



CRITICAL REVIEW

Mast cells: Therapeutic targets for COVID-19 and beyond

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Abstract

Mast cells (MCs) are innate immune cells that widely distribute throughout all tissues and express a variety of cell surface receptors. Upon activation, MCs can rapidly release a diverse array of preformed mediators residing within their secretory granules and newly synthesize a broad spectrum of inflammatory and immunomodulatory mediators. These unique features of MCs enable them to act as sentinels in response to rapid changes within their microenvironment. There is increasing evidence now that MCs play prominent roles in other pathophysiological processes besides allergic inflammation. In this review, we highlight the recent findings on the emerging roles of MCs in the pathogenesis of coronavirus disease-2019 (COVID-19) and discuss the potential of MCs as novel therapeutic targets for COVID-19 and other non-allergic inflammatory diseases.

KEYWORDS

coronavirus, COVID-19, host defense, inflammation, innate immunity, mast cells

Abbreviations: ARDS, acute respiratory distress syndrome; BM, bone marrow; BMCP, basophil/mast cell progenitor; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; CD, cluster of differentiation; CMP, common myeloid progenitor; COVID-19, coronavirus disease-2019; CXCL, C-X-C Motif Chemokine Ligand; CXCR, C-X-C Motif Chemokine Receptor; DC, dendritic cell; DENV, dengue virus; ECM, extracellular matrix; EMP, erythro-myeloid progenitors; Fc ϵ RI, high-affinity receptor for immunoglobulin E; Fc γ RIIA, Fc-gamma type 2 receptor A; FDA, Food and Drug Administration; GI, gastrointestinal; GMP, granulocyte/monocyte progenitor; H1, histamine 1; HSC, hematopoietic stem cells; IgE, immunoglobulin E; IFN, interferon; IL, interleukin; LT, leukotriene; MC, mast cell; MCAS, mast cell activation syndrome; MC_T, tryptase only MC; MC_{TC}, tryptase and chymase positive MC; MCP, Mast cell progenitor; MERS-CoV, Middle East respiratory syndrome coronavirus; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MPP, multipotent progenitor; MRGPRX2, MAS-related G protein-coupled receptor-X2; NF- κ B, nuclear factor-kappa B; NK, natural killer cells; NKT, natural killer T cells; NOD, nucleotide-binding oligomerization domain; PAF, platelet-activating factor; PGD, prostaglandin D; PGE, prostaglandin E; RA, RHEUMATOID arthritis; RNA, ribonucleic acid; RSV, respiratory syncytial virus; SARS, Severe Acute Respiratory Syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCF, stem cell factor; SP, substance P; STAT3, signal transducers and activators of transcription -3; TAMC, tumor-associated mast cell; TGF- β , transforming growth factor β ; TLR, toll-like receptor; TME, tumor microenvironment; TNF- α , tumor necrosis factor- α .

1 | MAST CELL GENESIS AND BIOLOGY

Mast cells (MCs), found in all classes of vertebrates are innate immune cells which emerged more than 500 million years ago.^{1,2} Although MCs represent a minor cell population compared to other immune cells, MCs are distributed throughout almost all human tissues and are usually found in close proximity to blood vessels in tissues which serve as physical barriers and are constantly exposed to external stimuli such as the skin, respiratory and gastrointestinal tracts.^{1,2} MCs originate from hematopoietic stem cells (HSCs) in the bone marrow (BM) where they start their maturation through multipotent progenitors (MPPs),³ which do not have cytoplasmic granules and high-affinity IgE receptor (FcεRI) expression. Slightly further down the lineage, the more differentiated precursors, the mast cell progenitors (MCPs) in the BM do begin to have few small cytoplasmic granules, high expression of integrin β7 and expression of FcεRI.^{4–6} Unlike other hematopoietic cells which complete their differentiation within the BM, the MCPs exit the marrow into the bloodstream and migrate to peripheral tissues for completing their maturation and differentiation under the influence of a complex network of microenvironmental growth factors and cytokines including stem cell factor (SCF), interleukins (IL)-6, IL-9, IL-18, transforming growth factor beta (TGF-β) which govern a complex transcriptional program that dictates MCs fates.^{7–11} To date, there have been limited studies detailing the ontogenesis of MCs, in particular human MCs.^{12,13} Although mouse and human MCs share similarities in their development, studies have also revealed major differences.^{4–6} Some studies have suggested that mouse MCPs can be derived from common myeloid progenitors (CMPs) or directly from MPPs.³ In addition, mouse MCs may also be derived from the granulocyte/monocyte progenitors (GMPs) through basophil/mast cell progenitors (BMCPs) which were only identified in the spleen of adult mice.³ As for human MCs, a study by Dahlin et al. identified that an MCP population (Lin⁻ CD34^{hi} KIT^{int/hi} FcεRI⁺) derived from blood exclusively gives rise to granulated tryptase⁺ KIT⁺ FcεRI⁺ MCs¹⁴ while Salomonsson et al. have recently identified a MCP population in BM and both MCP populations show similar gene expressions of MC markers such as carboxypeptidase A3 (Cpa3), KIT and FcεRI alpha chain (FCERIA).¹⁵ CCR1 and CCR5 mediate the retention of MCPs in BM whereas integrin β7 promotes the transmigration of MCPs into tissues as MCPs from the BM express higher levels of CCR1 and CCR5¹⁶ but lower levels of integrin β7¹⁵ than those MCPs from the peripheral blood. Mature MCs are phenotypically and functionally heterogeneous and are commonly classified into two subtypes, based on their protease content. In humans, MC_{TC} which

are mainly found at the skin and the small bowel submucosa, contain both tryptase and chymase, while MC_T which are mainly located at the small bowel mucosa and in bronchial area, predominantly contain tryptase but not chymase.^{1–3,17} However, recent fate-mapping studies have revealed that murine MCs arise during distinct waves of embryonic development.^{18,19} In addition, Li et al. suggested that adult murine connective tissue MCs mainly arise from yolk sac late erythro-myeloid progenitors (EMPs) and are long-lived cells that self-maintain independently of the BM.¹⁸ On the contrary, adult murine mucosal MCs are mainly derived from fetal HSCs, are short-lived and hence need to be constantly renewed by the BM.¹⁸ Notably, recent single cell RNA-sequencing (scRNA-seq) performed by Popescu et al. has indicated the presence of human early MCs in the yolk sac.²⁰ Future studies are needed to further tease out the degree of similarity in the developmental origins of human versus murine MCs. Our understanding of MC-driven diseases such as mastocytosis,²¹ a rare disorder characterized by abnormal accumulation of MCs in one or more tissues, will fundamentally change if human MCs share a similar developmental mechanism as what is reported for murine MCs. Adults typically develop systemic chronic mastocytosis while mastocytosis in children is usually cutaneous and often regresses spontaneously and completely before adulthood.²¹ Indeed, these clinical observations fit well with the distinct developmental waves of MCs described by Li et al.¹⁸ and Gentek et al.¹⁹ Pediatric mastocytosis could be a result of aberrant MCs derived from the first wave that are cleared with age while mastocytosis in adults could result from aberrancies in MCs of the definitive hematopoiesis which accumulate with age.²¹ However, future studies are required to validate this hypothesis.

MCs are characterized by their cytoplasmic granules which store a wide array of preformed molecules such as histamine, tryptase, chymase, etc.^{1,2,17,22–24} MCs express a variety of cell surface receptors including FcεRI, toll-like receptors (TLRs), MAS-related G protein-coupled receptor-X2 (MRGPRX2), IgG receptors, Fc-gamma type 2 receptor A (FcγRIIA) and complement receptors.^{2,22} Upon activation via the receptors, MCs may undergo degranulation to release the preformed mediators in their granules in a time scale of seconds to minutes based on the stimuli strength and coexisting ligands.^{1,2,17,22,25} Once activated, MCs can also newly synthesize lipid mediators such as prostaglandins and leukotrienes.^{1,2,17,22,26–30} Hours later, numerous de novo synthesized cytokines and chemokines are also released from activated MCs as effectors of their functions.^{1,2,17,22,23,25,31–34} Due to their distribution and expression of numerous arrays of membrane receptors, as well as the broad spectrum of inflammatory mediators

they produce,^{22,35–37} MCs can act as the first-line responders in host defense against a number of pathogens and have long been recognized for their key effector role in allergic inflammation. However, recently there is evidence that MCs may be playing a key role in the pathogenesis of coronavirus/COVID-19 disease.^{34,43–47} In addition, over the years, there has been mounting evidence of their involvement in the pathogenesis of other diseases including but not limited to psoriasis, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis, autism spectrum disorders, multiple sclerosis, rheumatoid arthritis (RA), the development of tumors, cardiovascular diseases and other inflammation-related

diseases (See Figure 1).^{1,2,38–42,48–57} This review will aim to cover the existing evidence on the role of MCs in COVID-19 and discuss the potential of MCs and their mediators as therapeutic targets and as biomarkers for disease severity and treatment outcome.

2 | ROLE OF MCS IN INFECTIOUS DISEASES

MCs express a large variety of functional cell surface or intracellular receptors such as TLRs and nucleotide-binding oligomerization domain (NOD) like receptors

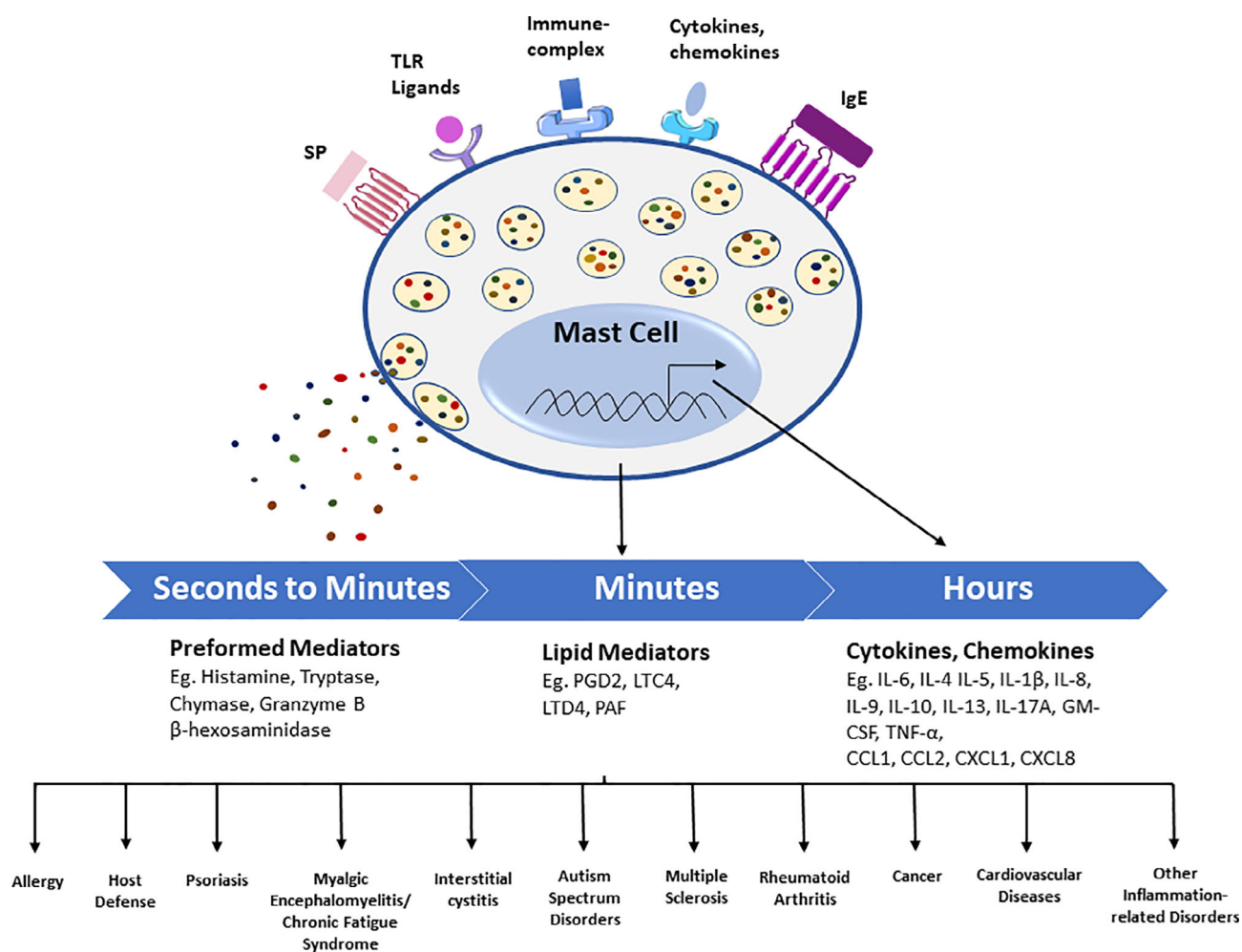


FIGURE 1 Mast cell activation and the release of their proinflammatory and immunomodulatory mediators. MCs express a wide range of surface receptors including Fc ϵ RI, toll-like receptors (TLRs), MAS-related G protein-coupled receptor-X2 (MRGPRX2), IgG receptors, Fc-gamma type 2 receptor A (Fc γ RIIA) and complement receptors. Once activated through their receptors, MCs release the preformed mediators such as histamine, tryptase, chymase, Granzyme B, β -hexosaminidase, from their secretory granules through degranulation within minutes or seconds. MCs also newly produce lipid mediators such as prostaglandins and leukotrienes in minutes and de novo synthesize cytokines (eg, IL-6, IL-4, IL-5, IL-1 β , IL-10, IL-13) and chemokines (eg, CCL1, CCL2, CXCL1, CXCL8) in hours. These proinflammatory and immunomodulatory mediators secreted by MCs contribute to host immunity and different diseases including but not limited to psoriasis, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis, autism spectrum disorders, multiple sclerosis, rheumatoid arthritis, cancer, cardiovascular diseases, and other inflammation-related diseases besides allergy

that can recognize pathogens.^{33,58} These properties provide MCs with advantages to very rapidly act as sentinels to guard against a plethora of invading pathogens. This role of MCs in defense against invading pathogens was first reported in the context of parasitic infections.⁵⁸ Crowle et al. demonstrated that *Nippostrongylus brasiliensis* is rejected after engraftment of Kit^{W/W^v} *c-kit* mutant MC-deficient mice with mucosal MCs.⁵⁹ Besides parasites, MCs can also protect the host against viral infections.^{44,58,60} Recent studies have demonstrated the ability of MCs to defend against common viruses such as dengue virus (DENV),^{61,62} influenza virus,⁶³ respiratory syncytial virus (RSV)⁵⁸ and more recently against coronaviruses.⁴⁴

For instance, initial studies on MCs response to DENV demonstrated that human MCs produce a number of cytokines and chemokines following infection.^{64,65} DENV infection of MCs in vitro results in the production of mediators such as IL-1 β that induce endothelial activation and chemokines are also released for the recruitment of a variety of inflammatory and effector cells.^{66,67} A study by St. John et al. has shown that MCs are required to recruit natural killer (NK) cells and natural killer T (NKT) cells into the infected tissues so as to inhibit the virus from spreading from the inoculation site in the foot pad to the draining lymph node of mice.⁶⁹ Studies also show that early innate response and subsequent acquired immunity are MC-dependent.⁶² However, besides its beneficial effects in DENV infections as demonstrated in the above studies, clinical studies have shown that MC degranulation is associated with dengue hemorrhagic disease and dengue shock syndrome, suggesting that MCs may have a detrimental role in more severe forms of DENV infection.^{61,62}

3 | ROLE OF MCS IN CORONAVIRUS INFECTION

Coronaviruses are single positive-strand, enveloped ribonucleic acid viruses.^{71,72} Within the last 20 years, there have been three highly pathogenic, zoonotic diseases caused by coronaviruses, with Severe Acute Respiratory Syndrome (SARS-CoV-1) first being detected in China in 2002 and then Middle East Respiratory Syndrome coronavirus (MERS-CoV) in Saudi Arabia in 2012, both caused outbreaks and spread globally.^{71,73,74} There were more than 8000 SARS-CoV-1 cases with about 10% mortality rate whereas MERS-CoV had about 2500 cases and an almost 40% mortality rate.^{73,74} The novel COVID-19 pandemic is the third outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which can be transmitted between

humans, primarily through inhalation or contact with droplets from infected individuals.^{71,74} SARS-CoV-2 is very contagious and pathogenic and has infected more than 100 million people worldwide and caused more than 2 million deaths since it was first detected in December 2019.⁴⁴ The COVID-19 pandemic presents an unprecedented challenge to the healthcare system globally and causes a huge stress on the economy worldwide.^{72,74}

SARS-CoV-2 has glycoprotein spikes projecting from its envelope, giving it a crown-like structure.^{71,74} Four structural proteins, spike glycoprotein (S), small envelope glycoprotein (E), membrane glycoprotein (M) and nucleocapsid protein (N) and 16 non-structural proteins have been identified.^{71,72} SARS-CoV-2 recognizes and binds to the angiotensin-converting enzyme 2 (ACE2) to attach to the host cells.^{71,72} The host serine protease, transmembrane serine protease 2 (TMPRSS2) cleaves the spike protein into S1 and S2 fragments, enabling the viral membrane to fuse with the cellular membrane.^{71,72} The virus can then enter the cell through endocytosis and releases its mRNA into the cytoplasm and uses the host translation machinery to facilitate viral replication.^{71,72} Humans infected by coronavirus may be asymptomatic or display cold-like symptoms while some patients might experience severe respiratory syndrome such as acute pneumonia, acute respiratory distress syndrome (ARDS), systemic inflammation and dysfunction of internal organs that can be fatal.^{44,71,74} There are limited treatment options for COVID-19 and the Food and Drug Administration (FDA) - approved anti-viral medication, remdesivir, needs to be administered intravenously to patients in hospitals⁷³ and the therapy is suboptimal as the clinical trial (NCT04257656) reported that the use of remdesivir in patients with severe COVID-19 is not significantly associated with clinical benefits.⁷⁶ Hence, the development of additional therapeutic options for COVID-19 which are effective, safe and easy to administer is urgent.⁷³

There is mounting evidence demonstrating the involvement of MCs in the pathogenesis of coronavirus, including COVID-19. Indeed, recent studies have revealed an elevated density of perivascular and septal MCs in the post-mortem lung biopsies from COVID-19 patients⁷⁷ and a higher number of activated MCs in the bronchoalveolar lavage fluid of COVID-19 patients as compared to samples from healthy individuals.⁷⁸ Furthermore, there was more MC-specific protease, CPA3 found in the serum of COVID-19 patients comparing to control group and there was a significant positive correlation between CPA3 and circulating neutrophils as well as C-reactive protein which are associated with exacerbated inflammatory response and thereby disease severity in COVID-19 patients.⁷⁰ Similarly, Gebremeskel et al.

reported that serum from COVID-19 patients had significantly higher levels of chymase, β -tryptase and CPA3 comparing to uninfected controls, indicating systemic MC activation in these patients.⁷⁹ In addition, there were also elevated gene expression of TPSB2 and TPSAB1 which encode for MC tryptase in the lungs of COVID-19 patients comparing to those of healthy individuals, suggesting activation of lung MCs in these patients.⁷⁹ In line with this, Tan et al. have reported that blood from severe COVID-19 patients during the acute phase had upregulation of genes associated with MC functions and MC precursor maturation.⁸⁰ Further, Tan et al. have also shown that severe COVID-19 patients have elevated plasma chymase, again indicating MC activation in COVID-19 patients.⁸⁰

The entry of coronavirus into the host activates innate immune cells including MCs which reside at the submucosa of the respiratory tract and in the nasal cavity, that represent a barrier of protection against pathogens.⁴⁴ Based on our previous knowledge on the role of MCs in viral infections, it can be postulated that the viral RNA are detected through TLR3, TLR7, TLR8, and retinoic acid-inducible gene-I-like receptors (RIG-I) expressed by MCs^{44,81,82} and this leads to MC activation and the release of CXCL8 to recruit cluster of differentiation (CD)8⁺ T cells and NK cells⁴⁴ which are critical players in anti-viral immunity through mediating cytotoxic functions and cellular immune responses.⁸³ In addition, these RNA viruses also stimulate MCs to produce anti-viral cytokine, type I interferon (IFN)⁶³ which enhances the cytotoxic activity by NK cells to target the virus-infected cells.⁸⁴ Yet, coronavirus can suppress the IFN and NF- κ B signaling pathways to evade the innate immune responses.^{85,86} Furthermore, SARS-CoV-2 can produce viral proteins to antagonize IFN.⁸⁵ Notably, patients included in the study of Trouillet-Assant et al. that had no IFN- α production presented poorer outcome as all of these patients required invasive ventilation and needed longer stay at the intensive care unit.⁸⁷ Further, TLR3-activation of MCs by poly I:C leads to upregulation of MHC class I molecules on MCs and thereby enhance antigen presentation to activate CD8⁺ T cells, resulting in increased intracellular Granzyme B in CD8⁺ T cells and thus enhance the cytotoxic potential of these CD8⁺ T cells.⁸⁸

Contrarily, MCs might also release proinflammatory cytokines including IL-6, TNF- α , IL-1 β which promote inflammation and pathogenesis of the infection seen in SARS.^{34,44,47} Importantly, Mazzone et al. showed that COVID-19 patients who required intensive care had high IL-6 levels in their serum which were inversely correlated to the number of circulating NK cells that are critical for anti-viral response.⁸³ In addition, Yang et al. demonstrated that high plasma levels of CCL3 and CXCL10,⁸⁹

which can be produced by Poly (I:C)-activated MCs,⁹⁰ are highly associated with disease severity during COVID-19 infection, suggesting that uncontrolled inflammation results in “cytokine storm” and thereby disease deterioration and fatal outcome of COVID-19. Additionally, histamine, prostaglandin (eg. PGD₂) and leukotrienes (eg. leukotriene C4 [LTC4]) produced by virus-activated MCs also lead to acute bronchoconstriction and lung inflammation.⁴⁴ The histamine secreted by MCs binds to the H2 receptors on peripheral monocytes to enhance the production of IL-1 which then induce the synthesis of IL-6 by macrophages, contributing to the high degree of inflammation seen in COVID-19 patients.⁴⁷ Along with elevated chymase levels in the blood of severe COVID-19 patients comparing to patients with mild disease or to healthy controls, Tan et al. have also found enhanced angiotensin (Ang) 2 levels in these patients, suggesting activation of the endothelial leading to microvascular abnormalities observed in severe COVID-19 patients.⁸⁰ MC-chymase is a potent converter of angiotensin I to angiotensin II, which regulates microvascular blood flow and systemic blood pressure and angiotensin II can upregulate the expression of Ang2.⁸⁰ Importantly, higher levels of angiotensin II in the plasma of COVID-19 patients have been correlated with lung injury. These suggest that activated MCs might be associated with the vascular barrier dysfunctions, such as shunting and hypoxemia due to abnormalities of pulmonary blood flow as well as tissue edema resulting from loss of endothelial integrity observed in COVID-19 patients.⁸⁰

Recently, as many as 50% of COVID-19 patients, regardless of their disease severity, have been reported to exhibit long-COVID syndrome even months after SARS-CoV-2 viral infection, presenting symptoms such as malaise, fatigue, joint pain, brain fog, chest tightness, shortness of breath, which are very similar to the symptoms observed in Mast Cell Activation Syndrome (MCAS) patients.^{46,91–93} Pulmonary fibrosis might result in pulmonary dysfunction, accounting for the chest pain and shortness of breath in long-COVID patients⁹² and pulmonary fibrosis has also been reported in SARS survivors post recovery and might represent one of the main complications in COVID-19 patients.⁴³ Indeed, Tan et al. have reported sustained MC activation at late time point post-infection even when patients were no longer tested positive for SARS-CoV-2 by polymerase chain reaction (PCR), suggesting ongoing, unresolved inflammation in the tissues and thereby long-term tissue damage after infection clearance.⁸⁰ Therefore, such sustained MC activation that continues to release inflammatory mediators as well as other fibrotic factors including matrix metalloproteinases 9 (MMP9) and TGF- β ⁴⁶ may contribute to the pulmonary fibrosis^{43,92} as MCs have been demonstrated to promote

proliferation of fibroblasts⁹⁴ which can cause enhanced fibrosis in different organs.^{92,95} For instance, there is increased expression of MC chymase in human idiopathic interstitial pneumonia⁹⁶ and there is elevated number of connective tissue MCs in the fibrotic areas of the alveolar parenchyma in idiopathic pulmonary fibrosis patients.⁷⁵ These studies suggest that MCs might also be involved in pulmonary fibrosis in COVID-19 patients. In addition, MCs produce platelet-activating factors (PAF) and thromboxane that might play a role in microthrombosis in the lungs of COVID-19 patients as Motta Junior et al reported MC degranulation in the alveolar septa of deceased COVID-19 patients which was associated with interstitial edema and immunothrombosis observed in these patients.^{46,77,97} Taken together, MCs might have dual effects during infection by coronavirus (see Figure 2) and the positive immune responses by MCs to fight against virus should be strengthened while dampening the inflammatory responses by MCs during coronavirus infection.

Since severe COVID-19 patients display impaired anti-viral response and “cytokine storm” is a common feature as well as the major cause for ARDS and multi-organ failure observed in these severe COVID-19 patients,^{71,98} it has been proposed that early intervention of recombinant IFN- α 2 which is required for the cytotoxic function of NK cells,⁸⁷ together with the off-label use of anti-inflammatory drugs to control hyperinflammation and respiratory distress could be a promising therapeutic intervention strategy for COVID-19 treatment.^{87,99,100} Several preliminary and cohort studies have been conducted to evaluate the efficacy of tocilizumab (anti-IL-6R),^{101–103} anakinra (IL-1RA)^{104,105} and methylprednisolone^{106,107} on alleviating systemic inflammation in COVID-19 patients and the results are encouraging and clinical trials have been approved to further assess their efficacy and safety in COVID-19 patients. These findings, together with the fact that MCs may be key players in the hyperproduction of inflammatory mediators in severe COVID-19 patients, prompt us to propose blockade of inflammatory mediators produced by virus-induced MCs or to inhibit MC activation as strategies to impede the “cytokine storm”. The feasibility of this strategy has recently been supported by animal models in which ACE2-humanized mice treated with antihistamines, Ebastine or Loratadine which might have MC-stabilizing properties, had significantly reduced MC degranulation, proinflammatory cytokine production and lung injury after SARS-CoV-2 infection comparing to untreated controls.¹⁰⁸

Thus far, several biologics or small molecules have been developed to target different MC mediators and MC activation and are approved by FDA to be used to treat

human diseases. For example, montelukast and zafirlukast are leukotriene receptor antagonists widely used in the management of chronic asthma¹⁰⁹ and might be used to prevent the actions of leukotrienes in bronchoconstriction and lung inflammation during SARS-CoV-2 infection. Moreover, montelukast might also possess anti-viral effect by targeting the 3CL protease of SARS-CoV-2¹¹⁰; Methylprednisolone, which is a corticosteroid that has been used to treat cutaneous mastocytosis,^{24,111,112} might be able to alleviate the hyperinflammation in COVID-19 patients caused by uncontrolled MC activation; Ketotifen and azelastine that are commonly used in asthma and allergic rhinitis, respectively, act as histamine 1 (H1) receptor antagonists to inhibit airway inflammation and bronchoconstriction^{24,109}; Sodium cromoglicate which is generally considered as a mast cell stabilizer and is used in asthmatic and allergic rhinitis patients, may also be applied to inhibit MC activation to alleviate bronchoconstriction and control the cytokine storm during COVID-19.^{43,113} However, only <5% of sodium cromoglicate can be absorbed orally and rapid tachyphylaxis develops against sodium cromoglicate.^{46,48} Similarly, luteolin and its analogue, tetramethoxyluteolin can inhibit MC degranulation and the secretion of proinflammatory cytokines and chemokines from MCs^{48,57,93,97,114} through blocking the intracellular calcium increase and NF- κ B activation in MCs.⁴⁸ Indeed, luteolin is a much more potent inhibitor for histamine release from MCs comparing to sodium cromoglycate⁴⁶ and luteolin can also suppress neuroinflammation and brain fog.^{57,91,93} Further, luteolin exhibits broad anti-viral properties as it can bind to the spike protein of SARS-CoV-2 to prevent the virus from entering into the host cells^{57,93,97} and can also inhibit SARS-CoV 3CL protease which is required for viral infectivity⁹⁷ and therefore luteolin and tetramethoxyluteolin, which are generally considered to be safe, are recommended as dietary supplement for COVID-19 patients^{45,46,57,97}; Avapritinib, Midostaurin and Imatinib which are used in systemic mastocytosis might reduce the number of MCs to prevent hyperinflammation and lung fibrosis in COVID-19 patients¹⁰⁹; Rupatadine, which is a dual H1 receptor and PAF antagonist being used to treat rhinitis and chronic spontaneous urticaria patients, might also be applied to inhibit the effects of histamine and PAF released by MCs as well as the activation of MCs by PAF in SARS-CoV-2-infected individuals to suppress their bronchoconstriction, microthrombosis and inflammation⁹⁷; Anti-inflammatory cytokines, such as IL-37 that inhibit IL-1 are also recommended for dampening the “cytokine storm”.⁴⁴ Canakinumab can be used as a therapy for cryopyrin-associated periodic syndromes to block IL-1 β ²²; Infliximab, adalimumab, certolizumab pegol, golimumab and etanercept can be applied to neutralize TNF- α for RA

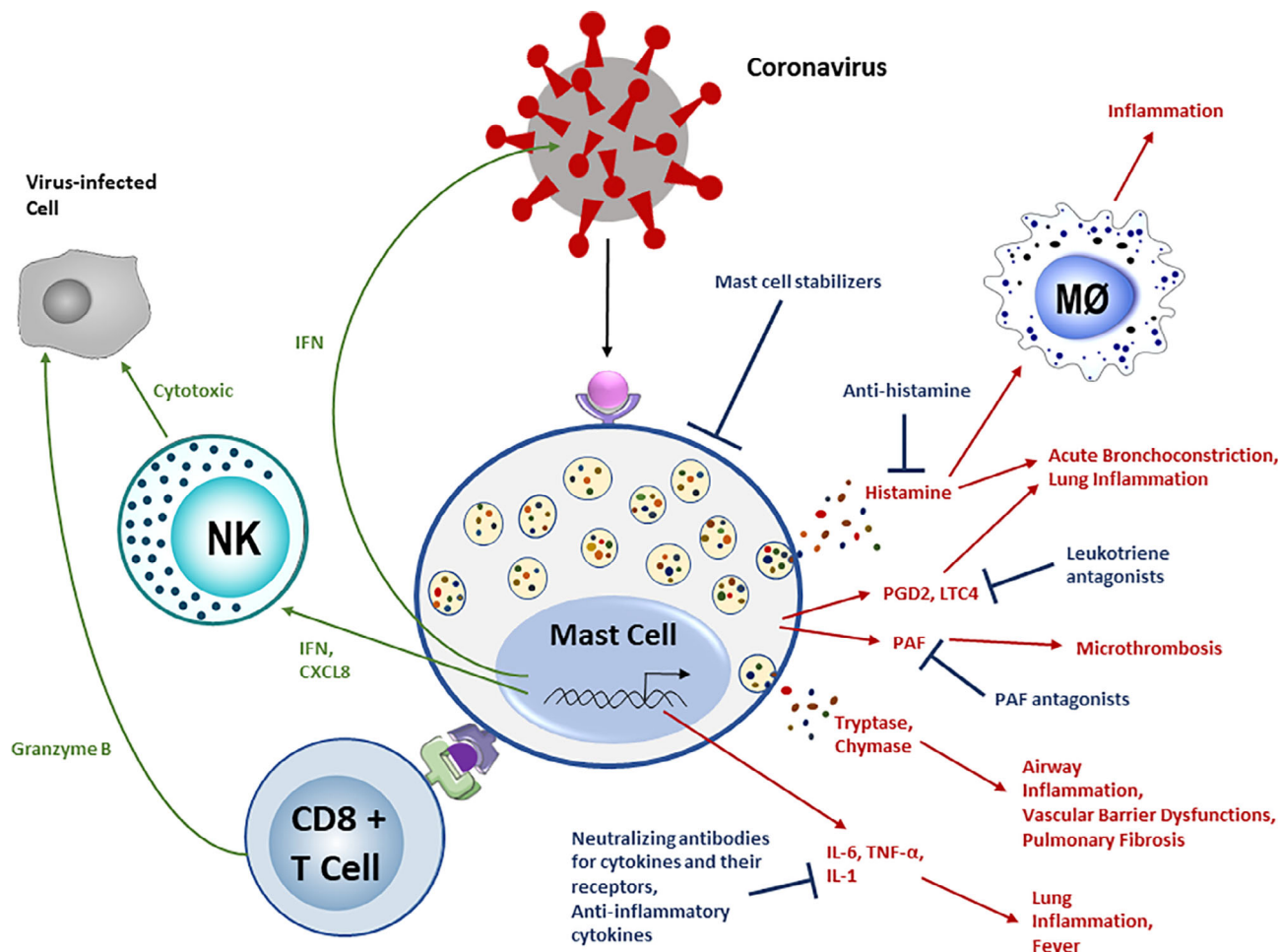


FIGURE 2 Positive and negative effects of mast cells on coronavirus. MCs are activated through the TLR3, TLR7, TLR8, and RIG-I by RNA virus such as coronavirus. This leads to the production of anti-viral IFN and CXCL8 by MCs. These IFN and CXCL8 recruit NK cells that produce more IFN which are anti-viral. These IFN also further enhance the cytotoxic activity of NK cells against virus-infected cells. MCs also present antigen to CD8⁺ T cells through MHC class I and these CD8⁺ T cells release granzyme B which is cytotoxic to viral-infected cells. On the contrary, MCs may degranulate to release chymase and tryptase which lead to airway inflammation, vascular barrier dysfunctions and pulmonary fibrosis. Additionally, MCs may also release proinflammatory cytokines such as TNF- α , IL-1, and IL-6 that promote the lung inflammation and cause fever. Virus-activated MCs may also release histamine, PGD2 and LTC4 which lead to acute bronchoconstriction and lung inflammation. The histamine secreted may also activate macrophage to exacerbate inflammation while PAF released by MCs will lead to microthrombosis. Several therapeutic agents are proposed to block inflammatory mediators produced by virus-induced MCs or to inhibit MC activation as strategies to control the “cytokine storm” and lung injury. Montelukast and zafirlukast are leukotriene receptor antagonists; Ketotifen and azelastine act as histamine (H1) receptor antagonists; Rupatadine is a dual H1-receptor and PAF antagonist; Sodium cromoglicate and luteolin inhibit mast cell activation; Canakinumab can be used to block IL-1 β ; Infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept can be applied to neutralize TNF- α ; Anti-inflammatory cytokines, such as IL-37 can inhibit IL-1. Refer to Table 1 for the details of these drugs and their clinical status

patients¹⁰⁹; Similarly, tocilizumab and sarilumab against IL-6 receptors are used for treating RA.¹⁰⁹ Therefore, applying these biologics to block proinflammatory cytokines released by MCs or the receptors for these cytokines might help to control the hyperinflammation in COVID-19 patients. Indeed, several of these biologics and small molecules are being assessed in clinical trials for COVID-19 patients currently, with some of them already reaching Phase 4 (Table 1). Recent results from clinical trial (NCT04331795) have shown that low-dose tocilizumab,

anti-IL6 receptor monoclonal antibody, was associated with rapid improvement for hyperinflammation in hospitalized COVID-19 patients.⁶⁸ Note that some of these drugs do not target MC-specific mediators, for instance, IL-6, IL-1 and TNF- α are also produced by macrophages.⁷¹ However, given that both MC and macrophages are key players in the “cytokine storm”, these drugs might be powerful to restrain the hyperinflammation in COVID-19 patients. Table 1 lists the drugs that suppress MC activation or block the mediators released by MCs and these drugs are either

TABLE 1 Potential MC and MC product-directed therapeutics for COVID-19 patients

Potential mode of action on MC function	Intervention	Clinical trial stage and the corresponding disease	Clinical trial for COVID-19 ClinicalTrials.gov identifier
Anti-IL-6R	Tocilizumab	FDA-approved for RA	NCT04445272, Phase 2, completed NCT04730323, Phase 4, completed NCT04479358, Phase 2 NCT04345445, Phase 3 NCT04317092, Phase 2 NCT04600141, Phase 3 NCT04435717, Phase 2 NCT04412772, Phase 3 NCT04331795, Phase 2, completed NCT04377750, Phase 4 NCT04332094, Phase 2 NCT04577534, Phase 3 NCT04361032, Phase 3 NCT04377659, Phase 2 NCT04424056, Phase 3 NCT04412291, Phase 2 NCT04678739, Phase 3, completed NCT04320615, Phase 3, completed NCT04363736, Phase 2, completed NCT04372186, Phase 3 NCT04356937, Phase 3, completed NCT04377503, Phase 2 NCT04409262, Phase 3, completed NCT04363853, Phase 2 NCT04335305, Phase 2 NCT04693026, Phase 3 NCT04779047, Phase 4 NCT04560205, Phase 1 NCT04339712, Phase 2, completed NCT04871854, Phase 2 NCT04315480, Phase 2 NCT04476979, Phase 2 NCT04361552, Phase 3 NCT04423042, Phase 3 NCT04330638, Phase 3 NCT04381936, Phase 3 NCT04331808, Phase 2 NCT04347031, Phase 3, completed NCT04349410, Phase 3, completed NCT04346693, Phase 3, completed
Anti-IL-6R	Sarilumab	FDA-approved for RA	NCT04357808, Phase 2, completed NCT04386239, early Phase 1 NCT04315298, Phase 3, completed NCT04661527, Phase 2 NCT04341870, Phase 3, completed NCT04359901, Phase 2 NCT04357860, Phase 2 NCT04327388, Phase 3, completed NCT04324073, Phase 3 NCT04380519, Phase 3, completed NCT02735707, Phase 4
Anti-IL-6	Siltuximab	FDA-approved for idiopathic multicentric Castleman's disease	NCT04329650, Phase 2 NCT04330638, Phase 3
Anti-IL-6	Sirukumab	Not yet FDA-approved	NCT04380961, Phase 2

(Continues)

TABLE 1 (Continued)

Potential mode of action on MC function	Intervention	Clinical trial stage and the corresponding disease	Clinical trial for COVID-19 ClinicalTrials.gov identifier
Anti-IL-6	Olokizumab	Not yet FDA-approved	NCT04380519, Phase 3, completed NCT04452474, Phase 2
Anti-IL-6	Clazakizumab	Not yet FDA-approved	NCT04381052, Phase 2 NCT04348500, Phase 2 NCT04363502, Phase 2 NCT04343989, Phase 2, completed NCT04494724, Phase 2 NCT04659772, Phase 2, completed
Anti-IL-1R	Anakinra	FDA-approved for RA	NCT04680949, Phase 3 NCT04412291, Phase 2 NCT04424056, Phase 3 NCT04603742, Phase 2 NCT04357366, Phase 2 NCT04643678, Phase 3 NCT04339712, Phase 2, completed NCT04362111, Phase 3 NCT04330638, Phase 3 NCT04341584, Phase 2, completed NCT04381936, Phase 3 NCT02735707, Phase 4
Anti-IL-1 β	Canakinumab	FDA-approved for cryopyrin-associated periodic syndromes	NCT04362813, Phase 3, completed NCT04365153, Phase 2, completed NCT04510493, Phase 3
Anti-TNF- α	Infliximab	FDA-approved for RA	NCT04593940, Phase 3 NCT04425538, Phase 2 completed NCT04922827, Phase 2 NCT04381936, Phase 3
Anti-TNF- α	Adalimumab	FDA-approved for RA	N/A
Anti-TNF- α	Certolizumab pegol	FDA-approved for RA	N/A
Anti-TNF- α	Golimumab	FDA-approved for RA	N/A
Anti-TNF- α	Etanercept	FDA-approved for RA	N/A
Leukotriene receptor antagonist	Montelukast	FDA-approved for asthma, allergic rhinitis	NCT04389411, Phase 3 NCT04718285, Phase 2 NCT04695704, Phase 3
Leukotriene receptor antagonist	Zafirlukast	FDA-approved for asthma	NCT04871828, Phase 3
Corticosteroid	Methylprednisolone	FDA-approved for allergic rhinitis, atopic dermatitis	NCT04603729, Phase 3, completed NCT04673162, Phase 3 NCT04485429, Phase 3 NCT04909918, Phase 3 NCT04499313, Phase 3 NCT04377503, Phase 2 NCT04636671, Phase 3 NCT04341038, Phase 3 NCT04345445, Phase 3 NCT04438980, Phase 3, completed NCT04244591, Phase 3, completed NCT04329650, Phase 2 NCT04765371, Phase 3 NCT04826588, phase 3 NCT04263402, Phase 4 NCT04780581, Phase 4

TABLE 1 (Continued)

Potential mode of action on MC function	Intervention	Clinical trial stage and the corresponding disease	Clinical trial for COVID-19 ClinicalTrials.gov identifier
			NCT04528888, Phase 3 NCT04349410, Phase 3, completed NCT03852537, Phase 2, completed NCT04843761, Phase 3 NCT04843761, Phase 3 NCT04381936, Phase 3
Anti-histamine	Ketotifen	FDA-approved for asthma	N/A
Anti-histamine	Azelastine	FDA-approved for allergic rhinitis	N/A
Mast cell stabilizer	Sodium Cromoglicate	FDA-approved for asthma, allergic rhinitis	N/A
Mast cell stabilizer	Luteolin	Not yet FDA-approved	NCT04853836, Phase 4
Kit inhibitor	Imatinib	FDA-approved for aggressive systemic mastocytosis without KitD816 mutation	NCT04394416, Phase 3 NCT04346147, Phase 2 NCT04422678, Phase 3 NCT04794088, Phase 2 NCT04357613, Phase 2
Kit inhibitor	Avapritinib	FDA-approved for advanced systemic mastocytosis	N/A
Kit inhibitor	Midostaurin	FDA-approved for aggressive systemic mastocytosis	N/A

FDA-approved for MC-related or other inflammatory diseases, or are under COVID-19 clinical trials, or under both categories (in blue). These therapeutic agents might be repurposed for COVID-19 treatment, however, large, randomized, double-blinded, placebo - controlled trials with more harmonized protocols across different clinical trial centers are needed to provide further evidence on the efficacy and safety of these drugs on COVID-19 patients. Worldwide collaboration for clinical research and sharing of scientific findings are imperative to improve our understanding on the immunopathogenesis of COVID-19, which is of paramount importance in developing therapies and vaccines to combat the pandemic.

Besides allergic inflammation and infectious diseases, a number of reviews have previously reported the potentially functional roles of MCs in other human ailments, including but not limited to neuroinflammation, cancer and autoimmune disorders, where MCs may play underappreciated roles.^{1,51,57,93,115–119} Therefore, the abovementioned therapeutic agents may also be useful for treatment of these other human ailments.

4 | CONCLUDING REMARKS

In conclusion, there is compelling evidence that MCs are key players in the pathogenesis of COVID-19 and other

pathophysiological processes besides their well-recognized roles in allergic disorders. However, how exactly MCs contribute to these processes remain to be elucidated and many unanswered questions are needed to be addressed (see Outstanding Questions). Most of the human studies mentioned here demonstrate a correlation between MCs and the diseases. There is currently no method to deplete MCs in humans. Intriguingly, no human MC deficiency has been reported thus far. This could either be because MC deficiency in humans is embryonically lethal or MC deficiency is simply asymptomatic in humans and further large-scale genetic screening and studies are needed to tease out these distinct ideas. Therefore, to demonstrate the casual link between MCs and a disease, MC-deficient mouse models have been widely used to investigate the role of MCs in the pathogenesis of diseases. However, results obtained from c-Kit-dependent MC-deficient mice (WBB6F1-Kit^{W/W-v120,121} and C57BL/6-Kit^{W-sh/W-sh122–124} mice) should be interpreted carefully as these mice also present other immunological abnormalities related to c-Kit mutation besides MC deficiency and lead to non-reproducible results compared to studies which use more recently generated c-Kit-independent MC-deficient mice that are driven by the Cre-loxP recombination system (*Mcpt5-Cre*^{125–127} and *Cpa3-Cre*^{120,128}) and have normal c-Kit function. Hence, future MC in vivo studies should use Cre-based c-Kit-independent models and the in vivo role

of human MCs could be investigated using the more recently developed humanized mouse models which provide a rich source of human MCs^{129–131} and could be employed to develop various disease models for testing new therapeutics in the future. To date, there is still no medication that solely and selectively targets MC activity.^{2,48} Better understanding of the functions of MCs in the pathophysiological processes can be achieved through genome-wide transcriptomic,^{132,133} epigenomic,^{132,133} proteomic^{134–136} and lipidomic analysis¹³⁷ of MCs during different stages of the human diseases such as COVID-19, cancer and autoimmune diseases using healthy individuals as control. This will allow us to identify novel MC-related biomarkers for disease severity which can be employed to stratify patients as well as to develop new, powerful therapeutic strategies which aim to “re-educate” these tunable MCs into the subtypes (eg. improve anti-viral immunity but suppress inflammation in COVID-19 patients) that result in improved disease outcome. Additionally, by analyzing the MC profiles at different time points of treatment versus placebo controls using “omics” approaches, biomarkers will be identified for predicting patients’ response to treatment and thereby tailor therapy for each individual to ensure better patient care and clinical outcome.

5 | OUTSTANDING QUESTIONS

1. Do human mast cells (MCs) arise by a similar mechanism of differentiation through distinct waves as the murine MCs?
2. How exactly are human MCs activated in response to the multitude of stimuli present in different microenvironment and what mediators will these activated MCs produce as a result? What is the genomic and proteomic profile of single MCs during normal physiological processes and during different human diseases?
3. Therapeutically, how can we ensure that MCs promote anti-viral immunity during COVID-19 infection without invoking the violent “cytokine storm”?
4. Do the elevated numbers of MCs at inflammatory sites during disease states mean to drive the disorder, or is it a compensatory strategy to control and terminate the pathogenic process or these MCs are just innocent bystanders?

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AUTHOR CONTRIBUTIONS


Hiu Yan Lam conceived and wrote the manuscript. Vinay Tergaonkar, Alan Prem Kumar, and Kwang Seok Ahn provided suggestions and edited the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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