Mast cells: Therapeutic targets for COVID-19 and beyond

Hiu Yan Lam1,2,3 | Vinay Tergaonkar2,3,4 | Alan Prem Kumar5,6 | Kwang Seok Ahn7

1Cancer Science Institute of Singapore, National University of Singapore, Singapore, Singapore
2Laboratory of NF-kB Signaling, Institute of Molecular and Cell Biology (IMCB), Singapore, Singapore
3Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
4Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
5Cancer Science Institute of Singapore and Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
6National University Cancer Institute, National University Health System, Singapore, Singapore
7Department of Science in Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

Correspondence
Huu Yan Lam, Cancer Science Institute of Singapore, National University of Singapore, Singapore, 117597, Singapore.
Email: e0081745@u.nus.edu
Kwang Seok Ahn, Department of Science in Korean Medicine, College of Korean Medicine, Kyung Hee University, 24 Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Republic of Korea.
Email: ksahn@khu.ac.kr

Funding information
National Research Foundation of Korea, Grant/Award Number: NRF-2021R1I1A2060024; Singapore Ministry of Education; National Medical Research Council of Singapore; Singapore Ministry of Education Tier 2, Grant/Award Number: MOE-T2EP30120-0016; SINGA scholarship from Agency for Science, Technology and Research, Singapore (A*STAR); National Research Foundation, Singapore, Grant/Award Number: NRF-CRP17-2017-02

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
- FcεRI: high-affinity receptor for immunoglobulin E
- FcγRIIA: Fc-gamma type 2 receptor A
- FDA: Food and Drug Administration
- G1: 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
- MCT: tryptase only MC
- MCTC: tryptase and chymase positive MC
- MCP: Mast cell progenitor
- MERS-CoV: Middle East respiratory syndrome coronavirus
- MHC: major histocompatibility complex
- MMP: matrix metallopeptidase
- MPP: multipotent progenitor
- MRGPRX2: MAS-related G protein-coupled receptor-X2
- NF-κB: 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
- TAME, 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 (FceRI) 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 \( \beta \)7 and expression of FceRI.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-\( \beta \)) 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– CD34hi KIThi/hi FceRIhi) derived from blood exclusively gives rise to granulated tryptase+ KIT+ FceRI+ 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 FceRI alpha chain (FCERIA).15 CCR1 and CCR5 mediate the retention of MCPs in BM whereas integrin \( \beta \)7 promotes the transmigration of MCPs into tissues as MCPs from the BM express higher levels of CCR1 and CCR516 but lower levels of integrin \( \beta \)715 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\( _{C} \) 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 FceRI, toll-like receptors (TLRs), MAS-related G protein-coupled receptor-X2 (MRGPRX2), IgG receptors, Fc-gamma type 2 receptor A (Fc\( \gamma \)RIIA)) 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. 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. 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). 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...
that can recognize pathogens. 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. Crowle et al. demonstrated that Nippostrongylus brasiliensis is rejected after engraftment of Kit \(\text{W}^{+/+}\) c-kit mutant MC-deficient mice with mucosal MCs. Besides parasites, MCs can also protect the host against viral infections. Recent studies have demonstrated the ability of MCs to defend against common viruses such as dengue virus (DENV), influenza virus, respiratory syncytial virus (RSV) and more recently against coronaviruses.

For instance, initial studies on MCs response to DENV demonstrated that human MCs produce a number of cytokines and chemokines following infection. DENV infection of MCs in vitro results in the production of mediators such as IL-1 which induce endothelial activation and chemokines are also released for the recruitment of a variety of inflammatory and effector cells. 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. Studies also show that early innate response and subsequent acquired immunity are MC-dependent. 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.

**3 | ROLE OF MCS IN CORONAVIRUS INFECTION**

Coronaviruses are single positive-strand, enveloped ribonucleic acid viruses. 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. 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. 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. 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. The COVID-19 pandemic presents an unprecedented challenge to the healthcare system globally and causes a huge stress on the economy worldwide.

SARS-CoV-2 has glycoprotein spikes projecting from its envelope, giving it a crown-like structure. 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. SARS-CoV-2 recognizes and binds to the angiotensin-converting enzyme 2 (ACE2) to attach to the host cells. 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. 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.

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. 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 hospitals 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. Hence, the development of additional therapeutic options for COVID-19 which are effective, safe and easy to administer is urgent.

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 patients and a higher number of activated MCs in the bronchoalveolar lavage fluid of COVID-19 patients as compared to samples from healthy individuals. 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. 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. 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. 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. Further, Tan et al. have also shown that severe COVID-19 patients have elevated plasma chymase, again indicating MC activation in COVID-19 patients.

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, which represent a barrier of protection against pathogens. 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 and this leads to MC activation and the release of CXCL8 to recruit cluster of differentiation (CD)8 T cells and NK cells which are critical players in anti-viral immunity through mediating cytotoxic functions and cellular immune responses. In addition, these RNA viruses also stimulate MCs to produce anti-viral cytokine, type I interferon (IFN) which enhances the cytotoxic activity by NK cells to target the virus-infected cells. Yet, coronavirus can suppress the IFN and NF-xB signaling pathways to evade the innate immune responses. Furthermore, SARS-CoV-2 can produce viral proteins to antagonize IFN. 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. 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.

Contrarily, MCs might also release proinflammatory cytokines including IL-6, TNF-α, IL-1β which promote inflammation and pathogenesis of the infection seen in SARS. Importantly, Mazzoni 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. In addition, Yang et al. demonstrated that high plasma levels of CCL3 and CXCL10, which can be produced by Poly (I:C)-activated MCs, 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. 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. 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 angiopoietin (Ang) 2 levels in these patients, suggesting activation of the endothelial leading to microvascular abnormalities observed in severe COVID-19 patients.

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. 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.

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. Pulmonary fibrosis might result in pulmonary dysfunction, accounting for the chest pain and shortness of breath in long-COVID patients and pulmonary fibrosis has also been reported in SARS survivors post recovery and might represent one of the main complications in COVID-19 patients. 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. 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 may contribute to the pulmonary fibrosis as MCs have been demonstrated to promote...
proliferation of fibroblasts which can cause enhanced fibrosis in different organs. For instance, there is increased expression of MC chymase in human idiopathic interstitial pneumonia and there is elevated number of connective tissue MCs in the fibrotic areas of the alveolar parenchyma in idiopathic pulmonary fibrosis. 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. 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, it has been proposed that early intervention of recombinant IFN-α2 which is required for the cytotoxic function of NK cells, 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. Several preliminary and cohort studies have been conducted to evaluate the efficacy of tocilizumab (anti-IL-6R), anakinra (IL-1RA), and methylprednisolone 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.

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 asthma 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-2. Methylprednisolone, which is a corticosteroid that has been used to treat cutaneous mastocytosis, 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. 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. However, only <5% of sodium cromoglicate can be absorbed orally and rapid tachyphylaxis develops against sodium cromoglicate. Similarly, luteolin and its analogue, tetramethoxy luteolin can inhibit MC degranulation and the secretion of proinflammatory cytokines and chemokines from MCs through blocking the intracellular calcium increase and NF-κB activation in MCs. Indeed, luteolin is a much more potent inhibitor for histamine release from MCs comparing to sodium cromoglicate and luteolin can also suppress neutrophil infiltration and brain fog. 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 and can also inhibit SARS-CoV 3CL protease which is required for viral infectivity and therefore luteolin and tetramethoxy luteolin, which are generally considered to be safe, are recommended as dietary supplement for COVID-19 patients; 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 patients; 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 inflammation. Anti-inflammatory cytokines, such as IL-37 that inhibit IL-1 are also recommended for dampening the “cytokine storm”. Canakinumab can be used as a therapy for cryopyrin-associated periodic syndromes to block IL-1β; Infliximab, adalimumab, certolizumab pegol, golimumab and etanercept can be applied to neutralize TNF-α for RA.
Similarly, tocilizumab and sarilumab against IL-6 receptors are used for treating RA. 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. 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. 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
| 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-6                              | 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)
| 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                                    |
|                                        |                         |                                                    | NCT0438500, Phase 2                                     |
|                                        |                         |                                                    | NCT04363502, Phase 2                                    |
|                                        |                         |                                                    | NCT04343989, Phase 2                                    |
|                                        |                         |                                                    | NCT04494724, Phase 2                                    |
|                                        |                         |                                                    | NCT04659772, Phase 2                                    |
| 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                                    |
|                                        |                         |                                                    | NCT04362111, Phase 3                                    |
|                                        |                         |                                                    | NCT04330638, Phase 3                                    |
|                                        |                         |                                                    | NCT04341584, Phase 2                                    |
|                                        |                         |                                                    | NCT04381936, Phase 3                                    |
|                                        |                         |                                                    | NCT02735707, Phase 4                                    |
| Anti-IL-1β                             | 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                                    |
|                                        |                         |                                                    | 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                                    |
|                                        |                         |                                                    | NCT04244591, Phase 3, completed                         |
|                                        |                         |                                                    | NCT04329650, Phase 2                                    |
|                                        |                         |                                                    | NCT04765371, Phase 3                                    |
|                                        |                         |                                                    | NCT04826588, phase 3                                    |
|                                        |                         |                                                    | NCT04263402, Phase 4                                    |
|                                        |                         |                                                    | NCT04780581, Phase 4                                    |
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 is 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. Therefore, the abovementioned therapeutic agents may also be useful for treatment of these other human ailments.

| Potential mode of action on MC function | Intervention | Clinical trial stage and the corresponding disease | Clinical trial for COVID-19 ClinicalTrials.gov identifier |
|----------------------------------------|--------------|---------------------------------------------------|-------------------------------------------------------|
| 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                                  |
| Kit inhibitor                           | Avapritinib  | FDA-approved for advanced systemic mastocytosis    | N/A                                                   |
| Kit inhibitor                           | Midostaurin  | FDA-approved for aggressive systemic mastocytosis    | N/A                                                   |

### Table 1 (Continued)

### 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<sup>W/W-v1</sup>120,121 and C57BL/6-Kit<sup>W-sh/W-sh</sup>122–124 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<sup>125–127</sup> and Cpa3-Cre<sup>120,128</sup>) 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 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. Better understanding of the functions of MCs in the pathophysiological processes can be achieved through genome-wide transcriptomic, epigenomic, proteomic, and lipidomic analysis 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 a 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?

ACKNOWLEDGMENTS
This study was supported by the National Research Foundation (NRF) grant funded by the National Research Foundation, Singapore [grant number NRF-CRP17-2017-02]. Hiu Yan Lam was supported by the SINGA scholarship from Agency for Science, Technology and Research, Singapore (A*STAR). The work was supported by a grant from the Singapore Ministry of Education Tier 2 (MOE-T2EP30120-0016) to Alan Prem Kumar. Alan Prem Kumar is also supported by the National Medical Research Council of Singapore and the Singapore Ministry of Education under its Research Centers of Excellence initiative to Cancer Science Institute of Singapore, National University of Singapore. This work was also supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (NRF-2021R1I1A2060024).

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.

ORCID
Hiu Yan Lam □ https://orcid.org/0000-0001-5007-5375
Alan Prem Kumar □ https://orcid.org/0000-0002-3754-5712
Kwang Seok Ahn □ https://orcid.org/0000-0002-2882-0612

REFERENCES
1. Varricchi G, Galdiero MR, Loffredo S, et al. Are mast cells MASTers in cancer? Front Immunol. 2017;8:424.
2. Varricchi G, De Paulis A, Marone G, Galli SJ. Future needs in mast cell biology. Int J Mol Sci. 2019;20:4397.
3. Aponte-López A, Fuentes-Panana EM, Cortes-Muñoz D, Muñoz-Cruz S. Mast cell, the neglected member of the tumor microenvironment: role in breast cancer. J Immunol Res. 2018;2018:2584243.
4. Dahlin JS, Hallgren J. Mast cell progenitors: origin, development and migration to tissues. Mol Immunol. 2015;63:9–17.
5. Jamur MC, Moreno AN, Mello LFC, et al. Mast cell repopulation of the peritoneal cavity: contribution of mast cell progenitors versus bone marrow derived committed mast cell precursors. BMC Immunol. 2010;11:32.
6. Schmetzer O, Valentin P, Church MK, Maurer M, Siebenhaar F. Murine and human mast cell progenitors versus bone marrow derived committed mast cell precursors. BMC Immunol. 2010;11:32.
7. Gurish MF, Austen KF. Developmental origin and functional specialization of mast cell subsets. Immunity. 2012;37:25–33.
8. Kitamura Y, Oboki K, Ito A. Molecular mechanisms of mast cell development. Immunol Allergy Clin North Am. 2006;26:387–405.
9. Chopra P, Sethi G, Dastidar SG, Ray A. Polo-like kinase inhibitors: an emerging opportunity for cancer therapeutics. Expert Opin Investig Drugs. 2010;19:27–43.
10. Kirtonia A, Sethi G, Garg M. The multifaceted role of reactive oxygen species in tumorigenesis. Cell Mol Life Sci. 2020;77:4459–4483.
11. Gupta B, Sadaria D, Warrier VU, et al. Plant lectins and their usage in preparing targeted nanovaccines for cancer
imunotherapy. Semin. Cancer Biol. 2020. http://dx.doi.org/10.1016/j.semcancer.2020.02.005

12. Kirshenbaum AS, Goff JP, Semere T, Foster B, Scott LM, Metcalfe DD. Demonstration that human mast cells arise from a progenitor cell population that is CD34+, c-kit+, and expresses aminopeptidase N (CD13). Blood. 1999;94:2333–2342.

13. Maaninka K, Lappalainen J, Kovanen PT. Human mast cells arise from a common circulating progenitor. J. Allergy Clin. Immunol. 2013;132:463–469.e3.

14. Dahlén JS, Malinovschi A, Öhrvik H, et al. Lin– CD34hi CD117int/hi FcεRI+ cells in human bone contribute a rare population of mast cell progenitors. Blood. 2016;127(4):383–391. http://dx.doi.org/10.1182/blood-2015-06-650648

15. Salomonsson M, Ungerstedt J, Alvarado-Vazquez PA, Hallgren J. Demonstration of human mast cell progenitors in the bone marrow. Allergy. 2020;75:456–460.

16. Salomonsson M, Dahlén JS, Ungerstedt J, Hallgren J. Localization-specific expression of CCR1 and CCR5 by mast cell progenitors. Front Immunol. 2020;11:321.

17. Galli SJ, Gaudenzio N, Tsai M. Mast cells in inflammation and disease: recent progress and ongoing concerns. Annu Rev Immunol. 2020;38:49–77.

18. Li Z, Liu S, Xu J, et al. Adult connective tissue-resident mast cells originate from late erythro-myeloid progenitors. Immunity. 2018;49:640–653.e5.

19. Gentek R, Ghigo C, Hoeffel G, et al. Hemogenic endothelial fate mapping reveals dual developmental origin of mast cells. Immunity. 2018;48:1160–1171.e5.

20. Popescu DM, Botting RA, Stephenson E, et al. Decoding human fetal liver haematopoiesis. Nature. 2019;574:365–371.

21. Nilsson G, Dahlén JS. New insights into the origin of mast cells. Allergy. 2019;74(4):844–845. http://dx.doi.org/10.1111/all.13668

22. Cildir G, Pant H, Lopez AF, Tergaonkar V. The transcriptional program, functional heterogeneity, and clinical targeting of mast cells. J Exp Med. 2017;214:2491–2506.

23. Theoharides TC. Neuroendocrinology of mast cells: challenges and controversies. Exp Dermatol. 2017;26:751–759.

24. Theoharides T, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med. 2015;373:1884–1886.

25. Lam HY, Tergaonkar V, Ahn KS. Mechanisms of allergen-specific immunotherapy for allergic rhinitis and food allergies. J Biol. Regul. Homeost Agents. 2020;34:9–1633–1636.

26. Puar YR, Shanmugam MK, Fan L, et al. Evidence for the involvement of the master transcription factor NF-xB in cancer initiation and progression. Biomedicine. 2018;6:82.

27. Siveen KS, Nguyen AH, Lee JH, et al. Negative regulation of signal transducer and activator of transcription-3 signalling cascade by lupeol inhibits growth and induces apoptosis in hepatocellular carcinoma cells. Br J Cancer. 2014;111:1327–1337.

28. Cai W, Xiong Chen Z, Rane G, et al. Wanted DEAD/H or alive: helicases winding up in cancers. J Natl Cancer Inst. 2017;109(6):djw278. http://dx.doi.org/10.1093/jnci/djw278

29. Ahn KS, Sethi G, Jain AK, Jaiswal AK, Aggarwal BB. Genetic deletion of NAD(P)H:quinone oxidoreductase 1 abrogates activation of nuclear factor-kappaB, IkappaBalpha kinase, c-Jun N-terminal kinase, Akt, p38, and p44/42 mitogen-activated protein kinases and potentiates apoptosis. J Biol Chem. 2006;281:19978–19808.

30. Tewari D, Nabavi SF, Nabavi SM, et al. Targeting activator protein 1 signaling pathway by bioactive natural agents: possible therapeutic strategy for cancer prevention and intervention. Pharmacol Res. 2018;128:366–375.

31. Lam HY, Arumugam S, Bae HG, et al. ELKS1 controls mast cell degranulation by regulating the transcription of Stxbp2 and Syntaxin 4 via Kdm2b stabilization. Sci. Adv. 2020;6:eabb2497.

32. Chen Y, Ho L, Tergaonkar V. sORF-encoded MicroPeptides: new players in inflammation, metabolism, and precision medicine. Cancer Lett. 2021;500:263–270.

33. Akinci-Il SC, Wu L, Ng QF, et al. NAIL: an evolutionarily conserved lncRNA essential for licensing coordinated activation of p38 and NFκB in colitis. Gut. 2021;70:1857–1871. http://dx.doi.org/10.1136/gutjnl-2020-322980

34. Theoharides T, Conti P. COVID-19 and multisystem inflammatory syndrome, or is it mast cell activation syndrome? J. Biol. Regul. Homeost Agents. 2020;34:1633–1636.

35. Ozturk MB, Li Y, Tergaonkar V. Current insights to regulation and role of telomerase in human diseases. Antioxidants. 2017;6:17.

36. Wang T, Zhang M, Ma Z, et al. A role of Rab7 in stabilizing EGFR-Her2 and in sustaining Akt survival signal. J Cell Physiol. 2012;227:2788–2797.

37. Chipurupalli S, Kannan E, Tergaonkar V, D’Andrea R, Robinson N. Hypoxia induced ER stress response as an adaptive mechanism in cancer. Int J Mol Sci. 2019;20:749.

38. Koh CP, Wang CQ, Ng CE, et al. RUNX1 meets MLL: epigenetic regulation of hematopoiesis by two leukemia genes. Leukemia. 2013;27:1793–1802.

39. Morgan D, Garg M, Tergaonkar V, Tan SY, Sethi G. Pharmacological significance of the non-canonical NFκB pathway in tumorigenesis. Biochim. Biophys. Acta, Rev. Cancer. 2020;1874(2):188449. http://dx.doi.org/10.1016/j.bbcan.2020.188449

40. Xu X, Li Y, Bharath SR, et al. Structural basis for reactivating the mutant TERT promoter by cooperative binding of p52 and ETS1. Nat Commun. 2018;9:3183.

41. Khatarr E, Maung KZY, Chew CL, et al. Rap1 regulates hematopoietic stem cell survival and affects oncogenesis and response to chemotherapy. Nat Commun. 2019;10:5349.

42. Li F, Shanmugam MK, Chen L, et al. Garcinol, a polyspreneylated benzophenone modulates multiple proinflammatory signaling cascades leading to the suppression of growth and survival of head and neck carcinoma. Cancer Prev Res. 2013;6:843–854.

43. Kilinc E, Baranoğlu Y. Mast cell stabilizers as a supportive therapy can contribute to alleviate fatal inflammatory responses and severity of pulmonary complications in COVID-19 infection. Anatol Clin J Med Sci. 2020;25:111–118.

44. Kritas SK, Ronconi G, Caraffa A, Gallenga CE, Ross R, Conti P. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. J. Biol. Regul. Homeost Agents. 2020;34:9–14.

45. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors. 2020;1289. http://dx.doi.org/10.1002/biof.1633

46. Theoharides T. Potential association of mast cells with coronavirus disease 2019. Ann Allergy Asthma Immunol. 2021;128(3):279–2797.

47. Conti P, Caraffa A, Tetè G, et al. Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels
causing cytokine storm and inflammatory reaction in COVID-19. J. Biol. Regul. Homeost Agents. 2020;34:1629–1632.

48. Theoharides T, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation: or should it be mast cell mediator disorders? Expert Rev. Clin Immunol. 2019;15:639–656.

49. González-de-Olano D, Álvaro-Twose I. Mast cells as key players in allergy and inflammation西班牙语，中英文，朝语，法语，等。mastocytosis (REMA). J Invest Allergol Clin Immunol. 2018;28:365–378.

50. Taracanova A, Alevizos I, Karagkouni A, et al. SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. Proc Natl Acad Sci U S A. 2017;114:E4002–E4009.

51. Rivellese F, Rossi FW, Galdiero MR, Pitzalis C, de Paulis A. Mast cells in early rheumatoid arthritis. Int J Mol Med. 2019;20:1–13.

52. Ragipoglu D, Dudeck A, Haffner-Luntzer M, et al. The role of mast cells in bone metabolism and bone disorders. Front Immunol. 2020;11:163.

53. Komi DEA, Redegeld FA. Role of mast cells in shaping the tumor microenvironment. Clin Rev Allerg Immunol. 2020;58(3):313–325. http://dx.doi.org/10.1007/s12016-019-08753-w

54. Varricchi G, Marone G. Mast cells: fascinating but still elusive players in allergy and inflammation Spanish network on mast cell mediator disorders? Expert Rev. Clin Immunol. 2019;15:639–656.

55. Crowle PK. Mucosal mast cell reconstitution and neurotrauma. Biofactors. 2021;47:190–213.

56. Forsythe P. Mast cells in neuroimmune interactions. Trends Immunol. 2020;31:464–470.

57. Merarchi M, Dudha N, Das B, Garg M. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. Phytother Res. 2021. http://dx.doi.org/10.1002/ptr.7151

58. Yuan S, Yin X, Meng X, et al. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature. 2021;593:418–423.

59. Zeyaullah M, AlShahrani A, Muzammil K, et al. COVID-19 and SARS-CoV-2 variants: current challenges and health concern. Front Genet. 2021;12:693916.

60. Andersson CK, Andersson-Sjöland A, Mori M, et al. Activated MCTC mast cells infiltrate diseased lung areas in cystic fibrosis and idiopathic pulmonary fibrosis. Respir Res. 2011;12:139–139.

61. Wang Y, Zhang D, Du G, et al. Complex level (NK) and NKT-cell recruitment and viral clearance. Proc Natl Acad Sci U S A. 2011;108:9190–9195.

62. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–1581.

63. Merarchi M, Dudha N, Das B, Garg M. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. Phytother Res. 2021. http://dx.doi.org/10.1002/ptr.7151

64. Zhou Z, Ren L, Zhang L, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe. 2020;27:883–890.e2.

65. Gehremeskel S, Schanin J, Coyle KM, et al. Mast cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-siglec-8 antibody. Front Immunol. 2021;12:1–12.

66. Brown MG, McAlpine SM, Huang YY, et al. RNA sensors enable human mast cell anti-viral chemokine production and IFN-mediated protection in response to antibody-enhanced dengue virus infection. PLoS One. 2012;7:e34055.

67. Strohbehn GW, Heiss BL, Rouhani SJ, et al. COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of noncritical COVID-19 pneumonia. Clin Pharmacol Ther. 2021;109:688–696.

68. St. John AL, Rathore APS, Yap H, et al. Immune surveillance by mast cells during dengue infection promotes natural killer (NK) and NKT-cell recruitment and viral clearance. Proc Natl Acad Sci U S A. 2011;108:9190–9195.

69. Soria-Castro R, Meneses-Preza YG, Rodríguez-López GM, et al. Severe COVID-19 is marked by dysregulated serum levels of carboxypeptidase A3 and serotonin. J Leukocyte Biol. 2021;110(3):425–431. http://dx.doi.org/10.1002/jlb.4hi0221-087r

70. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–1581.

71. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75:1564–1581.

72. Merarchi M, Dudha N, Das B, Garg M. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. Phytother Res. 2021. http://dx.doi.org/10.1002/ptr.7151

73. Yuan S, Yin X, Meng X, et al. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature. 2021;593:418–423.

74. Zeyaullah M, AlShahrani A, Muzammil K, et al. COVID-19 and SARS-CoV-2 variants: current challenges and health concern. Front Genet. 2021;12:693916.

75. Andersson CK, Andersson-Sjöland A, Mori M, et al. Activated MCTC mast cells infiltrate diseased lung areas in cystic fibrosis and idiopathic pulmonary fibrosis. Respir Res. 2011;12:139–139.

76. Wang Y, Zhang D, Du G, et al. Complex level (NK) and NKT-cell recruitment and viral clearance. Proc Natl Acad Sci U S A. 2011;108:9190–9195.

77. Motta Junior JS, Miggiolaro AFRDS, Nagashima S, et al. Mast cells in alveolar septa of COVID-19 patients: a pathogenic pathway that may link interstitial edema to immunothrombosis. Front Immunol. 2020;11:574862.

78. Zhou Z, Ren L, Zhang L, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe. 2020;27:883–890.e2.

79. Gehremeskel S, Schanin J, Coyle KM, et al. Mast cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-siglec-8 antibody. Front Immunol. 2021;12:1–12.

80. Tan J, Anderson DE, Rathore AP, et al. Signatures of mast cell activation: or should it be mast cell mediator disorders? Expert Rev. Clin Immunol. 2019;15:639–656.

81. Witczak P, Brzeziński A, Szwarc-Dobrzańska E. Mast cells in viral infection. Postepy Hig Med Dosw. 2012;66:231–241.

82. Tsutsui-Takeuchi M, Ushio H, Fukuda M, et al. Roles of retinoic acid-inducible gene-I-like receptors (RLRs), toll-like receptor (TLR) 3 and TLR5 oligoadenylate synthetase as viral recognition receptors on human mast cells in response to viral infection. Immunol Res. 2015;61:240–249.
84. Oki S, Miyake S. Invariant natural killer T (iNKT) cells in asthma: a novel insight into the pathogenesis of asthma and the therapeutic implication of glycolipid ligands for allergic diseases. Allergol Int. 2007;56:7–14.

85. Shokri S, Mahmoudvand S, Taherkhani R, Farshadpour F. Modulation of the immune response by Middle East respiratory syndrome coronavirus. J Cell Physiol. 2019;234:2143–2151.

86. Wong AHH, Shin EM, Tergaonkar V, Chng WJ. Targeting NF-κB signaling for multiple myeloma. Cancer. 2020;121:1–20.

87. Trouillet-Assant S, Viel S, Gaymard A, et al. Type I IFN immunoprofiling in COVID-19 patients. J. Allergy Clin. Immunol. 2020;146:206–208.e2.

88. Stelekati E, Bahri R, D’Orlando O, et al. Mast cell-mediated antigen presentation regulates CD8+ T cell effector functions. Immunity. 2009;31(4):665–676. http://dx.doi.org/10.1016/j.immuni.2009.08.022.

89. Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J. Allergy Clin. Immunol. 2020;146(1):119–127.e4. http://dx.doi.org/10.1016/j.jaci.2020.04.027.

90. Witzczak P, Brzezińska-Blaszczyk E, Agier J. The response of tissue mast cells to TLR3 ligand poly(I:C) treatment. J Immunol Res. 2020;2020:2140694.

91. Theoharides TC, Conti P. Be aware of SARS-CoV-2 spike protein: there is more than meets the eye. J. Biol. Regul Homeost Agents. 2021;35:833–838.

92. Kazama I. Stabilizing mast cells by commonly used drugs: a novel therapeutic target to relieve post-COVID syndrome? Drug Discov Ther. 2020;14:259–261.

93. Theoharides TC, Cholevas C, Polyzoïdis K, Politis A. Long-COVID syndrome-associated brain fog and chemofog: luteolin to the rescue. Biofactors. 2021;47:232–241.

94. Garbozenko E, Puxeddu I, Levi-Schaffer F, Berkman N, Kramer M, Nagler A. Mast cells induce activation of human lung fibroblasts in vitro. Exp Lung Res. 2004;30:705–721.

95. Battle M, Pérez-Villa F, Lázaro A, et al. Correlation between mast cell density and myocardial fibrosis in congestive heart failure patients. Transplant Proc. 2007;39:2347–2349.

96. Hirata K, Sugama Y, Ikura Y, et al. Enhanced mast cell chymase expression in human idiopathic interstitial pneumonitis. Int J Mol Med. 2007;19:565–570.

97. Demopoulos C, Antonopoulou S, Theoharides TC. COVID-19, microthromboses, inflammation, and platelet activating factor. Biofactors. 2020;46:927–933.

98. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. Immunity. 2020;52:910–933.

99. Yankova R, Abadjieva T, Belovezh dov. Cutaneous mastocytosis with persistent blistering: successful treatment with methylprednisolone. J. Allergy Clin. Immunol. 2020;146:213–214.

100. Pontali E, Volpi S, Antonucci G, et al. Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease. J Allergy Clin Immunol. 2020;146:213–215.

101. Ku A, Jou AL, Yeh F, et al. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol. 2020;146:325–327.

102. Theoharides TC. Substance P and IL-33 administered together: there is more than meets the eye. J. Biol. Regul Homeost Agents. 2021;117:202005615.
antibody- and T cell-mediated autoimmunity. Immunity. 2011;35:832–844.

121. Mancardi DA, Jönsson F, Iannascoli B, et al. Cutting edge: the murine high-affinity IgG receptor FcγRIV is sufficient for autoantibody-induced arthritis. J Immunol. 2011;186:1899–1903.

122. Grimbaldeston MA, Chen CC, Piliponsky AM, Tsai M, Tam SY, Galli SJ. Mast cell-deficient W-sash c-kit mutant kitW-sh/W-sh mice as a model for investigating mast cell biology in vivo. Am J Pathol. 2005;167(3):835–848. http://dx.doi.org/10.1016/s0002-9440(10)62055-x

123. Mukai K, Karasuyama H, Kabashima K, Kubo M, Galli SJ. Differences in the importance of mast cells, basophils, IgE, and IgG versus that of CD4+ T cells and ILC2 cells in primary and secondary immunity to Strongyloides venezuelensis. Infect Immun. 2017;85:e00053–e00017.

124. Piliponsky AM, Chen CC, Grimbaldeston MA, et al. Mast cell-derived TNF can exacerbate mortality during severe bacterial infections in C57BL/6-KitW-sh/W-sh mice. Am J Pathol. 2010;176:926–938.

125. Dudeck A, Dudeck J, Scholten J, et al. Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. Immunity. 2011;34:973–984.

126. Förster A, Blissenbach B, Machova A, et al. Dicer is indispensable for the development of murine mast cells: to the editor. J. Allergy Clin. Immunol. 2015;135:1077–1080.e4.

127. Reitz M, Brunn ML, Rodewald HR, et al. Mucosal mast cells are indispensable for the timely termination of Strongyloides ratti infection. Mucosal Immunol. 2017;10:481–492.

128. Lilla JN, Chen CG, Mukai K, et al. Reduced mast cell and basophil numbers and function in Cpa3-Cre; Mcl-1 fl/fl mice. Blood. 2011;118(26):6930–6938. http://dx.doi.org/10.1182/blood-2011-03-343962

129. Bryce PJ, Falahati R, Kenney LL, et al. Humanized mouse model of mast cell-mediated passive cutaneous anaphylaxis and passive systemic anaphylaxis. J Allergy Clin Immunol. 2016;138:769–779.

130. Mencarelli A, Gunawan M, Yong KSM, et al. A humanized mouse model to study mast cells mediated cutaneous adverse drug reactions. J Leukoc Biol. 2020;107:797–807.

131. Burton OT, Stranks AJ, Tamayo JM, Koleoglou KJ, Schwartz LB, Oettgen HC. A humanized mouse model of anaphylactic peanut allergy. J. Allergy Clin. Immunol. 2017;139:314–322.e9.

132. Cildir G, Yip KH, Pant H, Tergaonkar V, Lopez AF, Tunes DJ. Understanding mast cell heterogeneity at single cell resolution. Trends Immunol. 2021;42:523–535.

133. Cildir G, Toubia J, Yip KH, et al. Genome-wide analyses of chromatin state in human mast cells reveal molecular drivers and mediators of allergic and inflammatory diseases. Immunity. 2019;51:949–965.e6.

134. Shubin NJ, Glukhova VA, Clauson M, et al. Proteome analysis of mast cell releasates reveals a role for chymase in the regulation of coagulation factor XIIIa levels via proteolytic degradation. J Allergy Clin Immunol. 2017;139:323–334.

135. Plum T, Wang X, Rettel M, Krijgsveld J, Feyerabend TB, Rodewald HS. Human mast cell proteome reveals unique lineage, putative functions, and structural basis for cell ablation. Immunity. 2020;52:404–416.e5.

136. Shin EM, Huynh VT, Neja SA, et al. GREB1: an evolutionarily conserved protein with a glycosyltransferase domain links ERα glycosylation and stability to cancer. Sci. Adv. 2021;7:eabe2470.

137. Shimazaki Y, Kono N, Taketomi Y, et al. Omega-3 fatty acid epoxides are autocrine mediators that control the magnitude of IgE-mediated mast cell activation. Nat. Med. (N. Y., NY, U. S.). 2017;23:1287–1297.

How to cite this article: Lam HY, Tergaonkar V, Kumar AP, Ahn KS. Mast cells: Therapeutic targets for COVID-19 and beyond. IUBMB Life. 2021;73:1278–92. https://doi.org/10.1002/iub.2552