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ORIGINAL ARTICLE

The Role of Mast Cells in the Pathogenesis of Covid-19

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ABSTRACT

Background: The Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan. The problem of COVID-19 treatment is still relevant, and it is necessary to study in details the pathogenesis of COVID-19, including the role of mast cells (MCs).
Aim: The aim of the review is to reveal the role of MCs, their receptors and mediators in the pathogenesis of the COVID-19.
Results: This review demonstrates a possible role of MCs in the pathogenesis of COVID-19.
Conclusion: MCs may be key elements of inflammation caused by COVID-19. MCs express various receptors on their surface that ensure the interaction of SARS-CoV-2 and MCs. Activated MCs release inflammatory cytokines, chemokines and proteases, which are involved in both the protective function and hyperinflammation in COVID-19.
Keywords: Coronavirus Disease 2019, mast cells, mast cells' mediators**,** mast cells' receptors

INTRODUCTION

COVID-19 caused by SARS-CoV-2 was reported firstly in December 2019 in Wuhan, Hubei province, China and became a global public health emergency leading to a global medical and financial crisis. Virus exposure can results in asymptomatic infection or development of symptoms which may range from mild upper respiratory tract symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, hypercoagulation, hyperinflammation and eventually death due to multiple organ failure. The issue of the effective treatment of coronavirus disease is still relevant and in order to solve this problem, it is necessary to investigate in details the pathogenesis of COVID-19, including the role of MCs.

MCs are immune cells of the myeloid lineage, which are presented throughout the body. MCs regulate the functions of immune cells such as dendritic cells, monocytes/macrophages, granulocytes, T-cells, B-cells and natural killer cells (NK-cells) and also recruit immune cells to inflamed tissue by secreting chemokines and other mediators [1]. MCs are implicated in the pathophysiology of allergic reactions, anaphylaxis, immune response, inflammation, gastrointestinal disorders, many types of malignancies, and cardiovascular diseases [2]. The important role of MCs in the pathogenesis of asthma is already known, and their participation in the chronic obstructive pulmonary disease is considered [3]. Furthermore, there is growing evidence about the role of MCs in the lung damage in patients with COVID-19.

The aim of the review is to reveal the role of MCs., their receptors and mediators in the pathogenesis of the COVID-19.

DISCUSSION

Mast cells' receptors: Entered into the host, pathogens activate innate immune cells including MCs located in the submucosa of the respiratory tract and in the nasal cavity, which are protective barriers against various microorganisms including SARS-CoV-2 [4]. MCs express various receptors on their surface: Fc-receptors for immunoglobulins, including Fc epsilon RI, high-affinity IgE receptor, also known as FcεRI, which play a role in hypersensitivity, IgG receptors, which allows MCs to take a part in the immune response [5], Toll-like receptors (TLRs), which allow MCs to recognize pathogens and its special molecules directly, Fc-gamma type 2 receptor A (FcγRIIA), MAS-related G protein-coupled receptor-X2 (MRGPRX2) (most abundant on cutaneous mast cells) [6], adenosine A2A and A3 receptors, (activated by adenosine, facilitate antigen-mediated MCs degranulation), histamine H1-receptors and H2-receptors, acetylcholine receptors, adrenaline receptors [7], complement component 3a receptors, chemokine receptors, leukotriene receptors, prostaglandin receptors, the receptors for stem-cell factor, sphingosine 1-phosphate receptors, etc. [8].

Direct interaction between MCs and pathogens is realized through Toll-like receptors. Bacteria can be recognized by Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) [9].Besides bacterial and parasitic infections, MCs can also protect the host against viral infections [4,10]. Several studies have demonstrated that MCs can protect from different viruses such as influenza virus [11], respiratory syncytial virus [10] and coronaviruses [4]. Viral ribonucleic acid can be identified through TLR3, TLR7, TLR8, and retinoic acid-inducible gene-I-like receptors (RIG-I) expressed by MCs. Viral detection causes MCs activation and recruitment of cluster of differentiation $(CD)8^+$ T-cells and NK-cells, which play a role in anti-viral immunity [4]. There is an evidence that direct recognition of SARS CoV-2 via TLRs, can lead to the pro-inflammatory cytokines (Interleukin- 1 (IL-1) and Interleukin-6 (IL-6) synthesis without triggering MCs degranulation and facilitate pulmonary inflammation and fibrosis [12].

The interaction between coronavirus and MCs is mediated by a large variety of cell surface or intracellular receptors expressed by MCs not just through pathogen associated molecular pattern (PAMPs) receptors, such as intracellular TLR3, TLR4 and TLR7, but also indirectly through IgRs (immunoglobulin receptors) or CRs (complement receptors). MCs activation bound to Ig, triggers MCs degranulation of prestored chemical mediators (tryptase, histamine, etc.) and production of newly generated cytokines such as IL-1 and IL-6, lipid mediators and chemokines [13].

Angiotensin-converting enzyme 2 (ACE2) is known as a main cell receptor for SARS-CoV-2 [14] and is expressed on alveolocytes type II, macrophages, bronchial and tracheal epithelial cells, smooth muscle cells and endothelium of vessels, heart, kidney, liver, skin, brain, intestine, colon, testis cells, etc. [15]. MCs also express ACE2, thus giving a way how MCs could become hosts for this virus [1, 16]. In addition, MCs express serine proteases, including Transmembrane protease, serine 2 (TMPRSS2), required for priming of the corona spike protein [16].

Thus, coronavirus and MCs relations can be realized through a large variety of cell surface or intracellular receptors directly or indirectly triggering the production of pro-inflammatory cytokines and chemokines contributing to lung inflammation and fibrosis.

Mast cells' mediators: Dependent on tissue condition and the series of triggered receptors, SARS-CoV-2 can induce special profiles of MCs chemical mediators. There is an evidence that the state of epithelial - MCs interaction while viral encounter also influences on the phenotype of MCs response to SARS-CoV-2 [13]. Activated MCs can release a variety of preformed mediators from their secretory granules and newly synthesize a wide range of inflammatory and immunomodulatory mediators, total number >1000 [6]. The preformed mast cell mediators include biogenic amines (histamine, serotonin), serglycin proteoglycan, heparin, chondroitin sulfate A and C, etc. and a number of MCs -specific proteases: chymase, tryptase and CPA3 [17]. Biologically active substances synthesized de novo include IL-6, Interleukin-1-beta (IL-1β), Interleukin-31 (IL-31), Interleukin-33 (IL-33), prostaglandin D2 and E2, Leukotriene B4 and C4, chemokines (C-C motif ligand 2 (CCL2), C-C motif ligand 3 (CCL3), C-C motif ligand (CCL4), C-X-C motif chemokine ligand 8 (CXCL8), growth factors, reactive oxygen species, etc., many of which are known to be associated with the inflammation and cytokine storm seen in COVID-19. TNFα can be both preformed and synthesized de novo [17].

Furthermore mast cells synthesize PAF, which plays an important role in pulmonary microthromboses, leading to lung damage in COVID-19 [18]. In its turn, PAF not just induces platelets activation, but also stimulates perivascular MCs activation, causing inflammation implicated in severe acute respiratory syndrome [19]. PAF also affects on the renin angiotensin system including ACE2, which serves as a necessary receptor for SARS-CoV-2 [20].

MCs contain histamine, which is stored in cytoplasmic granules. It can be activated by various immune and non-immune stimuli, and is released with other mediators when inflammation is activated [21]. Histamine, Leukotrienes C4 and Prostaglandin D2 produced by MCs under SARS-CoV-2 exposure lead to lung inflammation and cause acute bronchial obstruction [4]. Histamin binds directly to H2-receptors on peripheral monocytes, thereby increasing the production of IL-1, which stimulates IL-6 synthesis by macrophages [6, 22]. The presence of MCs in human tissues promotes the release of histamine and other vasoactive mediators which activate the endothelium in inflamed alveolar septa, can indirectly affect platelet adhesion and lead to the formation of fibrin and under the influence of cytokine storm, increases the risk of microthrombosis, coagulopathy, which adversely affect the course of the disease [23, 24].

Friedberg D.E. et al. investigated the role of histamine in the clinical retrospective cohort study. The study included 1620 patients with COVID-19 and 84 patients (5,1%) who received famotidine within 24 hours after admission to the hospital. It turned out that the group taking famotidine had a reduced risk of complications leading to intubation and a reduced risk of death [25].This explains the positive effect of famotidine, which has an immunomodulatory effect mediated by the H2-receptors on the cross–interaction of histamine and MCs cytokines, and not a direct effect on SARS-CoV-2 [26].

At the same time, Ka Shing Cheung, et al. in the retrospective cohort study included all patients with COVID-19 from Hong Kong, did not confirm any connection between the use of famotidine and the severity of the disease. [26].

Besides histamine blockers, MCs membrane stabilizers can also be used as a potential treatment for patients with COVID-19 and post-COVID-19 syndrome [27, 28].

Thus, MCs mediators play an important role in the development of hyperinflammation in COVID-19 and determine the possibility of using MCs-targeted medicines in the treatment of patients with COVID-19.

Mast cells' proteases: Tryptase and chymase are the most significant MCs proteases, which are the key factors influencing the phenotype formation of tissue microenvironment [29], whose role in the pathogenesis of COVID-19 is being actively studied. However, the involvement of CPA3 is also of great interest.

Chemase is a powerful converter of angiotensin I to angiotensin II, which regulates microvascular blood flow and systemic blood pressure, In turn, angiotensin II enhances the expression of angiopoietin 2 (Ang2) level, which proves a direct connection with COVID 19. Since elevated levels of Ang 2 were found in the blood of patients with severe COVID 19, this indicates activation of the endothelium, which leads to microvascular disorders. Higher levels of angiotensisn II in the plasma of COVID-19 patients have been correlated with lung injury. Thus, activated MCs affect the dysfunction of the vascular barrier, which leads to hypoxia, tissue edema as a result of endothelium disintegrity [30].

There are studies indicating levels of chymase, β-tryptase, and CPA3 in the blood serum of patients with COVID-19. Gebremeskel S. et al. determined the levels of inflammatory mediators and the MCs proteases chymase, β-tryptase, and CPA3 in the blood serum of 19 SARS-CoV-2 positive patients and 20 uninfected controls in order to check whether MC activation was associated with SARS-CoV-2 inflammation [31].The study demonstated significantly higher levels of inflammatory mediators in serum from SARS-CoV-2 patients compared to uninfected controls, including CCL2 ($p<0,0001$), CCL3 ($p<0,0001$), CCL4 ($p < 0,0001$), IP-10 (Interferon-gamma inducible protein 10 ($p<0,0001$), IL-6 ($p<0,0001$), IL-8 ($p<0,0001$), VEGF (vascular endothelial growth factor) ($p<0,0001$), TNF ($p<0,0001$), and IFN-γ (interferon gamma) ($p<0,0001$). Authors also found significantly elevated levels of chymase ($p<0,0001$), β-tryptase ($p<0,01$), and CPA3 ($p<0,0001$) in SARS-CoV-2 patient serum, strongly suggesting systemic MCs activation. Moreover, protease levels positively correlated with levels of many inflammatory cytokines and chemokines associated with COVID-19 disease severity, including IP-10, CCL2, and CCL4. These results suggest MCs activation is a feature of COVID-19 pathogenesis.

Other authors also obtained similar results from a study of the CPA3 level in the blood serum of patients with COVID-19. Soria-Castro R. et al. analyzed levels of histamine, CPA3, serotonin and heparin in blood serum of 21 patients with mild and moderate COVID-19, 41 patients with severe COVID-19 and 10 patients from the control group [32]. The study demonstrated elevated CPA3 levels ($p<0,5$) and, on the contrary, decreased serotonin levels ($p<0,01$) in patients with COVID-19 compared to control group. Histamine and heparin levels did not change in patients with COVID-19. Authors also examined MCs' biomarkers levels depending on the severity of COVID-19: patients with severe COVID-19 showed elevated CPA3 ($p<0,01$) compared to patients with mild or moderate disease, serotonin was reduced in patients with severe COVID-19 only ($p<0,05$). The study demonstrated a significant positive correlation between CPA3 and markers associated with inflammation: level of circulating neutrophils ($p=0,0447$) and C-reactive protein ($p=0,00703$). CPA3 was also associated with the assessment of the severity of the disease in the quick assessment of organ failure associated with sepsis (qSOFA - quick Sepsis Related Organ Failure Assessment) ($p =0,00862$). Thus, changed serotonin and CPA3 levels in patients with COVID-19 may indicate the involvement of MCs in the COVID-19 pathogenesis and these substances can be considered as potential biomarkers during COVID-19.

In addition, studies are conducted not only on the patients' blood serum, but also on autopsy material of those who died from COVID-19. Motta Junior J.S. et al. conducted a histopathological study to compare the distribution of MCs in post-mortem lung biopsies of 6 patients with COVID-19, 10 patients with H1N1-induced pneumonia and 10 control patients died from neoplastic or cardiovascular diseases [33]. The study demonstrated a significant difference in the number of CD117+ cells and MCs in post-mortem lung biopsies between the COVID-19 group and H1N1 ($p=0,002$ and $p=0,001$, respectively) and control ($p=0,001$ and $p=0,001$ respectively) groups. MC degranulation identified by the toluidine blue (TB) stain was consistently seen in the alveolar septa of COVID-19. Moreover, significantly higher expression of Interleukin -4 (IL-4) was demonstrated in COVID-19 group compared to H1N1

(p=0,003) and control (p=0,0509, borderline) groups. Authors concludes that the proliferation (differentiation) of MCs in the alveolar septa may be due to a shift towards IL-4 expression in inflamed alveolar septa. MCs also promote cytokine networks by releasing IL-4 and IL-6, which play a role in the systemic cytokine storm associated with the severe COVID-19. Due to comparing with H1N1-induced pneumonia, the study showed an importance of MCs exactly in COVID-19-assosiated lung damage. Increased MCs density can be considered as a pathological hallmark in the lungs of patients with COVID-19.

CONCLUSION

Analyzing available evidence given above, we can conclude that MCs may be the key elements not just in allergic reactions, anaphylaxis and immune response, but also in the COVID-19 inflammation. It should be noted that MCs express on their surface various receptors providing SARS-CoV-2 и MCs interaction. Being activated, MCs release inflammatory cytokines (IL-6, IL-4, IL-1β, IL-31, IL-33, TNF-α,), chemokines (CCL2, CCL3, CCL4, CXCL8), histamine, heparin, proteases such as chymase, tryptase and CPA3, PAF, etc. which are involved in both the protective function and hyperinflammation in COVID-19. MCs play an important role in the cytokine storm in COVID-19, releasing many pro-inflammatory cytokines and chemokines mentioned before. Studies conducted by different authors have similar results showing that proteases, especially CPA3, levels positively correlate with the levels of many inflammatory cytokines associated with the severity of COVID-19. Activated MCs, due to their mediators including histamine and PAF, cause dysfunction of the vascular barrier, affect platelets, lead to the formation of fibrin and results in severe consequences of COVID-19 such as microthrombosis and coagulopathy. Few authors suggest the use of MCs membrane stabilizers и histamine blockers as a potential treatment for patients with COVID-19 and post-COVID-19 syndrome.

Summing up, it should be noted that further clinical studies concerning relationship between COVID-19 and MCs and their components should be continued in order to create new both therapeutic and preventive medicines that can be used to treat patients with COVID 19 and to improve the health and life prognosis.

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