolonged course of coronavirus infection [12-28]. This may be due to the presence of a specific non-Th2 phenotype in patients. It seems likely that the presence of a specific asthma phenotype will contribute to both a more severe course of coronavirus infection and prolongation of symptoms, leading to the formation of post-COVID syndrome.

Inflammasomes: their role in maintaining the inflammatory process in COVID-19 and bronchial asthma

At present, there is no unified pathogenetic theory of COVID-19 formation. It is known that the virus enters the host cell by means of the fusion of the viral envelope with the host cell membrane. Angiotensin-converting enzyme 2 (ACE2) is one of the key cell receptors that binds to the spike (S) protein of the SARS-CoV-2 viral envelope. The activation of the S protein is mediated by the transmembrane serine protease 2 (TMPRSS2) [29].

Accumulated scientific evidence confirmed the inhibition of intracellular innate immune response associated with type I, II, and III interferons during coronavirus infection. This contributes to active viral replication and rapid spread. The virus, upon entry, activates various immune cells: endothelial cells, dendritic cells, macrophages, monocytes, natural killer T cells (*Figure 1*) [11, 13, 25-27].

Mechanisms of inflammasome-mediated inflammatory response

Scientists now believe that in addition to ACE2, there are other protein compounds that help the coronavirus penetrate the host cell. These compounds include toll-like receptors, NOD-like receptors (nucleotide-binding oligomerization domain-like receptors, NLRs), which are a class of cytosolic structures formed during tissue damage. Over 20 types of NLRs have been described in humans. The most studied are those NLRs that form inflammasomes: NLRP1, NLRP3, NLRC4, NLRC5, NLRP6, NLRP7 and NLRP12 [31, 32]. The term '*inflammasome*' refers to the macromolecular complexes formed by different types of NLRs upon their activation. These complexes serve as a molecular platform for the activation of caspase-1 (a cysteine protease that mediates proteolysis and activation of the cytokines IL-1 and IL-18). In typical cases, the inflammasome contains three components: 1) NLR protein; 2) adaptor protein with caspase activation domain (ASC); 3) caspase-1 molecules (effector caspases). Inflammasomes are named by the NLR protein they contain. Among the mentioned types of inflammasomes, the most studied is NLRP3, which not only participates in the immune response against bacteria, viruses and fungi [34,35,36], but also recognizes danger signals such as ATP, urate crystals, increased generation of reactive oxygen species, amyloid beta (Aβ) [37], oxidized low-density lipoprotein and cholesterol crystals). NLRP3 is mainly expressed in airway epithelial cells, T cells, monocytes and neutrophils [38, 39].

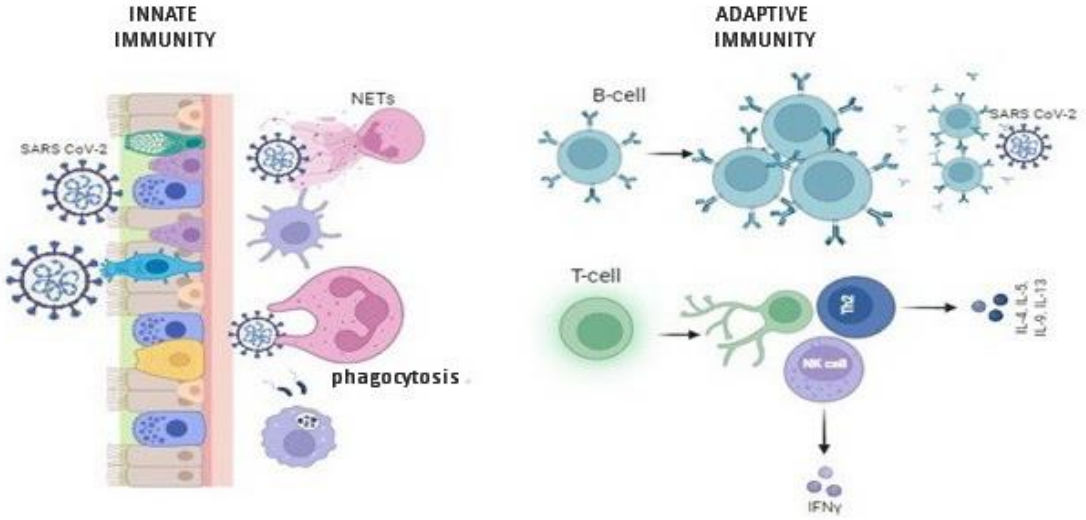

Figure 1. SARS-CoV-2 impact on innate and adaptive immune responses.

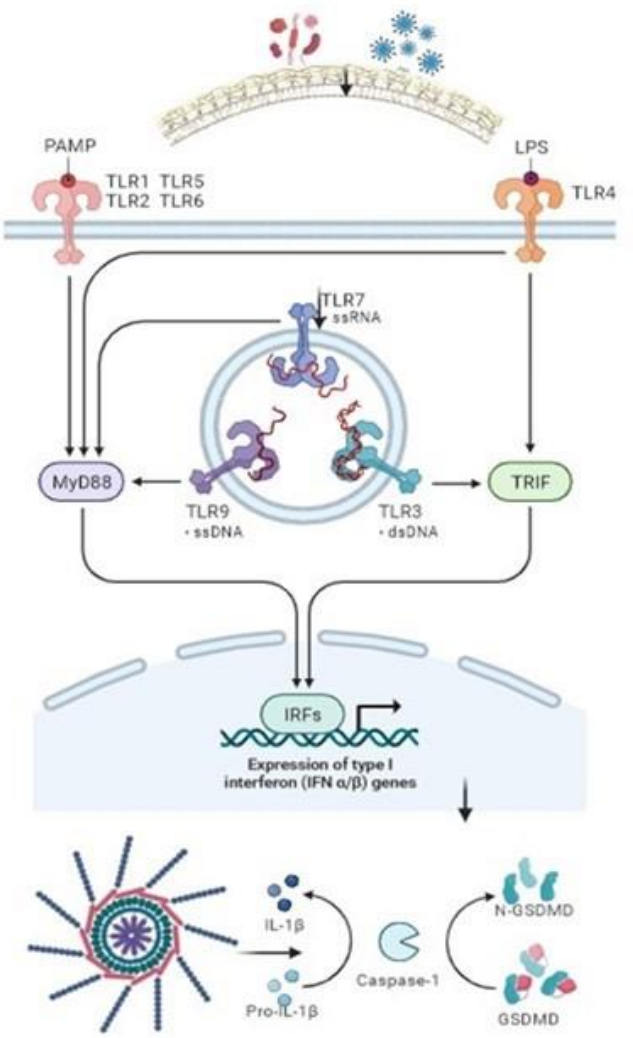

Figure 2. Assembly of the inflammasome.

Viruses and bacteria act as triggers of inflammasome formation, which leads to activation of the NF-κB signaling pathway and increased expression of the NLRP3 protein through receptors, interleukins and toll-like receptors (TLRs) for interferon alpha.

Activation of NLRP3-mediated inflammation occurs via three different molecular pathways: canonical, non-canonical and alternative [40-42]. The non-canonical pathway involves caspase-11 in mice or caspase-4/5 in humans inducing IL-1β and IL-18 release and pyroptosis following lipopolysaccharide (LPS) stimulation [42, 43]. An alternative pathway exists only in human monocytes, where TLR4 recognizes extracellular lLPS and induces NLRP3 activation, along with cytokine maturation through the caspase-8/FADD/RIPK3 signaling pathway without inducing pyroptosis [43].

Assembly of the NLRP3 inflammasome through the canonical pathway requires two signals. The source of the first signal is microbial products, viruses and cytokines. TNF-α, IL-1β, IL-1α, toll-like receptor TLR ligands (such as LPS) or NLR receptor (such as muramyl dipeptide) induce activation of the NF-κB signaling pathway, leading to increased NLRP3 protein expression and regulation of pro-IL-1β [30, 31, 40]. The second signal is transmitted by extracellular molecules such as ATP, pore-forming toxins and crystals of various substances (calcium pyrophosphate, cholesterol, microbial RNA) [43]. These agents activate the NLRP3 protein, which leads to its oligomerization and then to the recruitment of ASC molecules culminating in formation of the NLRP3 inflammasome (*Figure 2*), while ASC connects NLRP3 to caspase-1 allowing its activation. When activated, caspase-1 can cleave pro-IL-1β to produce IL-1β, specifically its mature, active, secreted form. Once IL-1β leaves the cell, it binds to the IL-1 receptor leading to inflammation (*Figure 3*).

Furthermore, activated caspase-1 can cleave gasdermin D (GSDMD) leading to lytic cell death known as pyroptosis. N-GSDMD perforates the cell membrane to form non-selective pores with an internal diameter of 10-14 nm, causing cell swelling and pyroptosis [44]. On the other hand, caspase-1 also cleaves IL-1β and IL-18 precursors to form mature IL-1β and IL-18, which are released through the pore created by GSDMD, resulting in pyroptosis [45, 46]. Pyroptosis also leads to the release of damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1) and lactate dehydrogenase (LDH), which recruit immune cells and further enhance inflammation [47]. GSDMD perforates the cell membrane forming nonselective pores, which subsequently leads to water influx, lysis, and cell death. Activated caspase-1 not only cleaves GSDMD, which leads to the formation of N-GSDMD and induces pyroptosis, but also processes IL-1β/IL-18 precursors, causing the release of IL-1β/IL-18 through the pores [47, 48]. High levels of pyroptosis can aggravate inflammatory symptoms leading to cell death and severe tissue and organ failure [49]. It currently remains unresolved whether cell death is required for IL-1β release. An attractive hypothesis suggests that because caspase-1 is required for both pyroptosis and cleavage of IL-1β, IL-1β is passively released following plasma membrane rupture along with DAMPs and intracellular cytosolic proteins such as LDH. Recent studies using single-cell imaging technology on monocyte cell lines or macrophages suggested that cell death is inevitable following caspase-1 activation, and therefore IL-1β is released solely from dying cells [50, 51].

Pyroptosis in COVID-19 and asthma

Cells activated by the coronavirus stimulate multiple inflammatory pathways, leading to hyperinflammation and cytokine storm, which deters the spread of the virus in the body. At the same time, hyperinflammation contributes to tissue damage by causing acute respiratory distress syndrome and multiple organ failure [52]. These processes are observed in the peripheral blood of patients in the form of considerable cell death in the leukocytes. Pyroptosis is one of such cell death mechanisms in coronavirus infection [53] (*Figure 3*). On the one hand, it deprives SARS-CoV-2 of its replicative niche via causing lysis of infected cells, subjecting the virus to extracellular immune response. However, SARS-CoV-2 has developed complex mechanisms to employ this mode of cell death for its own survival, replication, and dissemination. Viral products of SARS-CoV-2 modulate various key components of the pyroptotic pathways, including caspase and gasdermin. Pyroptosis induced by SARS-CoV-2 contributes to the development of the pathological process by causing outflow of the intracellular contents. Thus, pyroptosis is an important immunopathogenesis mechanism in COVID-19 [47, 48, 54]. Proinflammatory factors originating from pyroptotic cells enter the lungs and other organs through the circulation, ultimately leading to multiple organ involvement in COVID-19 [55].

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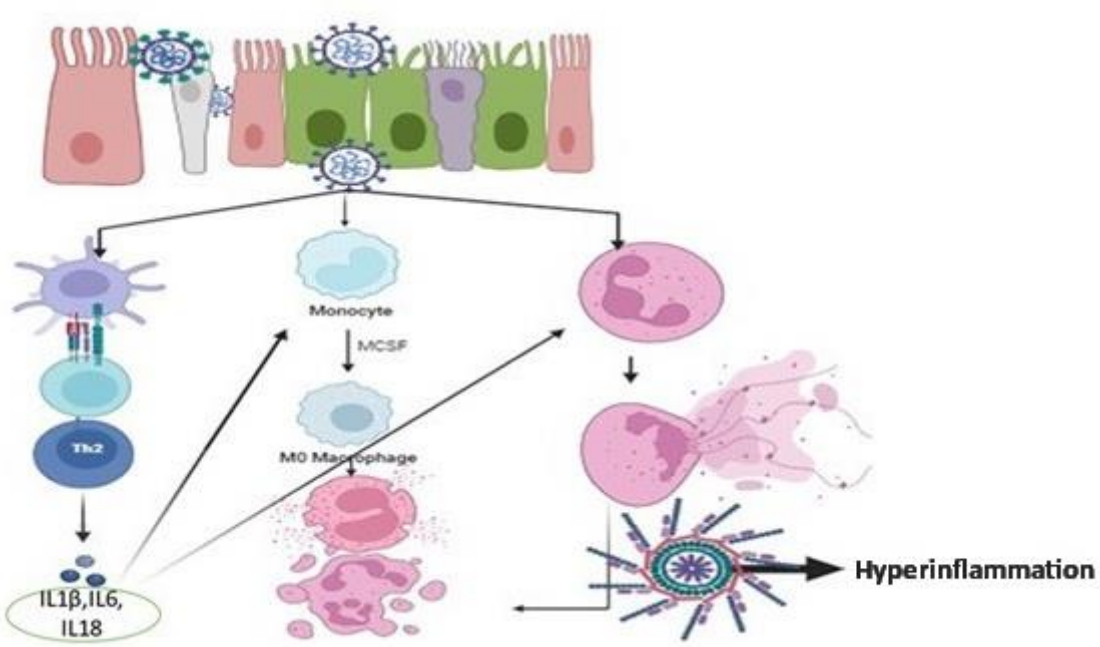

Figure 3. Diagram of coronavirus-mediated immune cell damage leading to cell death and hyperinflammatory response.

Pyroptosis in COVID-19 involves various subpopulations of immune cells. In a study by A.C. Ferreira et al., monocytes isolated from patients with severe COVID-19 demonstrated high activation of caspase-1 accompanied by intense death of monocytes. It has been demonstrated that SARS-CoV-2 infection induce pyroptotic cell death in human microvascular endothelial cells, which coincide with the activation of the NLRP3/caspase-1 signaling cascade and the maturation of IL-1β [56]. This contributes to the disruption of the pulmonary endothelial barrier and induced neutrophil recruitment, leading to a state of hyperergic inflammation [57,58]. Pyroptotic macrophages that phagocytize viruses may trigger the release of numerous alarmins, such as cytokines, chemokines, LDH, and reactive oxygen species, leading to a rapid response from neighboring immune cells and a chain reaction of pyroptosis. Pyroptosis may contribute to the release of viral components into circulating blood leading to the formation of immune complexes and the accumulation of immune cells in target tissues, thereby triggering a critical inflammatory cascade. Alveolar macrophage pyroptosis causes acute lung injury, promoting the infiltration of neutrophils and macrophages into lung tissues and increasing the levels of proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) [59, 61]. These events contribute to excessive release of inflammation mediators, cell death, and further recruitment of innate immune cells in patients with COVID-19. Additionally, pyroptotic immune cells secreting proinflammatory cytokines IL-1β and IL-6 may aggravate lymphopenia, thereby contributing to adaptive immune dysfunction in COVID-19 [62]. It is worth noting that suppressing pyroptosis in macrophages may alleviate abnormal blood coagulation by preventing the release of tissue factor, which acts as the initiator of coagulation cascades in patients with COVID-19 [63].

In recent years, some studies showed that bronchopulmonary pathology also involves pyroptotic mechanisms in its pathogenesis [60,64]. Pyroptosis plays an important role in airway remodeling in asthma [64]. Epithelial cell pyroptosis may represent a pathological mechanism contributing to inflammatory airway damage [65]. Among the various asthma phenotypes, pyroptosis seems more closely associated with severe, corticosteroid-resistant neutrophilic asthma [66]. There is a correlation between the level of pyroptosis and airway inflammation, symptom control, and lung function in neutrophilic asthma. Some authors discovered that in the airways of patients with severe asthma, there are numerous activated neutrophils, and extracellular neutrophil traps and their products may stimulate pyroptosis, which could be a decisive cause of insensitivity to glucocorticoid treatment [67]. Some researchers conducted transcriptomic sequencing of the lungs in three different phenotypes of asthma (eosinophilic, mixed, and neutrophilic), which demonstrated that genes associated with pyroptosis, such as Nlrp3, Nlrc4, Casp-1, and IL-1β, were frequently encountered in neutrophilic asthma [68]. In the process of transitioning from eosinophilic asthma to glucocorticoid-resistant neutrophilic asthma, the pyroptotic pathway in lung tissue is noticeably activated, and targeted blockade of pyroptotic signaling can impede this transitional process [69, 70]. These findings imply that pyroptosis may contribute to the development of refractory corticosteroid-resistant neutrophilic asthma and therefore should be a potential therapeutic target.

Clinical and experimental studies demonstrated the association between pyroptosis and the severity of COVID-19 in severe asthma. It was established that pyroptosis is associated with the development of critical conditions after infection with the novel coronavirus in patients with severe asthma [71]. It is likely that antecedent severe asthma may enhance pyroptosis induced by SARS-CoV-2 infection, and targeted correction of pyroptosis can be a promising method of treating COVID-19 in this category of patients [72, 73].

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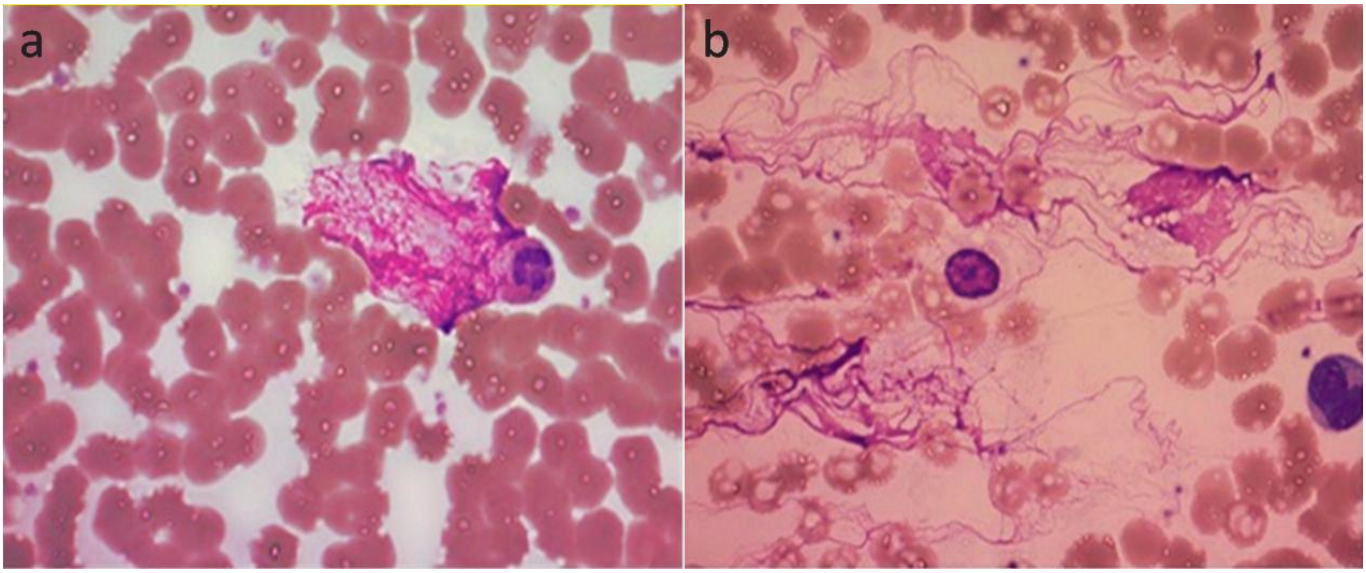

Figure 4. Neutrophil traps.

In Figures 4a, 4b, arrows indicate neutrophil traps. In Figure 4b, the neutrophil trap takes up almost the entire image. Photos were taken using Zen software with AxioCam ER5s Con.

NETosis in COVID-19 and asthma

In addition to pyroptosis, inflammatory diseases initiate an alternative form of cell death known as NETosis. The term '*NETosis*' refers to the process of neutrophil death accompanied by extrusion of DNA networks and formation of neutrophil extracellular traps (NETs) [74, 75]. Histones and antimicrobial proteins aggregate within the decondensed DNA structure, serving as a scaffold for trapping pathogens [76]. The formation of NETs can be triggered by various inducers, including microorganisms, bacterial components, activated platelets, complement peptides, autoantibodies and interleukins. IL-18 released during NLRP3 assembly induces NETosis [77]. In turn, NET formation activates NLRP3 assembly [77]. The antimicrobial function of NETs is associated with the destruction of microorganisms and the prevention of their spread. However, viruses that produce nucleases can destroy traps and be released from them, facilitating the spread of the virus beyond the site of entry [78-80].

NETs promote blood coagulation by dysregulation during viral infections, which is especially relevant given the massive neutrophil infiltration of pulmonary capillaries in COVID-19 [81, 82]. Circulating neutrophils in the blood of patients with COVID-19 exhibit increased activation of NETs [81, 82]. NETs affect the coagulation system by inducing the expression of tissue factor by captured leukocytes and monocytes. NETs can trap platelets and modulate platelet activation, adhesion, and aggregation. The synthesis of NETs in the microcirculatory system promotes the formation of microthrombi there [83, 84].

The appearance of a significant number of neutrophil traps may be associated with existing chronic conditions in patients who suffered from coronavirus infection. Interestingly, the formation of NETs has also been described in bronchopulmonary pathologies, in particular in bronchial asthma [85, 86]. Studies have documented the formation of NETs in a specific asthma phenotype: neutrophilic asthma. Excessive trap formation is associated with an increase in the intensity of the inflammatory response. NETs have been found to cause airway obstruction by increasing cell-rich aggregates in the small airways [87]. These findings suggested that increased NET formation in patients with asthma may be associated with disease severity. It was demonstrated that NETs can disrupt the integrity of the airway epithelium, causing cell death and detachment, thereby leading to increased epithelial permeability. Besides, NETs stimulate epithelial cells to produce IL-8, which can generate a positive feedback loop to attract more neutrophils to the airways and activate them, which exacerbates the inflammatory response [87].

Some published sources described abnormal immune responses in peripheral blood in patients with simultaneous COVID-19 and asthma [88, 89]. For example, it has been shown that six months after coronavirus infection, patients with asthma exhibited high levels of NETs in their peripheral blood, which may indicate a hyperactivation of their immune response [90] (*Figures* 4a, 4b).

It was also revealed that the products of NETosis stimulate type 17 T helper cells, leading to the secretion of IL-17, thereby resulting in an extended uncontrolled inflammatory process [91, 92]. Clearly, excessive formation of NETs can have serious consequences. Increased trap formation may serve as a diagnostic criterion for differentiating various phenotypes of chronic obstructive respiratory diseases predicting disease progression and determining disease severity [92]. However, it is essential to more precisely define their role in the mechanisms of various diseases, as this may lead to the development of more effective diagnostic and treatment methods.

Features of the inflammasome-mediated response in asthma and asthma with COVID-19

Since recently, chronic inflammatory lung diseases were associated with activation of the inflammasome pathway [93]. Recent reports revealed that NLRP3-related inflammatory response is a key factor in the pathogenesis of asthma [94]. It was found that the expression of NLRP3 and caspase-1 in bronchoalveolar lavage (BAL) of asthma patients is higher than in healthy individuals [95]. The expression of NLRP3 and IL-18 is also

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increased in the airway epithelium of asthmatic patients vs. healthy controls [96]. Some animal studies demonstrated that activation of NLRP3, caspase-1, and IL-1β causes steroid-resistant neutrophilic inflammation and airway hyperresponsiveness. Several studies established an association between NLRP3 activation, IL-1β levels, and NET formation in severe asthma. Sputum NLRP3 and IL-1β gene expression levels were higher in severe asthma, compared with mild asthma, and were associated with both increased sputum neutrophil counts and poorer lung function [97].

Other studies demonstrated the involvement of the inflammatory pathway in patients with different asthma phenotypes [98]. Some evidence suggests that NLRP3 promotes the activation of allergen-specific Th2 cells. Animal models confirmed that NLRP3 plays an important role in the development of allergic asthma [99]. Inflammatory activation of NLRP3 may promote the production of the cytokines TNF-α and IL-13 and participate in the pathogenesis of mucus hypersecretion in the airways [99]. Nlrp3-/- mice were shown to have smaller eosinophil recruitment and less mucus secretion in the airways. Additionally, NLRP3 in bronchial epithelial cells or Th2 cells was demonstrated to promote type II immune response in eosinophilic asthma [100, 101].

Neutrophilic asthma deserves special attention, since neutrophilic pneumonia is closely associated with disease severity and resistance to traditional corticosteroid therapy. J.L. Simpson et al. showed on experimental animals that the expression of NLRP3 genes was higher in neutrophilic asthma vs. eosinophilic asthma. Recent studies revealed that the pathogenetic mechanism of neutrophilic asthma is associated with the activation of NLRP3, IL-1β, caspase-1 and IL-18 [102]. IL-1β is a well-known inducer of neutrophilia, potentially contributing to significant airway inflammation [103]. IL-18 triggers numerous proinflammatory responses and is involved in airway hyperresponsiveness [103]. In a mouse model of asthma, animals deficient in IL-18 exhibited reduced neutrophilic inflammation and airway remodeling [104]. Furthermore, recent evidence established that IL-1β and IL-18 act synergistically with IL-23 to promote Th17 cell differentiation and IL-17A production, thereby stimulating neutrophilic airway inflammation [103, 104]. Increased expression of NLRP3 may promote the differentiation of CD4 cells into Th17 cells, and IL-17 expressed by Th17 cells may in turn promote NLRP3 expression, suggesting a positive feedback regulatory mechanism between NLRP3 and Th17 [102]. Blocking the NLRP3/caspase-1/IL-1 pathway significantly reduces airway hyperresponsiveness, inhibits the infiltration of inflammatory cells in the bronchi, reduces their number in bronchoalveolar lavage fluid, and shifts the balance of Th17/Treg cells towards Tregs in asthmatic patients with neutrophilic airway inflammation. As shown by Ling Chen et al. (2022), inhibition of NLRP3 activation increases Foxp3 mRNA expression and Treg immunological response, thereby helping to restore Th17/Treg balance in asthma patients [102].

A study by Jack Seok-Jin described those differences in levels of inflammasome activation across different asthma phenotypes may be due to contributions from both neutrophils and macrophages. The importance of neutrophil inflammasome NLRP3 was recently demonstrated by Xiangyong Que et al. [105], while several other studies showed that genetic variations in NLRP3 lead to delayed neutrophil apoptosis affecting the resolution of inflammation [105]. Putative disturbances in the inflammatory response in patients with asthma may be associated with the influence of viral, bacterial and allergenic products, as well as cytokines on the initiation of the inflammatory signaling pathway. The development of a Th17-oriented phenotype may be key to the development of an inappropriate immune response driven by inflammation. IL-17 can significantly increase the mRNA levels of IL-1β, IL-18, NLRP3 and caspase-1 [102]. Perhaps this creates conditions for chronic inflammatory process, which leads, as a consequence, to the formation of a vicious circle. Further studies are needed to elucidate the specific contribution of inflammasomes to the development of neutrophilic asthma.

Recent studies confirmed that NLRP3 inflammasome plays a critical role in the pathobiology of COVID-19 [89, 94, 97, 106]. It was revealed that the expression of NLRP3, ASC, caspase-1, IL-1β, IL-6 and TNF-α genes is significantly increased in the lungs of COVID-19 patients [107]. Using single-cell RNA sequencing of nasal swab samples from patients in the early stages of COVID-19, several clusters of macrophages and dendritic cells containing an activated NLRP3 inflammasome were described. Possible mechanisms of NLRP3 inflammasome activation induced by SARS-CoV-2 are primarily based on canonical activation pathways [95]. Accumulating evidence suggests that activation of NLRP3 is critical in the pathogenesis of asthma [94, 96]. Although NLRP3 promotes clearance of pathogens from the respiratory tract, persistent activation of NLRP3 by inhaled irritants and environmental allergens can lead to exacerbation of asthma [96].

The development of the NLRP3 inflammatory response in COVID-19 largely depends on the underlying conditions associated with bronchopulmonary pathology and its specific phenotype. It was established that antecedent asthmatic inflammation significantly influences SARS-CoV-2-induced NLRP3 activation in mouse lungs [108]. As expected, IL-1β blockade significantly reduced SARS-CoV-2-induced lung inflammation in these mice. Transcriptomic analysis of mouse lung tissue confirmed these results [109]. Analysis of a national cohort demonstrated higher severity of COVID-19 in patients with asthma who require systemic corticosteroids. W. Gao and J. Gong showed that the eosinophilic asthma phenotype plays a protective role during both SARS-CoV-2 infection and COVID-19. Meanwhile, the neutrophilic phenotype has an increased risk of infection and the development of severe forms of COVID-19. As the analysis of pathophysiological mechanisms presented in this review has shown, the development of an inflammasome-mediated response plays a key role in this process [100, 103].

Conclusion

Hence, the immune response mediated by inflammasomes plays an important role in protecting the body from infection, but inadequate activation of inflammasomes significantly contributes to the pathogenesis of a number of diseases, including COVID-19 and bronchopulmonary pathology. Activation of inflammasomes causes a complex set of disorders: severe inflammation, disseminated intravascular coagulation and prolonged recovery after coronavirus infection. Understanding the role of the inflammasome-mediated inflammatory response in asthma and COVID-19-induced asthma is critical for the development of biomarkers in combination with novel therapeutic agents. To develop standards of therapy and preventive measures, further detailed study of the characteristics of systemic inflammation in patients with bronchial asthma after COVID-19 is required.

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Conflict of interest

The authors declare no conflicts of interest.

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