

**COVID-19 Patogenezinde Mast Hücrelerin Etkisi**

Effect of Mast Cells in the Pathogenesis of COVID-19

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Dünya ölçeğinde pandemiye neden olan şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2), günümüz itibariyle 6 milyondan fazla insanın ölümüne ve yüz milyonlarca insanın da hastalanmasına neden oldu (17.06.2022 tarihi itibariyle dünya geneli: 6.32 milyon ölüm ve 538 milyon hasta). SARS-CoV-2 virüsünün bulaşmasından sonra pek çok savunma sistemi aktive olarak organizmayı korumaya çalışmakta ve savunma hattı oluşturmaktadır. İmmün sistemin önemli bir hücresi olan mast hücreleri de bu enfeksiyonda önemli işlevleri olan ve hastalığın seyrini etkileyen bir hücredir. Bu derlemede, mast hücresinin SARS-CoV-2 virüsü ile olan karşılıklı etkileşimi ve bu hücrenin salgı ürünlerinin COVID-19 seyrine etkileri hakkında bilgi sunumu yapılacaktır.

Anahtar Kelimeler: şiddetli akut solunum sendromu koronavirüs-2, immunité, mast hücresi**ABSTRACT**

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which caused a worldwide pandemic, has caused the death of more than 6 million people and the illness of hundreds of millions of people as of today (as of 16.06.2022, worldwide: 6.32 million deaths and 538 million patient). After the infection of the SARS-CoV-2 virus, many defense systems are activated and try to protect the organism and form a defense line. Mast cells, an essential cell of the immune system, also have important functions in this infection and affect the course of the disease. In this review, information will be presented about the interaction of the mast cell with the SARS-CoV-2 virus and the effects of this cell's secretion products on the course of COVID-19.

Keywords: severe acute respiratory syndrome coronavirus-2, immunity, mast cell.**Kabul Tarihi:** 11.11.2022**Correspondence:** Müge Toygar Deniz, Kocaeli Devlet Hastanesi, Enfeksiyon Hastalıkları Kliniği, Kocaeli, Türkiye**E-mail:** muggedeniz90@gmail.com

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes a highly contagious respiratory disease called COVID-19. SARS-CoV-2 enters the body primarily through the epithelial layer of the respiratory and gastrointestinal tract, but under certain conditions this pleiotropic virus can also infect peripheral nerves and enter the central nervous system (CNS). It is reported that an increasing number of COVID-19 patients also show neurological symptoms, and that SARS-CoV-2 can infect the nervous system under some conditions (1,2).

Mast cells (MCs) are hematopoietic cells found in almost all vascularized tissues and synthesize and secrete a wide variety of biologically active products, including various cytokines and growth factors. MCs are one of the proinflammatory cells of the immune system. MCs are strategically located in tissues and organs that are directly or indirectly related to the external environment of the body, such as the skin, lungs, and intestines (1). In such tissues, they are predominantly subepithelial and closely associated with blood vessels. This location allows them to act as sentinels against tissue damage and pathogen invasion (2). The relationship between MC and blood vessels is optimal to enhance rapid recruitment of effector cells from the bloodstream and into adjacent tissues. This process is facilitated by the MC's production of endothelium-activated cytokine mediators such as tumor necrosis factor (TNF) and interleukin 1 β (IL-1 β), lipid mediators that facilitate vasodilatation, as well as a number of chemokines that promote selective recruitment of certain subsets of effector cells (3).

Relation between Mast Cell and Viral Infection

Mast cells are considered to be important protective cells for host defense against different pathogens. Their location on mucosal surfaces and their ability to activate multiple aspects of early immune responses enable these cells to make important contributions to immunity in different situations. The interactions of MCs with viruses and pathogenic products are complex and can have both harmful and positive effects. There are important evidences for MC mobilization, activation of effector cells and mobilization of dendritic cells following viral contamination. These cells are a major and important local source of type I and III

interferons following viral loading. However, MCs are also known to cause inappropriate inflammatory responses, prolonged fibrosis, and vascular leakage associated with viral infections (3).

Mainly, upon entry of the coronavirus into the body, the virus is attacked by cells of the innate immune system, including MCs commonly found in the nasal passage and lower respiratory tract (2). SARS-CoV-2 can activate MCs in the respiratory tract in the initial phase of the disease. The severity and extent of the disease depend on the ability of the innate immune cells to stop viral and other infections. In vitro and in vivo studies have found that the number of MCs increases in viral conditions such as respiratory syncytial virus (RSV), rhinovirus (RV), reovirus, dengue virus (DENV), human immunodeficiency virus (HIV) and influenza (3). Hu et al (2012) showed that MCs play a direct role in viral infection by showing that MCs increase in the nasal mucosa, trachea and lungs in the early phase of infection with the H5N1 influenza virus in mice (4). MCs have important roles in many types of innate or adaptive immune responses, including making significant contributions to immediate and chronic IgE-related allergic disorders and enhancing host resistance to certain poisons and parasites (5). However, it is known to affect many other biological processes, including the response of mast cells to bacteria and viruses, angiogenesis, wound healing, fibrosis, autoimmune and metabolic disorders, and cancerization. The potential functions of MCs in many of these settings are thought to reflect their ability to secrete with a broad spectrum of cytokines and growth factors, after appropriate activation by a range of immune or non-immune stimuli. These secretory products of MC are known to have autocrine, paracrine or systemic effects (5).

When stimulated by allergens, MCs synthesize and secrete numerous pro-inflammatory and lipid mediators. Due to these secretion products, they have important functions in tissue inflammation and allergic reactions (7-10). MCs are an integral component of the immune system; they are known to have an active role in various infectious diseases, including bacterial and viral infections as well as fungal and parasitic diseases. Under the indicated conditions, their MCs are activated and once activated; these cells secrete a number of proinflammatory mediators. Some of the mediators produced from MCs can decompose microbial toxins and/or provide the recruitment of other

immune cells and phagocytic cells to the infection site (9,11-14).

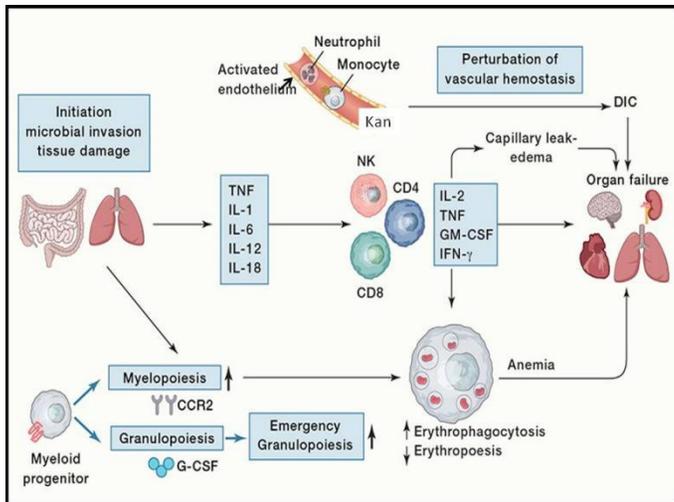


Figure 1. Pathophysiology of a Cytokine Storm. The early response to microbial invasion or tissue damage is characterized by the production of cytokines and the immediate induction of granulopoiesis leading to mobilization of neutrophils and monocytes. These events increase NK and T cell production of the proinflammatory cytokines (from reference No. 6).

Mast cells can also be activated by cytokines such as IL-33 and alarmins secreted in neighboring cells, such as endothelial cells infected by SARS-CoV-2/ACE2 interactions. As a result of this activation, MCs secrete numerous mediators, including Type I interferon (Type I IFN) and Type III IFN (3). In viral diseases, MCs may serve as viral reservoirs, as in HIV21. Overall, the possible role of MCs in coronavirus infections remains unclear. Various observations suggest that their MCs express coronavirus receptors such as CD26. MCs are also thought to possibly contribute to coronavirus-mediated inflammation in the lung (2). Moreover, MCs play a protective role at an early stage of coronavirus infection, while in later stages it is a critical factor of inflammation in the lungs. MCs and their proinflammatory products (cytokines, histamine, etc.) may play a role in exacerbating the disease (15). In addition, some cytokines secreted by other cells, such as T cells, damaged epithelial and endothelial cells (5) or even healthy forms of these cells (16), stimulate MC activation. MCs regulate the functions of immune cells such as dendritic cells, monocytes/macrophages, granulocytes, T cells, B cells and natural killer cells (NK). In addition, MCs facilitate the penetration of immune cells into the inflamed tissue by secreting MCs, chemokines, and other mediators that increase vascular permeability locally (17).

SARS-CoV-2 and Nervous Tissue

The brain is protected by various anatomical and physiological barriers, in particular the blood-brain

barrier, which prevents harmful substances, including pathogens and pro-inflammatory mediators, from entering the brain. The blood-brain barrier consists of highly specialized endothelial cells, pericytes, mast cells, and astrocytes that form the neurovascular unit that regulates the permeability of the barrier and maintains the integrity of the CNS. Viral entry from the blood to the CNS is restricted by the blood-brain barrier, which forms a structural and functional barrier between the peripheral circulation and the CNS (19,20). The neurovascular unit (blood-brain barrier) serves as the gatekeeper of the CNS, which protects the brain by regulating cerebral blood flow and limiting the access of pathogens, leukocytes and toxic substances (21,22).

Human neurotropic RNA viruses have evolved as opportunistic pathogens that can bypass the blood-brain barrier and enter the CNS by a variety of mechanisms: paracellular transport, transcellular transport, transport via extracellular vesicles (Trojan horse traffic), via receptor-mediated endocytosis, or "Trojan horse" trafficking. SARS-CoV-2 is thought to utilize a similar pathway(s) to come through the barriers separating the brain from peripheral blood and gain entry to the CNS. Mediators such as cytokines and chemokines can bind to specific receptors on the brain microvascular endothelium, causing disruption of the blood-brain barrier, neuroinflammation and encephalitis. Disruption of the blood-brain barrier can break the tight junctions between endothelial cells, which pave the way for paracellular transmission of SARS-CoV-2 to the CNS (23).

In the "Trojan horse" strategy of neuroinvasion, the virus lurks inside innate immune cells that can infect neurons and glial cells, circulating across the permeable blood-brain barrier using specific chemokine receptors. Studies on West Nile Virus (WNV) show that cell adhesion molecules may play a role in facilitating the migration of peripherally infected leukocytes to the CNS (24,25). The virus can migrate within infected leukocytes that enter the CNS (25). Indeed, human immunodeficiency virus (HIV)-infected leukocytes, which cross the blood-brain barrier, are one of the routes of spread to the CNS (26). HIV infects CD4+ T cells and uses the chemokine CCR5 as a co-receptor to enter the CNS (27).

In addition to severe pneumonia, COVID-19 can cause various neurological disorders including damage to the neurovascular unit, disruption of the

blood-brain barrier, elevated intracranial proinflammatory cytokines, and endothelial cell damage in the brain (18). In the many SARS-CoV-2 patients reported anosmia suggesting involvement of olfactory nerves in the early stages of the disease (28). It has been reported that ACE2 and TMPRSS2 (transmembrane serine protease 2), which SARS-CoV-2 uses as receptors to enter cells, are expressed by non-neuronal cells of the olfactory epithelium and olfactory bulbs in mice, non-human primates, and humans (29). It has been shown that neuropilin-1 (NRP1) is abundantly expressed in respiratory and olfactory epithelium, and highly expressed in endothelial cells of small and medium vessels of the nasal cavity. NRP1-mediated transport of SARS-CoV-2 virus has been demonstrated in the CNS of mice (30). Therefore, NRP1 in conjunction with ACE2 may also be used by SARS-CoV-2 as an additional receptor to enter the CNS via olfactory nerves (22).

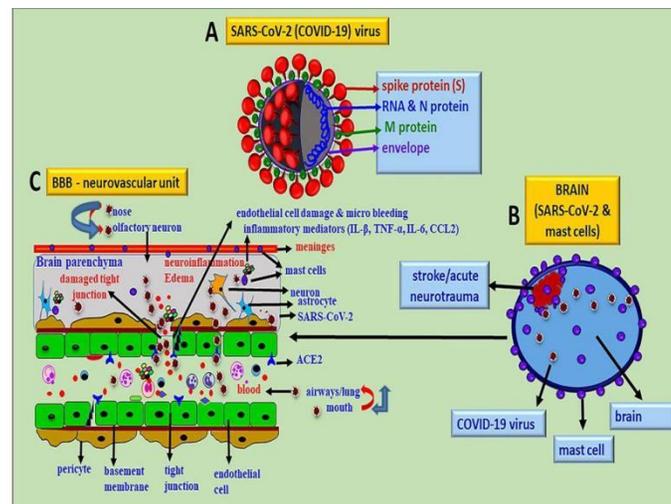


Figure 2. Schematic diagram showing that COVID-19 can cause and exacerbate a neuroinflammatory response in the brain. (A) SARS-CoV-2, (b) SARS-CoV-2 infected brain and (C) neurovascular unit, damaged blood-brain barrier/loss of tight junction, and neuroinflammation in brain parenchyma (from reference 18).

Mast Cell and COVID-19

Mast cells are cells of the innate immune system and are involved in adaptive immune reaction, stroke, traumatic brain injury, systemic inflammatory diseases, neuroinflammatory diseases, and stress disorders. SARS-CoV-2 can activate monocytes/macrophages, dendritic cells, T lymphocytes, mast cells, neutrophils and cause a cytokine storm in the lung. COVID-19 can activate MCs, endothelial cells, neurons, and glial cells.

SARS-CoV-2 infection can cause psychological stress and neuroinflammation, and accordingly, COVID-19 can induce MH activation, psychological stress, cytokine storm, and neuroinflammation (27,31). Studies report that stroke is associated with coagulopathy, antiphospholipid antibodies, and multiple infarctions in COVID-19 patients (32).

Multiple cytokine release, also called “cytokine release syndrome (Cytokine Release Syndrome - CRS)”, is closely related to the development of clinical symptoms of COVID-19. For example, IFN- γ can cause fever, chills, headache, dizziness, and fatigue; TNF- α can cause flu-like symptoms similar to IFN- γ , with fever, malaise, and fatigue. It may also cause cardiomyopathy, acute phase protein synthesis, lung injury and vascular leakage (33). IL-6 may lead to complement activation, vascular leakage, and coagulation cascade, revealing the characteristic symptoms of severe CRS such as intravascular coagulation (34,35). In addition, activation of endothelial cells may also be one of the hallmarks of severe CRS. Endothelial dysfunction causes capillary leakage, hypotension, and coagulopathy (36).

Mast cells are activated by SARS-CoV-2 and can be activated. Although lately identified, MH activation syndrome (MCAS) is a chronic multisystem disorder with inflammatory and allergic features, usually due to acquired MC clonality, with an estimated prevalence of 17%. It has been suggested that drugs with activity against MCs or their mediators are beneficial in patients with COVID-19 (38). Although MCs can recognize viruses by mechanisms such as Toll like receptor and IgE-Fc ϵ RI, they also express angiotensin-converting enzyme 2 (ACE2), which is known as the main receptor for SARS-CoV-2. This condition defines that MCs can become a host for this virus. MCs also express several serine proteases, including tryptase, required for SARS-CoV-2 infection (31).

Cytokine Storm and Mast Cell

COVID-19 cytokine storm is a condition characterized by rapid proliferation and hyperactivation of T lymphocytes, macrophages and natural killer cells and overproduction of more than 150 inflammatory cytokines and chemical mediators released by immune or non-immune cells (6,39). Cytokine storm associated with SARS-CoV-2 infection, TNF- α , IL-6, interferon gamma-inducible protein 10 (IP-10 or CXCL10), chemokine, macrophage inflammatory protein -1 α (MIP1- α) is characterized by high secretion of pro-inflammatory

cytokines such as ligand 2 (CCL2) and granulocyte colony stimulating factor (G-CSF), as well as C-reactive protein and ferritin (40). Hyper-inflammatory cytokine storms in most seriously symptomatic COVID-19 patients may be initiated by dysfunctional MCs of MCAS as an atypical response to SARS-CoV-2 rather than the normal response of normal MCs (38).

Decreased total T lymphocytes, CD4+ and CD8+ T lymphocytes, NK cells, and increased proinflammatory Th17 cells and perforin have been reported in COVID-19 patients with leukopenia (41,42). Increased IL-6 level in COVID-19 patients can trigger Th17 cell differentiation and cause cytokine storm, pulmonary inflammation and dysfunction (41,43). Recovery of lymphocyte number to normal levels indicates clinical amelioration of COVID-19 patients (44).

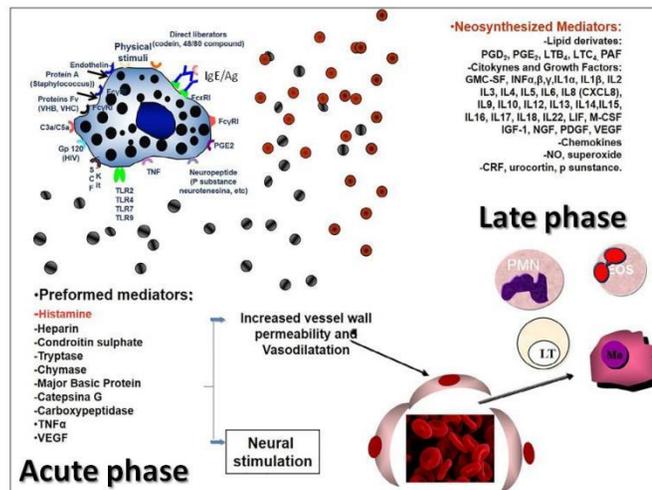


Figure 3. Mast cells can be activated by various stimuli due to different receptors on their membrane: These are proteins of the complement system (C3a, C5a), IgE, Toll-like receptors (TLR), receptors for IgG (FcγRI), prostaglandin E, viral proteins (hepatitis, HIV), bacteria, neuropeptides, TNF, and physical stimuli (from reference 37).

Viral Infection and Mast Cell Activation

Mast cells interact with the pathogen through a variety of natural surface pathogen recognition receptors (PRR) or cytosolic receptors that mediate its activation, degranulation, and release of different mediators (45). Following activation, released factors injury lung tissue, so using MC stabilizers to target MC mediators or restrict their degranulation can directly ameliorate SARS-CoV-2-related lung injury (46).

Production of C3a and C5a and activation of the

complement system have been observed in patients with COVID-19. Both components of complement can activate their MCs via receptors located on the cell membrane and cause urticaria-like lesions. Again, MHs also express IL-1 receptors and can also be activated by macrophages in the innate immune response process, which determines the release of mediators from their MCs and the formation of urticarial lesions (2,37).

Mast cell cytoplasm contains approximately 50 - 200 granules that store histamine, proteases, heparin, chondroitin sulfate, pro-inflammatory and anti-inflammatory cytokines/chemokines released after activation (47,48). MCs can release pre-stored TNF-α, histamine, and proteases from cytoplasmic granules by degranulation, and newly synthesized TNF-α and other cytokines and chemokines in the late phase of reactions (2,49). TNF-α activates E-selectin expression from vascular endothelial cells (50). By targeting TMPRSS2, camostat mesylate (which is an inhibitor of TMPRSS2) can block the entry of SARS-CoV-2 into cells, blocking the spread and action of the virus (51); and camostat mesylate partially blocks the S-protein of SARS-CoV-2, preventing the virus from entering the lung (52).

Suppression of mast cell activity by MC stabilizers can alleviate all the complications associated with a cytokine storm in SARS-CoV-2 infection. MC stabilizers prevent the release of histamine and related mediators by blocking MC degranulation. Studies have shown that MC stabilizers have the potential to improve patient survival and survival in wild-type mice in Dengue virus and influenza A virus models (10,53). They have broad efficacy in reducing inflammatory cytokine release from multiple cell types in SARS-CoV-2 infection, suggesting their potential benefit in reducing hypercytokinesia. The degranulation products of MC are known for their dominating role in starting an inflammatory reaction and cytokine storm in severe cases of SARS-CoV-2 (52,53). It results in acute respiratory distress syndrome, which facilitates the process of exacerbation of the disease and multi-organ failure (54). It is of great importance to target mediators in the treatment process of the disease. Many drugs are available that target and block the activity of specific MC mediators, including TNF-α, leukotrienes, and MC proteases. Many drugs are in this group, including cromolyn, ketotifen, quercetin, and luteolin (45).

As a result; MCs appear to play important roles in the

pathogenesis of SARS-CoV-2 virus and COVID-19 disease, and blocking the activation and degranulation of these cells suggests that it will be a good step in the prognosis of this disease.

Ethics Committee Approval: None

Authors' Contributions: All stages of this study were performed by a single author.

Conflict of Interest: None

Fundings: None

Informed Consent: This is a review study.

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