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Mini review

Mast cells in severe respiratory virus infections: insights for treatment and vaccine administration

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Abstract: Mast cells (MCs) are a part of the innate immune system and express receptors for microbial and viral pathogens characteristic of this system. The pathological role of MCs has been demonstrated for a number of highly virulent viral infections. The role of MCs and their Fc receptors for IgE in the immediate-type hypersensitivity reactions and in immunocomplex reactions is well-known, although the role of MCs and their Fc receptors for IgG (FcγR) in immunocomplex processes is much less studied. Antibody-dependent enhancement syndrome (ADE) has been observed in a number of viral infections and is associated with greater secondary infection. ADE is enhanced by virus-specific antibodies, which are not involved in the virus penetration into the cell but are capable of forming immune complexes. The role of MCs in ADE is well-established for dengue infection, RSV infection and coronavirus (CoV) infection. The involvement of IgG-mediated mast cell responses in other human viral infections including Coronavirus disease 2019 (COVID-19) is poorly understood. Recently discovered mast cell activation disease is considered one of the causes of severe post-infectious complications in COVID-19. If the role of MCs in the pathogenesis of severe viral infections, including ADE in recurrent viral infection is clarified, these cells and the products they release may serve as promising targets for such therapeutic agents as histamine receptor blockers or membrane stabilizers to prevent possible complications.

Keywords: mast cells; viral infections; innate immunity; antibodies; Fc receptors

Abbreviations: ADE: antibody-dependent enhancement; APC: antigen presenting cells; CNS: central nervous system; CoV: coronavirus; COVID-19: coronavirus disease; DENV: dengue virus; EV: extracellular vesicles; FcεR: high-affinity IgE receptor; FcγR: Fc receptors for IgG; IIV: inactivated influenza vaccines; IL: interleukin; MC: mast cell; MDA5: melanoma differentiation-associated protein 5; MCET: mast cells extracellular trap; MCT: MCs, containing only tryptase; MCTC: MCs containing tryptase and chymase; MCC: MCs containing only chymase; NOD: nucleotide-binding oligomerization domain; RIG-I: Retinoic acid-inducible gene I; RSV: respiratory syncytial virus; RV: rhinovirus; SARS: severe acute respiratory syndrome; TLRs: Toll-like receptors; TNFα: tumor necrosis factor alpha; VAERD: vaccine-associated enhanced respiratory disease

1. Introduction

Influenza viruses and coronaviruses (CoV) are some of the pathogens that cause pandemics in the modern world. The influenza virus is one of the few respiratory viruses against which vaccines have been developed and widely used. At the same time, a large group of non-influenza respiratory viruses contributes to the overall structure of the respiratory infection incidence. Several acute respiratory viral infections caused by a respiratory syncytial virus (RSV), rhinovirus or parainfluenza viruses may be complicated by post-infectious bronchial hyperreactivity [1–4], and vaccines have not yet been used against these infections. When developing vaccines against new emergent viruses, it is necessary to study immune-pathogenesis taking into account the role of various factors of innate and adaptive immunity including those in recurrent infections.

2. Mast cells

Mast cells (MCs) and basophils originate from the same myeloid lineage of hematopoietic progenitor cells (CD34+) with the difference that basophils come out the bone marrow mature. On contrary, MCs mature after migrating to tissues, and MC properties depend on their localization. MCs are located near the skin and mucous membranes, where infectious pathogens or foreign antigens most often enter the body [5]. MCs inhabit almost all peripheral tissues with the exception of the retina and the body's few types of avascular tissue [5]. MCs have been recognized for decades to be present in not only the tissues of the peripheral nervous system but also the central nervous system [6]. MCs synthesize and accumulate biologically active substances (histamine, prostaglandine, leukotrienes) and chronic inflammation factors (cytokines, chemokines), as well as tissue remodeling factors (proteases, growth factors) in cytoplasmic granules [7]. The components of MC granules are classified based on MC function characteristics into preformed components, providing for immediate MC reactions, and components synthesized in response to activation signals, which are associated with long-term forms of their response reactions [8]. Human MCs are usually classified depending on the content of neutral proteases—tryptases and chymases—in their granules. This classification includes three types of MC: MCT, containing only tryptase; MCTC containing tryptase and chymase; MCC containing only chymase in the composition of the granules [9]. In addition to pro-inflammatory action, MCs have the ability to suppress immunological responses; for example, by producing the anti-inflammatory

cytokine IL-10 or through the destruction of cytokines by proteases are released from granules [9]. Based on the induced ability of MCs to synthesize both pro-inflammatory cytokines and a variety of growth factors, there are proposals to separate MCs into pro-inflammatory MC1 and anti-inflammatory MC2 by analogy with macrophage populations [10].

Elimination of biologically active substances from MCs can occur gradually as necessary for homeostasis. On the contrary, in response to external pathogens and antigens effects, MC granules released immediately by cell degranulation. Following degranulation, MCs can restore the synthesis and accumulation process, i.e. capable of regranulation [11].

The most important mediator in the rapid degranulation phase is histamine, which affects the nerve structures of the immediate environment (afferent nerves—C-fibers and stretch receptors, efferent nerves, histamine receptors), epithelium, smooth muscle and mast cells themselves. Normally, histamine is an integral component of almost all organs, tissues, cavity fluids, secretions, and blood; its greatest content is noted in the skin (especially the eyelids, head, and neck) and in the lungs [12]. The content of calcium ions in cells producing histamine, as well as the permeability of cell membranes for these ions, is of great importance in the mechanism of synthesis and secretion of histamine [13]. The consequences of an increased release of histamine depend on its binding to a specific type of histamine receptor. The H1-receptor drives cellular migration, activity in afferent nerve fibers, vasodilatation and bronchoconstriction, whereas the H2-receptor modifies gastric acid secretion, airway mucus production, and vascular permeability [14].

Spatial colocalization of MCs and nerve terminals was shown for the mucous membranes in various organs and tissues, including airways [15]. A direct membrane-membrane interaction is shown between MC and nerve terminals [15]. Neuro-MC signaling occurs mainly through the secretion of mediators, but moving the whole granule to the neuron cytoplasm also possible [16]. Importantly, that MC can act as both a receptor cell and an effector cell. The results of numerous experiments indicate that mediators secreted by MCs are able to influence neuronal activity, providing the CNS with information about the onset of the inflammatory process and its localization [17].

There is also the mechanism of cross-communication of MCs using extracellular vesicles (EV). EVs can be released from several cell types that are implicated in allergy processes, including MCs, dendritic cells, T-lymphocytes, and the ciliary epithelium of the respiratory system. For example, EV secreted by MCs induces dendritic cell maturation [18]. The ability of EVs obtained from human and mouse mast cell lines to transfer biologically active RNA to other MCs was noted [19]. *In vitro* experiments have shown that MC-derived EV can induce epithelial to mesenchymal transition in human lung adenocarcinoma cell line (A-549) [20].

MCs express recognition receptors for pathogen-associated molecular patterns, such as superficial and intracellular Toll-like receptors (TLRs), intracellular Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Retinoic acid-inducible gene I (Rig-I) family receptors [21]. Also, complement binding receptors (CR3, CR5) and Fc receptors for immunoglobulin E (IgE) and immunoglobulin G (IgG) are expressed on the surface of MCs [9,21,22]. Accordingly, the activation of MCs occurs with the participation of both innate and adaptive immunity factors. However, special attention is paid to allergic inflammation, where the antigen-antibody complexes are the damaging agents. The role of MCs and their high-affinity IgE receptors (FcεR) in immediate hypersensitivity and immunocomplex reactions (the Arthus phenomenon, etc.) is well known. IgE binds to FcεR and persists for a long time on the MC surface. When the organism re-meets the allergen, IgE antibodies, formed during the first contact with this allergen and fixed on the surface

of MCs, bind the allergen, which leads to degranulation of MCs with the release of mediators [23]. On the contrary, the role of MC receptors for IgG (Fcγ), which are not related to allergies and hypersensitivity, is much less studied [24].

MCs may play a positive role in clearing pathogens in many bacterial, viral, and parasitic infections through degranulation, antimicrobial peptide secretion, neutrophil recruitment, or extracellular DNA trapping [25,26]. Data from epidemiological studies indicate that IgE antibodies play a protective role in parasitic infections in humans, since the levels of parasite-specific IgE and resistance to infection are positively correlated [27]. Moreover, mechanisms for killing bacteria with MCs continue to be elucidated. Thus, MC are able to perform phagocytosis like neutrophils and macrophages, which kill bacteria using a combination of oxidative and non-oxidative bactericidal systems, also inherent in MC [28]. Recently, it was shown that MCs exhibit extracellular activity involved in destroying bacteria. Extracellular traps, originally identified for neutrophils (NETs) [29] are able to provide physiological barriers, prevent the spread of microorganisms and increase the interstitial content of antimicrobial substances [30]. It turned out that MCs are also able to secrete their nuclear DNA to form extracellular traps [31]. The key components of mast cell extracellular traps (MCETs) are DNA molecules and histones of nuclear chromatin; bactericidal substances, such as tryptase and cathelicidin LL-37 [26].

In addition to secretory function, MCs may also act as non-typical antigen-presenting cells (APCs) [32]. It has been shown that there is an increase in the expression of MHC class II and co-stimulatory molecules in activated MCs *in vitro*. It was demonstrated in animal studies that MCs can present antigens while interacting with different lymphocyte subsets including regulatory T cells (Treg) and CD8+ T lymphocytes thus participating in the adaptive immune response [33,34].

3. Mast cells in airways

Alveolar epithelial cells, endothelial cells, resident alveolar macrophages, dendritic cells, and several MC types are involved in protecting the lung from pathogens. Of the various types of MCs, MCT predominates in the alveoli, whereas MCTC was found in the submucosa. MCC, being a rare type of mast cell, is sometimes found in the nasal mucosa, as well as in the alveoli and lymph nodes [8,10]. As mentioned earlier, MCs can have different properties depending on the localization, so MCs of the same type may differ in the expression patterns in terms of the number of receptors, enzymes, and growth factors. For example, MCT in the bronchi are characterized by a higher level of expression of the enzyme histidine decarboxylase compared to MCT in the alveoli; MCT and MCTC in the conducting airways have a high level of FcεRI expression, while similar cells in the alveolar parenchyma practically do not contain this receptor on their surface [35]. Pathogenic roles of MCs in airways include immune-modulatory, pro-inflammatory and pro-fibrotic activities. The released MC histamine increases vascular permeability, causes vasodilation and stimulates the contraction of bronchial smooth muscles. The inflammatory cytokine TNF-α promotes local and systemic inflammation while enhancing the recruitment of neutrophils to the site of infection. Granular proteases are also capable of increasing vascular permeability and enhancing the recruitment of neutrophils to the site of inflammation, or may act directly to degrade toxic proteins [36]. Nasal and bronchial MCs are involved in allergic rhinitis and asthma, as well as chronic obstructive pulmonary disease, respiratory infections and lung fibrosis [37,38].

4. The role of mast cells in viral infections

MCs can be infected with a number of viruses, including HIV, hantavirus, reovirus, rhinovirus, dengue virus (DENV) and influenza A virus [39–43], and have been shown to selectively produce neurotransmitters that activate the vascular endothelium and recruit immune effector cells [43,44]. MC activation in viral infections occurs by: (1) inflammatory mediators of epithelial infection (IFN, chemokines, IL-33); (2) viral particles; (3) viral replication intermediates. The importance of mast cells in viral infections is well-studied in dengue fever [39,41]. DENV, which enters the body through the skin, can directly bind to the MC surface [40]. MCs react to the impact of DENV by degranulation and the release of preformed mediators. The eicosanoid leukotriene B4 and proteases released by MCs increase vascular permeability, and synthesized TNF-α, IL-6, IFN-α, and chemoattractants recruit NK cells and T cells to the site of infection [41].

Viral replication intermediates, such as single-stranded or double-stranded RNA molecules can be recognized by membrane-bound and endosomal TLRs (TLR-3, TLR-7/8) and intracellular antiviral sensors (RIG-I, MDA-5) of MCs [21,45]. The dsRNA, an important intermediate in viral replication, induces the expression of type 1 interferons and other pro-inflammatory cytokines during the early stage of dengue or influenza infections. [46,47]. MC TLR-9 can recognize methylated regions of viral DNA, such as in Herpes Simplex Virus [40]. Additionally, IgG and IgE receptors can interact with MC by cross-linking with virus-specific antibodies and thus enhancing MC activation [40].

The main preformed mediators and components synthesized upon MC activation in viral infections are presented in Figure 1.

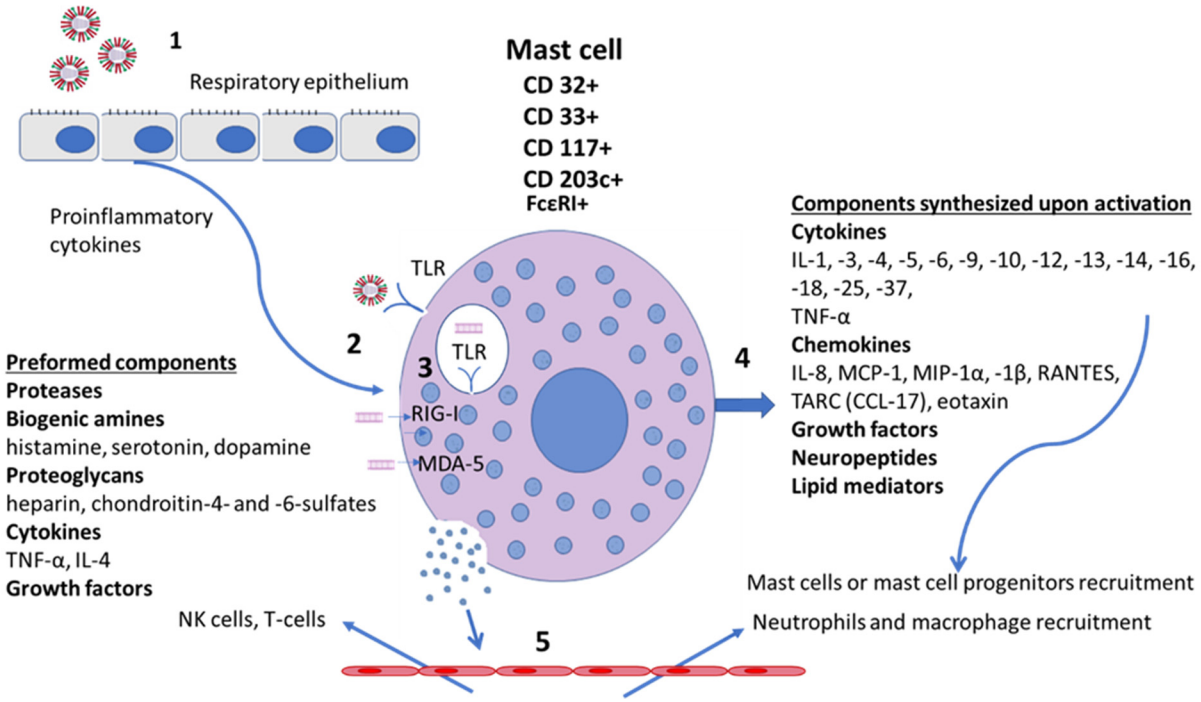

Figure 1. Effect of mast cell activation on viral-induced inflammatory responses. (1) Viruses infect epithelial cells, in response to this, pro-inflammatory cytokines are released. (2) Tissue mast cells can be activated by pro-inflammatory cytokines or directly by viruses. (3) Viral replication intermediates, such as single-stranded or double-stranded RNA

molecules can be recognized by membrane-bound and endosomal TLRs and intracellular antiviral sensors (RIG-I, MDA-5). (4) Mast cells activation leads to the secretion of effector molecules. IL: interleukin; TNFα: tumor necrosis factor-α; MCP-1: monocytic chemoattractant protein-1; MIP-1: macrophage inflammatory protein-1; RANTES: chemokine CCL5; TARC: chemokine CCL-17. (5) Mast cell products can activate and increase the permeability of endothelial cells, which, together with chemotactic molecules, leads to migration of inflammatory cells in infected tissues.

4.1. The role of IL-31-IL-33 axis in immune responses and mast cells activity

IL-31, a cytokine produced by CD4+ T helper cells, was identified for the first time in 2004 [48]. IL-31 controls signaling, induces proinflammatory cytokines, and regulates cell proliferation. The main targets of IL-31 are fibroblasts and eosinophils, which are activated through the IL-31 receptor (IL-31R). To date, several isoforms of the IL-31 receptor have been identified. Among them, CRL and the IL-31 receptor alpha (RA)v2 are the soluble forms showing no transmembrane region, whereas IL-31RAv1 and IL-31RAv4 display the classical features of type I cytokine receptors [49].

IL-33 is also known as an "alarmin" because its serum level increases as a consequence of necrosis processes and induces the augmentation of inflammatory cytokines. IL-31 and IL-33 seem to activate and enhance the maturation of MCs [50,51]. IL-33 increases its expression after cell death, and most likely results in the induction of other cytokines including IL-31. In many cases, IL-31 and IL-33 are related to each other and their expression correlates with the severity of the disease. The presence of one interleukin might stimulate the induction of the other, amplifying inflammation. Influencing their balance could be helpful in modulating the first responses of the immune system in order to prevent the development of many inflammation-related diseases. IL-33 plays an important role in many pathologies, especially in inflammatory ones, as well as in the balance of the immune response (Th2-associated). Thus IL-33 seems to be closely associated with allergic inflammatory diseases, including atopic dermatitis and asthma [52]. IL-33 could induce bronchial asthma because it is increased during the production of inflammatory cytokines by Th2 cells [53]. Th2 cells are one of the main producers of IL-31. Some studies demonstrated a positive correlation between IL-31 and atopic dermatitis (AD) severity, this suggests an important role of IL-31 in the regulation of AD. Some researchers demonstrated that the expression of IL-31 [54] and IL-31R [55] was increased in allergic diseases, especially in asthma.

Vocca et al. found very high serum levels of IL-31 and IL-33 in many inflammatory and autoimmune diseases, especially in lung illnesses [52,56]. According to these data, IL-33 has main target tissues like airways and skin. The activation of the IL-33/ST2 axis can be considered also as a biomarker of both Th2/IL-31 and Th17 immune response for diseases associated with cell damage like asthma, chronic obstructive pulmonary disease, AD, rheumatoid arthritis, and heart failure. For this reason, IL-33 can be useful for the diagnosis and the evaluation of the activity and progression of many inflammatory diseases [50,57,58].

Experimental mice models demonstrated that IL-33 blockade worsened contact hypersensitivity, and, on the other hand, injection of IL-33 inhibited contact hypersensitivity and induced regulatory T cells (Tregs) [59]. The study by Wang et al. [60] confirmed these results, noticing that IL-33 plays an anti-inflammatory effect targeting microRNA-155 in MCs. Moreover, a study conducted in a mouse model of poison ivy allergic contact dermatitis (ACD) showed that IL-33/ST2 signaling is present in

primary sensory neurons and promotes pruritus in affected mice [61]. The involvement of IL-31 and IL-33 was also confirmed among human models. More specifically, IL-31 was found to be expressed in skin biopsies of ACD patients, whereas IL-33 was induced in keratinocytes [62]. Beyond the effects on immune response, mast cells can modify bone metabolism and are capable of intervening in the genesis of pathologies such as osteoporosis and osteopenia [63].

4.2. The role of vitamin D and gut microbiota in immune responses

Vitamin D (VD) induces changes in bone metabolism, but it is also able to influence immune response, suppressing mast cell activation and IgE synthesis from B cells and increasing the number of dendritic cells and IL-10-generating regulatory T cells. Connections were revealed between MCs and VD, which contribute, through the activation of different molecular or cellular activation pathways, to the determination of bone pathologies and the onset of allergic diseases. B cells can produce VD [64] while naïve T cells grown with VD-primed B cells demonstrated decreased proliferation, provoked by the presence of CD86 on B cells [65]. VD receptors (VDr) connected to the promoter of TNF-α reduce the acetylation of RNA polymerase II and histone H3/H4, reducing the production of TNF-α in MCs. These findings make it evident that VD is necessary to preserve the steadiness of MCs, whereas the deficit of VD provokes the stimulation of MCs [66,67]. It is well known that the release of granules and the discharge of histamine from MCs are involved in the genesis of urticaria [68,69]. VD has been suggested for this therapy, as MCs have the VDr capable of blocking degranulation of compounds provoked by IgE [70]. As VD can produce IL-10, this indicates that VD/VDr-dependent stimulation of IL-10 generation by skin MCs can participate in the MCs' capability of reducing skin inflammation after chronic UVB irradiation [67]. These findings suggest that stimulating the anti-inflammatory effects of MCs by adding VD might be a new strategy for decreasing tissue injury and inflammation in different pathological conditions. The relationship between MCs and VD is not limited to the possibility of VD influencing the activity of MCs in allergic manifestations and both have been shown to have a role in determining bone pathology [63]. In fact, MCs generate mediators that alter bone metabolism. VD not only have a significant effect on DC development but also instructs the DCs to stimulate Tregs to generate IL-10 [71]. Almerighi, et al. have confirmed that VD reduces inflammation caused by CD40L and increases IL-10 generation by CD4+ T cells [72], stimulating the Tregs. There is growing evidence that the VD pathway is an important factor in the impact of gut microbiota on inflammatory diseases [73]. On the other hand, the gut microbiome, by participating in metabolism, modulates innate and adaptive immunity and mediates human interactions with pathogens [74]. Evidence shows that specific probiotic strains induce expression of transforming growth factor (TGF)-β and IL-10 cytokines with anti-inflammatory action thus counteracting inflammatory response and affecting immune cells [75]. Molecules of microbial origin such as short chain fatty acids (SCFAs, butyric acid, acetic acid, propionic acid) can induce MC activation [76]. Recent studies have demonstrated that probiotic strains, such as *Bifidobacterium longum* or *L. casei*, are able to counteract the inflammatory response and act on immune cells to reduce allergy-associated MC activation by downregulating IgE and histamine receptor gene expression or by controlling the amount of MC in the *lamina propria* [76,77]. Thus, the gut microbiota may influence the severity of inflammatory diseases through the release of cytokines and the activation of MC.

4.3. Mast cells involvement in influenza and non-influenza respiratory viral infections

It has recently been shown that MCs can be directly activated in response to influenza infection, releasing histamine, inflammatory cytokines and antiviral chemokines, which are involved in the excessive inflammatory and pathological responses during the course of the disease [78–81]. It has been shown in mice that MCs can contribute to the pathological changes during infections caused by highly pathogenic influenza viruses [78]. MCs can become infected with influenza viruses *in vitro*, and signaling pathways can differ depending on the subtype of the virus [43,81]. *In vitro* MC stimulation by influenza viruses A/H1N1 and A/H3N2 produced different expression profiles of cytokines, chemokines and antiviral genes [82].

Degranulation of MC in influenza infection may not be associated with direct exposure to dsRNA, as shown in the model of its synthetic analog: polyinosinic-polycytidylic acid (Poly I:C) [83], but is associated with a cytokine storm.

In addition to influenza infection, MCs are also of great importance in other respiratory seasonal infections of non-influenza etiology. For multiple paramyxoviruses (including RSV) as well as for rhinoviruses, the risk of developing allergic diseases increases after severe viral infections [84]. Despite low levels of infection, human MCs produce multiple chemokines in response to RSV through mechanisms that include responses to type I interferons. Such MC responses might enhance effector cell recruitment during RSV-induced disease [85]. It was shown that RSV infection of human lung fibroblasts contributes to inflammation via hyaluronan-dependent mechanisms that enhance MC binding as well as MC protease expression via direct interactions with the extracellular matrix [86].

Rhinovirus (RV) infection is strongly associated with asthma exacerbations, and induction of histamine release and IL-8 or granulocyte macrophage-colony stimulating factor production were the first observations regarding the rhinovirus-induced MC response [87]. The RV14 and RV16 infection of human mast cell-1 (HMC-1) cells *in vitro* lead to increased histamine and early cytokine response, as well as elevated caspase 3 activity and apoptotic responses [87,88].

4.4. Mast cells and COVID-19

The COVID-19 pandemic represents one of the hardest challenges of the 21st century. All CoV infections are primarily recognized by immune cells, including MCs, which are located near the body's physical barriers. SARS CoV-2 through TLRs can activate MCs [89–91] that secrete preformed inflammatory compounds, whereas late activation provokes the generation of members of the pro-inflammatory IL-1 family, including IL-1 and IL-33 [89]. In COVID-19, MC activation in the respiratory tract can contribute to the cytokine storm which exacerbates lung failure [92].

It was noted that COVID-19 patients had increased perivascular and septal MC density in the lungs, which was even more than in A/H1N1 pandemic influenza patients [93]. A study of pulmonary fibrosis biopsy specimens obtained from patients with COVID-19 showed a higher density of CD117+ cells, suggesting MCs proliferation/differentiation in the alveolar septa. In addition to proinflammatory cytokines, activated mast cells can release matrix metalloproteinase 9 and transforming growth factor beta, which can promote pulmonary fibrosis, as well as thromboxanes (thromboxane B2) and platelet-activating factor, which lead to the formation of microthrombosis in lungs as was identified in the lungs of deceased COVID-19 patients. Long-term multisystem lesions noted in many patients, even those who have undergone a mild form of COVID-19, are also potentially associated with idiopathic

MC activation [93]. It is hypothesized that the activation and degranulation of MCs, leading to Mast Cell Activation Syndrome (MCAS), is associated with antibodies to SARS-CoV-2 interacting with the Fc receptor [94]. It is known that hyperactivated MCs play a role in the development of fibrotic diseases. Therefore, people with these conditions may be at increased risk of developing chronic respiratory, neurological, or other complications following an acute COVID-19 infection [95,96].

5. The fundamental role of vaccination against SARS-CoV-2 in prevention of severe respiratory disease in patients with immune-mediated diseases

SARS-CoV-2 infection can become a great threat for people affected by comorbidities, causing increasingly severe clinical manifestations and death [97]. Data confirmed that about half of the rheumatologic patients (46%) who contracted the infection needed hospitalization, and 10% required invasive ventilation. Received data induced regulatory organizations and scientific societies worldwide to recommend vaccination to immunocompromised patients and patients affected by rheumatologic diseases [98–101].

The prevalence of systemic sclerosis (SSc) ranges from 7 to 700 cases per million worldwide [102]. Even if SSc pathogenesis is not completely clear [103] the excessive collagen production and the constant inflammatory state can lead to multi-organ involvement and several different and serious disease presentations [104]. Strong immunosuppressants are often used to reduce the chronic autoimmune insult, leading to a higher risk of communicable diseases. In fact, SSc mortality is the highest among rheumatic diseases [97], and infections are one of the leading causes of both hospital admission and mortality [105].

In patients with SSc at risk of severe COVID-19 because of organ involvement or use of specific immunosuppressive drugs, including rituximab and mycophenolate mofetil, early treatment with monoclonal antibodies (when available) should be considered, independent of vaccination status, to prevent hospitalization or death [106]. It is important to note that several of the monoclonal antibody therapies have been shown to be ineffective against the omicron variant [107,108].

The effectiveness of vaccines might be reduced in patients taking immunosuppressive therapy, because antibody responses might be blunted. New data on the use of the COVID-19 vaccines in patients with SSc continue to be collected [109,110] and will provide evidence for the most appropriate timing of vaccination as a preventive measure. Several studies have shown that in patients with rheumatic diseases a third dose of the COVID-19 vaccine is associated with an increased humoral response; as such, a third (and fourth) vaccination is advised for patients treated with immunosuppression, especially B-cell depleting agents [111].

A prospective observational study in 478 patients with systemic autoimmune diseases, including 265 patients with systemic sclerosis, evaluated seroconversion after COVID-19 vaccination compared with 502 healthy people (i.e., people with no systemic autoimmune diseases) [112]. In SSc patients, antibody concentrations were significantly lower than in the control group, and patients were more likely than controls to have no detectable anti-spike antibodies (13% vs 3%). In another study including 264 patients with a stable inflammatory rheumatic disease, of whom 50 had SSc, non-response was reported in 14%. Furthermore, a significantly lower percentage of patients with rheumatic diseases who were taking rituximab seroconverted in both studies [113].

Thus, the risk of SARS-CoV-2 infection and having a far worse outcome in patients suffering from immune-mediated diseases outweighs the risk of a wasted vaccine dose or the risk of a lower

response rate. For such patients, a third or fourth revaccination may be recommended, although, no specific recommendations are available regarding the different vaccine platforms. Perhaps, oral immunization using probiotics as live vectors for mucosal delivery of viral antigens may provide a safe and effective way to induce mucosal immunity to SARS-CoV-2 in frail patients [114,115].

6. Antibody-dependent enhancement in recurrent viral infections and possible involvement of mast cells

For some viral infections, antibody-dependent enhancement (ADE) has been described, which is manifested by a severe course of recurrent infection. ADE is used by various viruses as an alternative way of infecting host cells after natural primary infections with heterotypic viruses of the same type or after infection with antigenic variants in the course of chronic infection or due to immunizations that cause incomplete protective immunity [116]. In addition to the interaction between the viral protein and host cell receptors, viruses can enter cells (for example, monocytes/macrophages) through the binding of virus/antibody immune complexes to Fc receptors (FcRs) or complement receptors [117,118]. ADE syndrome is characteristic of dengue fever which first attracted attention and was described. Primary DENV infection induces lifelong immunity to the infecting virus serotype. It is assumed that serum antibodies after primary infection with DENV are not able to neutralize upon reinfection with DENV of a different serotype. Instead, antibodies can potentiate the endocytosis of the virus into myeloid cells (monocytes and macrophages), which are the main site of DENV replication after entering the [119]. Viruses belonging to the flavivirus family, influenza viruses, RSV, coronaviruses and many others use ADE for the infection of cells through Fc receptors [120–125]. Especially attention is drawn to such an important cause of bronchial complications, especially for children, as RSV infection. In young children, immunopathological pulmonary reactions involving Th2-type immunopathological reaction in the lung have been observed, when a formalin-inactivated RSV vaccine is administered, and later RSV infection occurs [126]. Most of these children suffered from severe infections, which led to a high rate of hospitalizations; two children died from the infection. Thus, RSV lung disease has been exacerbated by prior vaccination. A possible reason is the formation of high levels of antibodies with weak neutralizing activity, which contribute to increased infection of myeloid cells. Subsequent studies in animal models showed that the inactivated RSV vaccine causes an increase in the response of Th2 T lymphocytes, primarily CD4+ cells, and the formation of immunocomplex pathology in the lungs [127]. In mice, it was shown that virus-specific IgE plays a role in airway hyperreactivity through FcεRI in RSV infection [128]. Virus-specific IgE also increase in a number of other infections (Dengue, herpesvirus infection, parainfluenza) [129–131]. However, the MC activation mechanism through FcεR is not a single pathway of MC involvement in the immunocomplex process. MC involvement in ADE through IgG is well established in dengue fever [132] when life-threatening complications that lead to hemorrhagic manifestations are more common after secondary infection than after primary infection.

There is an assumption that non-neutralizing antibodies to influenza can participate in ADE. During the events of the 2009 influenza pandemic, the use of seasonal vaccines and the presence of non-neutralizing antibodies against the A/H1N1pdm09 were correlated with an increased risk of more severe influenza-like-illness in infected people [133–137]. Whole-virion inactivated influenza vaccines (IIV) may provide partial protection against drifted influenza viruses, but have been shown to induce vaccine-associated enhanced respiratory disease (VAERD) when challenged with an

antigenic variant of the same haemagglutinin (HA) subtype [138,139]. It was demonstrated in a swine model that aggravated pneumonia can result from a mismatch between the vaccine strain HA used in a IIV and the challenge strain [4]. Previously, it was shown that A/H1N2 IIV may provide only partial protection against drift variants of HA subtype in pigs, but also may induce VAERD [139]. It was shown that mismatched HA between vaccine and challenge virus was necessary to induce this, although vaccines containing a matched NA facilitated severity of infection due to HA mismatch and this was correlated with NA-inhibiting (NI) antibodies [140].

The problem in developing vaccines against the CoV causing severe respiratory syndrome (SARS) is that, after vaccination, eosinophilic reactions in the lungs or allergic reactions are observed—in an experiment, an increase in infection is observed [141–144]. Antibodies to the S-protein of the coronavirus envelope, produced in response to infection, promote the penetration of SARS-CoV-1 into monocytes (CD68+) and macrophages through the FcγRIIA receptor and aggravate the course of the disease [144].

During the SARS CoV-2 pandemic, severe post-infectious inflammation can be a direct result of ADE in infants previously infected with SARS-CoV-2 or in infants who have maternal SARS-CoV-2 antibodies or antibodies acquired through breast-feeding [94].

The involvement of antibody-mediated MCs responses in human CoV infections is poorly understood. At the same time, there is evidence of MC involvement in the pathogenesis of peritonitis in severe CoV infection in cats [145]. Cases of feline CoV peritonitis have been reported in cats immunized with the coronavirus vaccine [146,147]. Improved macrophage infection following antibody-mediated entry of feline CoV leads to overcoming the resistance of the gut-associated immune barrier, this cause hematogenous infection [147]. It has been shown that mainly IgG2a class of anti-feline CoV spike has a leading role in the initiation of ADE.

Thus, there are enough data indicating the possibility of ADE development in various viral infections. But the role of MCs in these reactions is not well studied. If MC involvement in ADE is proven, it will open up new perspectives for the use of drugs targeting MCs and their products to prevent adverse reactions in the development of new vaccines.

7. Histamine blockers and mast cells membrane stabilizers in the treatment of viral infections

Many MC-related components such as proteinases, cell adhesion molecules, chemoattractant receptors, and individual components of signaling pathways are potential therapeutic targets [148]. However, there is still insufficient clinical data on the use of these substances in viral infections.

A number of studies have suggested that H2 receptor antagonists may be beneficial among many other drugs. Since there is evidence that the pathogenesis of COVID-19 is associated with dysfunctional MC degranulation, various medical interventions using commercially available drugs useful for treating mast cell disorders can help reduce disease severity and mortality. These data are confirmed by the use of histamine receptor blockers in complex COVID-19 therapy [149,150]. Famotidine was included in the clinical guidelines for COVID-19 therapy. (https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik_Critical_Care_COVID-19_ Protocol.pdf).

From previous studies, the immunomodulatory effects of H2 receptor antagonists are well characterized, but further investigations are required to explore their potential implications in managing the immune response in COVID-19 [151]. Although, histamine receptor blockers affect only

the sensitivity of tissues to the released histamine, but not the quantity and quality of MCs, nor the level of released histamine. Administration of MC stabilizing drugs or the leukotriene B4 antagonist montelukast leads to a decrease in vascular permeability. Use of MC stabilizing drugs such as sodium cromoglycate and ketotifen, which prevent MCs degranulation and release of histamine, and inhibitors receptors that bind MC products such as leukotrienes have been shown promising in animal models of influenza and dengue virus infection [152].

Nevertheless, the therapeutic focus on MCs or their products will require careful scrutiny in order not to negate the beneficial effects of MC in both regulation and suppression of inflammation and immune response. Blocking anti-inflammatory functions or enhancing pro-inflammatory functions can lead to excessive tissue damage through infiltration and activation of cytotoxic cells [153]. Thus, the administration of a TNFα inhibitor to mice, which is usually used to treat rheumatoid arthritis, irritable bowel syndrome and psoriasis [154], although it increased survival, delayed the resolution of pathological changes in the lungs. This raises concerns about the risk of aggravated influenza infection in patients who are prescribed drugs that block TNFα.

8. Discussion

Thus, it becomes apparent that MCs, being a part of the innate immune system, are involved in the reactions of both innate and adaptive immune responses. Together with this, the MCs appear truly universal cells involved in complex processes, providing direct effects and indirect regulation of other cells and their functioning in various biological processes

In the respiratory tract, MCs are active participants in a wide range of immunological mechanisms, including functions of local immunomodulators, and balancing pro-inflammatory and anti-inflammatory responses. MCs are involved in the development of lung pathology in a number of viral infections. MCs can contribute to the development of asthma and other inflammatory and fibrotic diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

ADE in severe, often fatal infectious diseases, is believed to be caused by the binding of IgG-containing immune complexes to cellular Fc or complement receptors, which facilitates the penetration of the pathogen into cells and increases the severity of the disease. However, the involvement of MCs in antibody-dependent reactions has so far been clearly established only for dengue fever and systemic CoV infection in cats.

Obviously, the role of MC in respiratory infections can be twofold. Surprisingly, as a result of a 2016–2019 study in the Netherlands, pollen bioaerosols associated with seasonal hay fever have been recognized as one of the factors involved in curbing the incidence of influenza and influenza-like illnesses. One of the reasons is called the initiation of the immune system, in particular MC activation [155].

9. Conclusions

If the role of MCs in the pathogenesis of severe viral infections, including ADE in recurrent viral infection is clarified, these cells and the products they release may serve as promising targets for such therapeutic agents as histamine receptor blockers or membrane stabilizers to prevent possible complications. A new pathogenetic link in the development of severe viral and mixed infections will be identified, requiring special attention of doctors and health authorities to risk groups, and new

targets (in the form of MCs and their activation products) will be discovered for therapeutic and prophylactic effects for the prevention and treatment of severe post-infectious or post-vaccination complications of viral infections.

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Conflict of interest

The authors declare no commercial or financial conflict of interest.

Author contributions

AM: data analysis, manuscript preparation; AP: general leadership, data analysis, manuscript editing; YD: data analysis, manuscript preparation, final editing.

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