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Novel Strategies to Target Mast Cells in Disease

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Abstract
Mast cells (MCs) are versatile effector cells of the immune system, characterized by a large content of secretory granules containing a variety of inflammatory mediators. They are implicated in the host protection toward various external insults, but are mostly well known for their detrimental impact on a variety of pathological conditions, including allergic disorders such as asthma and a range of additional disease settings. Based on this, there is currently a large demand for therapeutic regimens that can dampen the detrimental impact of MCs in these respective pathological conditions. This can be accomplished by several strategies, including targeting of individual mediators released by MCs, blockade of receptors for MC-released compounds, inhibition of MC activation, limiting mast cell growth or by inducing mast cell apoptosis. Here, we review the currently available and emerging regimens to interfere with harmful mast cell activities in asthma and other pathological settings and discuss the advantages and limitations of such strategies.

Introduction

Mast cells (MCs) are multifaceted effector cells of the immune system [1–5]. They are widely distributed in the body but are particularly abundant in tissues that are portals of entry for external insults. MCs are equipped with a broad range of sensors that enable the recognition of various stimuli, and they respond to such stimuli by releasing a panel of inflammatory compounds. This enables MCs to play a key role in orchestrating inflammation, which can be utilized in the host defence against infectious agents [6–9]. On the other hand, dysregulated MC activation can contribute to the pathogenesis of allergic conditions, including asthma and atopic dermatitis, and also to other pathological settings such as cutaneous mastocytosis, fibrosis, cancer, and psoriasis [2–4, 10–12]. Thus, strategies that target MCs can potentially be adopted for treatment of such diseases. Here, we briefly describe the basic properties of MCs, with a particular emphasis on their role in asthma and then discuss available MC-directed therapies for treatment of asthma and other pathological conditions.

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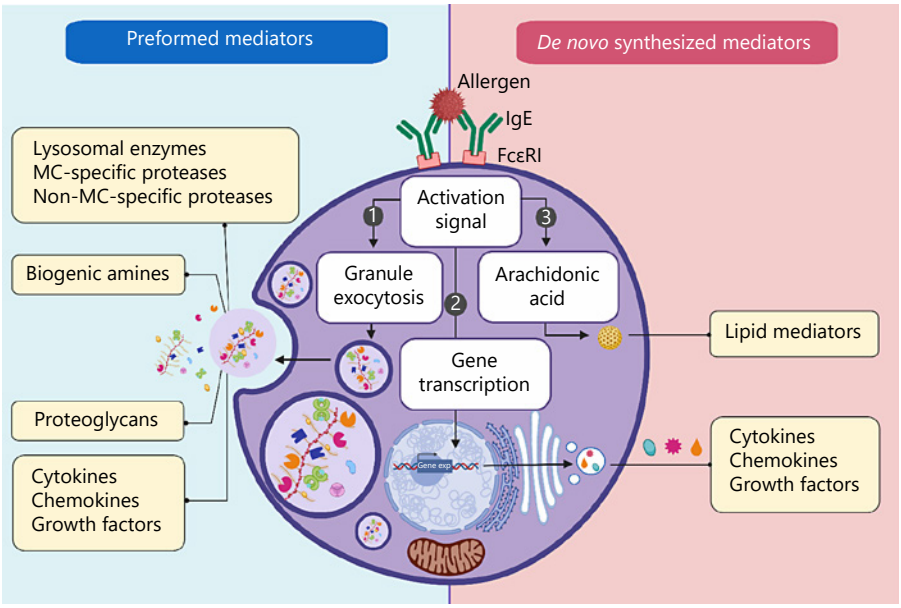

Fig. 1. MC activation and mediator release. MCs become activated when IgE molecules bound to surface FcεRI are cross-linked by antigens (e.g., allergen). Such activating signals lead to the release of preformed mediators through degranulation as well as de novo production and release of several other mediators. MC, mast cell.

Table 1. Examples of MC-derived mediators

Mediator class	Mediators
Preformed (immediate release)	
Lysosomal enzymes	Cathepsins (B, C, D, E, L) and β-hexosaminidase
Non-MC-specific proteases	Cathepsin G, Granzyme B,[1] and Active caspase-3
MC-specific proteases	Tryptases,[1] chymases,[1] and CPA3[1]
Proteoglycans	Serglycin (heparin and chondroitin sulphate)
Biogenic amines	Histamine[1] and serotonin[1]
Cytokines and chemokines	TNF, IL-4, CCL5, and CXCL8
Growth factors	SCF, VEGF, FGF, NGF, and TGF-β
De novo synthesized (delayed release)	
Lipid mediators	PGD2, PGE2, LTB4, LTC4, and PAF
Cytokines	TNF, IFNγ, IL-1, -2, -3, -4, -5, -6, -9, -10, -13, and -33
Chemokines	CCL1, 2, 3, 4, 5, 7, 11, 17, 20, and 22; CXCL2, 8, and 10
Growth factors	SCF, VEGF, FGF, NGF, TGF-β, PDGF, and GM-CSF

CPA3, carboxypeptidase A3; FGF, fibroblast growth factor; LTC4, leukotriene C4; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; LT, leukotriene; MC, mast cell; NGF, nerve growth factor; PAF, platelet activating factor; PDGF, platelet-derived growth factor; PG, prostaglandin; SCF, stem cell factor; TGF-β, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. [1] Examples of mediators that are dependent on serglycin for their storage. Data retrieved from [16, 19, 20].

MCs: General Properties and Role in Asthma

MCs are long-lived tissue-resident cells that originate from hematopoietic pluripotent progenitors in the bone marrow [13–17], but can also be derived from the yolk sac [18]. As MCs mature, they acquire an abundance of secretory granules [19]. The secretory granules are densely packed with large quantities of various preformed mediators, including biogenic amines, MC-specific proteases, lysosomal enzymes, certain cytokines, chemokines, growth factors, and serglycin proteoglycans [16, 19]. These preformed mediators are released into the extracel-

Table 2. Activating and inhibitory receptors expressed by MCs.

Ligands	Activating receptors	Ref.
Microbial products (PAMPs)		
Bacterial lipopeptides, PGN, dsRNA, LPS, flagellin, LTA, ssRNA, CpG-DNA	TLR1–9[m/h] [1] C-type lectin receptors (Dectin-1)[m/h] RIG-like receptors (RIG-I)[m/h]	[186–193]
FimH, *S. aureus*	CD48[m/h]	[194, 195]
Endogenous products (DAMPs or alarmins)		
IL-33, TSLP	IL-33R (ST2)[m/h], TSLPR[m/h]	[196–199]
Products of the innate immune system		
Cytokines and growth factors (GFs)	Cytokine/GF receptors (IL-3R[m/h], c-Kit[m/h])	[200–203]
Chemokines	Chemokine receptors (CCR1[m/h], CCR3[m/h], CCR4[h], CCR5[m/h], CXCR1[h], 2[h], 3[h], 4[h], CX3CR1[m/h])	[204–207]
Complement components	Complement receptors (C3aR[m/h], C5aR[m/h])	[208–210]
Products of the adaptive immune system		
IgE	FcεRI[m/h]	[211]
IgG	FcγRs (FcγRI[h], FcγRIII[m])	[212]
Endogenous and exogenous peptides/compounds		
Endogenous: Neuropeptides (Substance P, VIP) and antimicrobial peptides (β-defensin) *Exogenous*: Insect toxins (mastoparan), compound 48/80, and icatibant	MRGPRX2[h]/MRGPRB2[m]	[213, 214]
Endogenous: Bioactive peptides (Endothelin-1) *Exogenous*: Animal toxins (Sarafotoxin-B)	ET_A[m]	[215]
	Inhibitory receptors	
Products of the adaptive immune system		
IgG	FcγRIIb[m/h]	[212, 216]
Anti-inflammatory/immunomodulatory cytokines		
IL-10, TGF-β	IL-10R[h], TGF-βR[m/h]	[217–219]
Other ligands		
Sialic acid	Siglec-6[h]	[220, 221]
MC-stabilizing drugs (SCG, nedocromil sodium)	GPR35[h]	[117]

DAMP, damage-associated molecular pattern; dsRNA, double-stranded RNA; GPR35, G-protein-coupled receptor 35; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MC, mast cell; MRGPR, MAS-related G protein-coupled receptor; PAMP, pathogen-associated molecular pattern; PGN, peptidoglycan; SCF, stem cell factor; SCG, sodium cromoglycate; Siglec-8, sialic acid binding Ig-like lectin-8; ssRNA, single-stranded RNA; TGF-β, transforming growth factor-β; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin; VIP, vasoactive intestinal polypeptide. Data retrieved from [117, 222–229].
[1] m, expressed in mouse MCs; h, expressed in human MCs.

lular environment when MCs are activated to degranulate, a process that can be accomplished by IgE-mediated and a range of other mechanisms [2]. In addition to the release of preformed granule constituents, MC activation leads to de novo synthesis and release of a diverse array of additional bioactive mediators [16, 19, 20] (Fig. 1; Table 1).

MCs are present in virtually all vascularized tissues but are particularly abundant at junction points of the body and external environment (e.g., skin, gastrointestinal tract, and airways) [1, 16]. Mature MCs can express a large panel of sensory receptors, enabling them to respond to a wide variety of stimuli (Table 2) [2, 6, 16]. These features enable MCs to serve as immune sentinel cells acting in the first-line defence following encounter

with a tissue insult. MCs can also communicate with other immune cells to promote their recruitment to the affected tissues [2, 16]. Altogether, MCs thereby play an important role in initiating inflammation, in modulating both innate and adaptive immune responses, and in tissue repair and homeostatic maintenance [16, 21]. However, if the tissue insult is repeated or persistent, such as in chronic inflammatory conditions, sustained MC activation can have potentially harmful consequences [16, 22, 23]. MCs can thereby play both beneficial and detrimental roles for the organism. Examples of beneficial roles of MCs include their involvement in protection against certain animal venoms [24–26] and various types of infections [6–9, 27, 28]. However, MCs are undoubtedly best known for their detrimental roles in allergies and related diseases, such as asthma, allergic rhinitis, and atopic dermatitis [10, 29]. Moreover, a growing body of evidence is implicating MCs as detrimental players in several other human diseases, including various autoimmune disorders [30, 31], cancers [16, 32], mastocytosis [33, 34], chronic obstructive pulmonary disease [35, 36], and atherosclerosis [16, 37].

The central role of MCs in the pathogenesis of allergic diseases, for example, asthma, is supported by several lines of evidence. For example, asthmatic patients have increased numbers of lung MCs, especially in locations such as the airway smooth muscle layer, lung epithelium, and alveolar parenchyma [38–40]. Moreover, a higher number of MCs has been found in the distal airways of individuals with non-fatal and fatal asthma compared to non-asthmatic controls [41]. Of note, the abnormal accumulation of MCs in these lung compartments has been associated with enhanced asthma symptoms [38, 40, 42, 43]. In line with these observations, an increased percentage of degranulated MCs has been found in the mucous glands in cases of fatal asthma compared to non-fatal asthma and controls [44]. The extensive MC degranulation in fatal asthma suggests that MCs are highly activated in severe asthma [44, 45]. Importantly, a role for MCs in asthma is also supported by a number of studies conducted on mice [46–48]. In mouse models of allergic asthma, elevated numbers of airway MCs are found and MCs have been demonstrated to contribute in a major way to several symptoms associated with experimentally induced allergic airway inflammation, including eosinophilic airway inflammation, enhanced airway hyperresponsiveness (AHR) to methacholine or antigen, goblet cell hyperplasia, and enhanced mucus production [47].

MCs are recognized as effector cells in all phases of asthma, that is, the early, late, and chronic phases [23, 29]. Although MCs are thought to be of particular importance in allergic asthma, they can also have an impact on asthma caused by non-allergic mechanisms such as those seen in non-atopic, occupational, and exercise-induced asthma [23]. In the early phase, MCs release mediators such as histamine, prostaglandin D2 (PGD2), and leukotriene C4 (LTC4), hence contributing to the bronchoconstriction, respiratory mucosal oedema, and mucus secretion [16, 23, 49–56]. The central role of these MC mediators is supported by observations indicating that potent and selective receptor antagonists of histamine [57, 58], LTC4 [59, 60], and to a lesser degree PGD2 [61], can markedly attenuate early-phase asthmatic reactions. In late-phase asthmatic reactions, proinflammatory mediators released by MCs, including cytokines and chemokines, contribute to the recruitment of inflammatory cells such as eosinophils, basophils, $CD4^+$ T cells, and macrophages to the airways, leading to airway obstruction and AHR [23]. Notably, it has been found that anti-IgE therapy markedly attenuates the late-phase asthmatic reactions [62], indicating that MC (and/or basophil) activation during the early phase initiates events leading to the late-phase reactions [23]. Lastly, when allergen exposure is continuous or repetitive, early- and late-phase reactions develop into a chronic phase that is associated with persistent inflammation, tissue remodelling, and fibrosis [29]. In chronic allergic asthma, ongoing MC activation and degranulation is observed [23]. In line with this, increased levels of MC products, such as histamine and tryptase, have been found in bronchoalveolar lavage (BAL) fluid from asthmatics compared to healthy controls [52, 63–66]. Additionally, MCs within the bronchial mucosa of asthmatics produce various cytokines, including IL-4, IL-5, IL-6, IL-13, TNF-α, and TSLP [67–72].

Therapeutic Approaches to Target MCs in Disease

Given the well-recognized harmful role of MCs in allergic and other disorders, there is an urgent need to identify efficient strategies that can limit the detrimental effects of MCs in such settings. Currently, there are several therapeutic approaches available for this purpose. In general, the aims of these approaches are to either (i) inhibit MC-derived mediators or their effects, (ii) inhibit MC activation, or (iii) reduce MC numbers. Below, some of the therapeutic anti-MC options that are currently used in the clinic or are being considered for future use are discussed (Fig. 2).

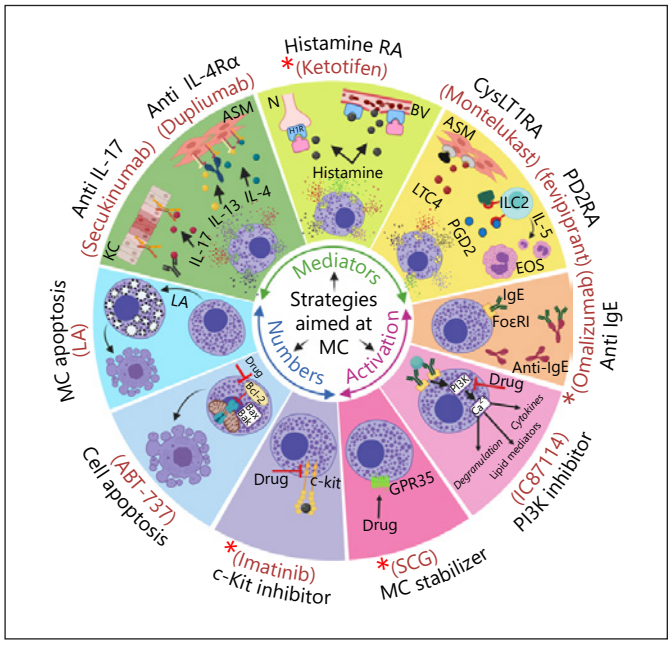

Fig. 2. Overview of therapeutic strategies aiming at the inhibition of mast cell mediators or activation, and reduction of mast cell numbers. ASM, airway smooth muscle; BV, blood vessel; CysLT1RA, cysteinyl leukotriene receptor 1 antagonist; EOS, eosinophils; GPR35, G-protein-coupled receptor 35; H1R, histamine H1 receptor; Histamine RA, histamine receptor antagonist; ILC2, type 2 innate lymphoid cells; KC, keratinocytes; LA, lysosomotropic agent; LTC4, leukotriene C4; MC, mast cell; N, neuron; PD2RA, prostaglandin D2 receptor 2 antagonist; PGD2, prostaglandin D2; PI3K, phosphatidylinositol 3-kinase; SCG, sodium cromoglicate (denotes inhibition). * Denotes regimens that are in current clinical use for intervention with MC-related activities.

Approaches Aimed at Inhibiting MC-Derived Mediators or Their Effects

Given that MCs are capable of releasing a large array of diverse biologically active mediators, one possible therapeutic option is to target individual MC mediators. For example, several MC mediators such as histamine, leukotrienes, prostaglandins, and cytokines are currently targeted effectively by available drugs [4] (Fig. 2). Moreover, multiple MC-specific proteases, for example, chymase and tryptase can be selectively inhibited [73–76]. Targeting any given MC mediator can be achieved either by direct inhibition of the mediator, for example, when the enzymatic activities of MC proteases are blocked by active site-directed inhibitors, or when neutralizing antibodies are used. Alternatively, downstream effects of MC-released compounds can be targeted by employing antagonists of receptors for compounds released by activated MCs.

Drugs that target histamine (e.g., ketotifen), leukotrienes (e.g., montelukast), and PGD2 (e.g., fevipiprant) represent receptor antagonists (Fig. 2), and these drugs are known to reduce symptoms of allergies and related disorders such as asthma in clinical settings [77–80]. Further, MC-produced proinflammatory cytokines and growth factors, such as TNF-α, IL-4, IL-13, IL-17, and VEGF, can be targeted by neutralizing antibodies. Although the latter proinflammatory cytokines/growth factors are not exclusively produced by MCs, MCs are known to be a dominant source of these compounds in several pathological settings [81]. For example, it has been proposed that MCs are the predominant source of IL-17 in patients with inflammatory skin and joint diseases including psoriasis [82], rheumatoid arthritis [83], and spondyloarthritis [84, 85]. Notably, monoclonal antibodies directed to IL-17 (Fig. 2) are currently being evaluated for efficacy in such conditions [86], and it is thus conceivable that anti-IL-17 therapy, at least to some extent, acts at the level of neutralizing IL-17 released from MCs.

Other MC-derived cytokines that constitute therapeutic targets include IL-4 and IL-13. These two cytokines play key roles in promoting several hallmark features of Th2 inflammation, including IgE production, smooth muscle contractility, mucus production, and inflammatory cell recruitment to the inflammation site [87–89]. In asthma patients, MCs were found to produce IL-4 [67], and IL-4 is also found as a preformed meditator stored in MC granules [90]. Furthermore, IL-4- and IL-13-expressing MCs accumulate within the airway smooth muscle layer of asthmatics, suggesting a role for these cytokines in MC:airway smooth muscle interactions [91]. MCs also produce IL-13 in response to various stimuli including IgE/antigen, IL-1β, IL-4, IL-33, LPS, and peptidoglycan [92–97]. Dupilumab is a monoclonal antibody directed against the α subunit of the IL-4 receptor (IL-4Rα) that blocks signal transduction pathways activated by IL-4 and IL-13 (Fig. 2). Of note, dupilumab has shown striking beneficial effects in improving several disease features in patients suffering from MC-associated allergic conditions such as asthma [98, 99] and atopic dermatitis [100–102].

Although targeting of individual MC mediators can have anti-inflammatory effects, the beneficial therapeutic effects of such treatments are often limited [81]. One major reason for this could be that the overall impact of MCs in a pathological setting is most likely a result of combined effects from several MC mediators, rather than due

to a single mediator acting on a single target [4]. Thus, targeting a single MC mediator will only partly interfere with detrimental MC effects. As an example, targeting only IL-13 by lebrikizumab or tralokinumab in asthma has shown a very limited beneficial effect, whereas targeting both IL-4 and IL-13 by dupilumab effectively improved lung function and symptoms [103]. Similarly, therapeutic regimens that include using a combination of leukotrienes and histamine antagonists were found to have greater beneficial effects on improving allergen-induced airway obstruction in asthmatics compared to those achieved by each drug alone [104–106]. Altogether, based on these clinical observations, in order to achieve efficient therapeutic effects, this class of anti-MC drugs (i.e., MC mediator targeting drugs) are required to be used in combination and often recommended as add-on therapy to inhaled corticosteroids [79, 107].

Approaches Aimed at Inhibiting MC Activation

Considering that MCs express a large number of activating and inhibitory receptors (Table 2), one option is to block MC activation by using drugs that interfere with such receptors. One approach to accomplish this is to use monoclonal antibodies to target IgE, thereby blocking the interaction of IgE with its high-affinity receptor (FcεRI) (Fig. 2). One such monoclonal antibody is omalizumab, a humanized IgG1 antibody against IgE. Omalizumab is approved for clinical use and was found to reduce asthma symptoms in adults and children [81, 108, 109]. Moreover, beneficial therapeutic effects of omalizumab have been observed in persistent allergic rhinitis [110], atopic dermatitis [111], urticaria [112, 113], and food allergies [114].

Although anti-IgE therapy represents a successful approach to inhibit MC activation, there are several disadvantages that limit its use. For example, anti-IgE therapy is beneficial in treatment of allergic disorders but has very limited efficacy, if any, in the treatment of non-allergic MC-driven diseases, in which MCs are activated by IgE-independent pathways [4]. Another limitation is its unpredictable efficacy, that is, some asthmatic patients show considerable improvement, whereas most patients experience little or no signs of clinical improvement [115]. Additionally, similar to other treatments that involve the use of humanized monoclonal antibodies, anti-IgE therapy is associated with high economic costs [81].

Another group of compounds that display inhibitory effects on MC activation are the MC stabilizers, which have the ability to inhibit MC degranulation and mediator release in response to various stimuli [116]. Sodium cromoglycate (SCG) and nedocromil sodium are the most common MC stabilizers used for treating asthma and other diseases that involve MC activation, including allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and mastocytosis [31]. Despite being in clinical use for decades, the mechanisms by which these drugs inhibit MC activation and degranulation are still not well-defined [4]. However, it has become more evident during the recent years that the effects of SCG and nedocromil sodium are mediated via GPR35, an inhibitory MC receptor [117] (Fig. 2).

Although MC stabilizers are generally well-tolerated, their inhibitory effects are moderate or negligible [4]. In fact, comparative studies suggest that the beneficial effect of SCG in controlling asthma symptoms is rather small in both children and adults [118, 119]. One possible reason for this could be that MC stabilizers do not inhibit human lung MCs effectively. In support of this notion, SCG has been found to be a weak inhibitor of histamine release from freshly isolated human lung MCs in response to IgE-mediated activation, even when high concentrations of SCG were used [120]. Another disadvantage of the MC stabilizers is that, due to their low potency and short half-life, high concentrations of the drugs need to be given at frequent intervals to have an effective inhibitory impact. Moreover, local administrations are preferred to maximize the concentration of the drug in the target tissue [116].

An alternative approach to inhibit MC activation is to interfere with the intracellular signalling pathways that are essential for MC degranulation and mediator release [4, 81, 121]. This can be achieved, for example, by using pharmacologic inhibitors to block the function of key cytoplasmic signalling proteins such as spleen tyrosine kinase (SYK), phosphatidylinositol 3-kinases, and Bruton's tyrosine kinase. Since these proteins are involved in early signalling events induced by IgE:FcεRI interaction, their inhibition could theoretically result in effective suppression of antigen-induced degranulation and mediator release [4]. In line with this, several inhibitors of the aforementioned signalling proteins exhibited beneficial effects when tested in preclinical in vivo models. For example, IC87114, a selective inhibitor of phosphatidylinositol 3-kinase-δ, was found to have a therapeutic potential for the treatment of allergic asthma and rheumatoid arthritis in the relevant disease models [122, 123] (Fig. 2). Furthermore, a number of different inhibitors are being tested in clinical trials for diseases such as allergic rhinitis, asthma,

urticaria, and rheumatoid arthritis [4, 81]. Although some of these inhibitors have been able to reduce certain disease symptoms in patients during initial phases of clinical trials, so far none of them have been approved for routine treatment of MC-related diseases [4]. For example, the SYK inhibitors, R112 and R343, both failed in clinical phase II studies for treatment of allergic rhinitis or asthma [81]. Another potential strategy for inhibition of MC activation is to target various ion channels involved in the signalling pathways leading to MC activation/degranulation, as exemplified by the Orai channels [124].

One major problem with approaches targeting signalling pathways is that they are not exclusive to MCs. Indeed, the fact that the signalling proteins are widely expressed by many different cell types gives rise to an increased risk of adverse effects when inhibitors of signalling protein are used [4]. Moreover, the majority of inhibitors that are available or being considered for clinical development, are directed against signalling pathways that operate downstream of classical IgE-mediated MC activation [23]. Thus, they predominantly suppress MC activation in allergic settings where MCs are activated by IgE-mediated stimulation, but have limited effectiveness in situations in which MCs are activated through other mechanisms [23].

Approaches Aimed at Reducing MC Numbers

The overall impact of MCs on any pathological setting is most likely multifaceted, that is, mediated by multiple activating mechanisms and a large number of secreted mediators. Thus, targeting individual mediators or single activation pathways in MCs, for example the IgE-mediated pathway, may not be sufficient to prevent the full panel of MC-driven pathological effects. Theoretically, a more effective strategy for global inhibition of harmful MC activities might therefore be to reduce MC numbers, for example, by blocking MC survival or inducing their apoptosis [81, 125, 126]. However, in order to avoid harmful side effects that may arise from off-targeting of other cell populations, it is essential to develop strategies that are selective for MCs. In the following section, the major strategies that can be employed for reducing MC survival or inducing MC apoptosis are discussed.

Strategies to Reduce MC Survival

Mature MCs depend on stem cell factor (SCF) for their survival [16], and targeting of SCF signalling thereby represents an attractive strategy for limiting MC survival. The interaction between SCF and its receptor, c-kit (CD117), which has tyrosine kinase activity [127], induces intracellular signalling that promotes MC differentiation, proliferation, chemotaxis, and maturation [16]. The pivotal role of SCF for MC survival and development is highlighted by the finding that mice deficient in SCF or c-kit essentially lack MCs [14, 128, 129]. Moreover, glucocorticoid-induced reduction of local SCF levels results in decreased numbers of tissue MCs in mice [130], and corticosteroids can also reduce the MC numbers in humans [131, 132]. Additionally, administration of SCF to humans, baboons, cynomolgus monkeys, mice, and rats promotes in vivo expansion of tissue MCs [133–135]. The ability of the SCF:c-kit axis to induce MC survival appears to be mediated, at least partly, through downregulation of pro-apoptotic proteins such as Bim [136].

It is thought that SCF and c-kit contribute to the MC accumulation and survival in MC-driven disorders. For example, in humans, gain-of-function mutations in c-kit lead to mastocytosis, a disorder characterized by an expansion of MC populations, due to constitutive SCF-independent activation of c-kit [137]. Furthermore, in individuals with various allergic diseases including asthma, allergic rhinitis, and atopic dermatitis, an increased production of SCF [138–142] and elevated MC numbers are commonly seen [143]. It is also known that increased SCF levels correlate with disease severity in patients with asthma or atopic dermatitis [139, 142].

Based on these findings, blockade of MC survival and development through inhibition of the SCF:c-kit axis has been considered as a potential treatment option to decrease MC numbers in certain pathological conditions [4] (Fig. 2). Imatinib is an inhibitor that is known to target c-kit and other tyrosine kinases. It was initially developed for targeting BCR-ABL (breakpoint cluster region-Abelson murine leukaemia viral oncogene homologue 1) in patients with chronic myeloid leukaemia but has also been shown to reduce MC numbers in endobronchial biopsy samples and to reduce serum tryptase levels and AHR in patients with severe asthma [144]. Moreover, imatinib is now approved for the treatment of adult patients with aggressive systemic mastocytosis in cases lacking the KitD816V mutation [145]; notably, in a phase IV clinical trial, imatinib caused a reduction of MC numbers in mastocytosis patients that had Kit mutations other than KitD816V [146]. In addition to imatinib, several other tyrosine kinase inhibitors including nilotinib, dasatinib, midostaurin, and masitinib are being evaluated for efficacy in several MC-driven diseases [81]. However,

none of these inhibitors are specific for c-kit, that is, they are capable of inhibiting multiple other tyrosine kinases [81]. Thus, the effects of available tyrosine kinase inhibitors extend far beyond MCs, resulting in a high risk of off-target effects on non-MC populations.

Strategies to Induce MC Apoptosis

Historically, cell death has been classified into two major forms: apoptosis and necrosis [147]. Apoptosis is a highly regulated mode of cell death and plays an essential role in development, morphogenesis, and maintaining homoeostasis through the removal of damaged, aged, and potentially dangerous cells [148]. Apoptosis is initiated by the activation of caspases, leading to cell shrinking, chromatin condensation, DNA fragmentation, plasma membrane blebbing, and formation of apoptotic bodies [149–151]. In contrast, necrosis is a less controlled cell death mode characterized by loss of cell membrane integrity and release of numerous cellular contents, such as danger signals, into the extracellular environment. Therefore, unlike apoptosis, necrosis can potentially induce an inflammatory response [147]. Apoptotic cell death can be induced via two major classical pathways: the intrinsic and extrinsic pathways [151]. The intrinsic pathway is initiated in response to cell stress stimuli such as DNA damage, oxidative stress, growth factor deprivation, and cytotoxic substances through activating pro-apoptotic proteins (e.g., BH3-only proteins) [152–154]. Once activated, these proteins inhibit anti-apoptotic proteins (e.g., Bcl-2 and Bcl-XL) leading to mitochondrial outer membrane permeabilization. This results in release of apoptogenic factors such as cytochrome c and apoptosis-inducing factor that can execute apoptotic cell death through caspase-dependent and/or caspase-independent mechanisms [151, 155]. The extrinsic pathway of apoptosis is triggered when cell surface death receptors bind to their ligands [156]. The death receptors include tumour necrosis factor receptor (TNFR), Fas, and TNF-related apoptosis-inducing ligand receptor (TRAIL-R), which all belong to the TNFR superfamily [157]. Interaction of the death receptors with their cognate ligands, that is, TNF, FasL, and TRAIL, provokes the intracellular assembly of a multiprotein complex known as death-inducing signalling complex and recruitment of adaptor proteins. This, in turn, leads to caspase activation and apoptosis [154, 156].

In addition to these classical pathways for initiating apoptotic cell death, it has been revealed that apoptosis can be caused by lysosome membrane permeabilization, which can occur in response to various triggers, including chemical compounds with lysosome membrane-permeabilizing properties ("lysosomotropic agents"). In this process, lysosomal enzymes such as various cysteine cathepsins escape from the lysosomes to the cytosolic compartment, where they cause apoptosis by proteolytic activation of pro-apoptotic compounds and/or degradation of anti-apoptotic proteins [154, 158–161].

The concept of selectively inducing MC apoptosis as a means to intervene with MC-driven diseases is emerging as an attractive therapeutic approach [125]. To achieve MC apoptosis, one strategy could be to activate pro-apoptotic pathways, for example, by using agonists of surface death receptors (e.g., TRAIL-R). Currently, several TRAIL-R agonists are being tested in preclinical and clinical studies for their therapeutic beneficial effects in different cancers [162]. However, although human MCs express TRAIL-R and were found to undergo apoptosis through engagement by TRAIL [163], the selectivity of TRAIL-mediated apoptosis for MCs is questionable. This is due to the fact TRAIL-R is widely expressed among many human tissues and cell types [162, 164, 165].

Another approach to induce MC apoptosis would be to interfere with the function of anti-apoptotic proteins. In line with this scenario, small molecule compounds known as BH3 mimetics were found to induce apoptosis in MCs through inhibiting the effect of anti-apoptotic proteins such as Bcl-2, Bcl-XL, and Mcl-1 [166–168]. However, due to the ubiquitous expression of these anti-apoptotic proteins, such compounds are not likely to act selectively on MCs. In line with this notion, the BH3 mimetic ABT-737 was shown to induce apoptosis in MCs (Fig. 2) but also in a variety of other cell types, including B lymphocytes, neuronal cells, and transformed cells of various origin [166, 169, 170]. Due to differences in their chemical structures and properties, various BH3 mimetic compounds can target individual anti-apoptotic proteins [168]. On the other hand, different MC types were found to express distinct levels of individual anti-apoptotic proteins, which results in differential sensitivities toward a certain BH3 mimetic compound [166]. For example, MCs with lower expression of Mcl-1 and higher expression of Bcl-2 are more sensitive to apoptosis induced by ABT-737, whereas MCs with an opposite expression profile of Mcl-1 and Bcl-2 were more resistant [166]. These findings suggest that in order to execute efficient MC apoptosis by BH3 mimetic compounds, a combination of several different compounds is likely required. This, in turn, increases the risk of causing apoptosis in cell types other than MCs, potentially resulting in adverse side effects.

Induction of MC Death by Granule Permeabilization

Given that most pro-apoptotic pathways are ubiquitously present among different cell types, it has been challenging to identify a cell death pathway that is selective to MCs. If a pro-apoptotic strategy is to be selective for MCs, it must be established based on their unique properties. This could potentially be accomplished by targeting MC-specific cell surface receptors, a strategy that was recently utilized by inducing MC death via the MRGPRX2 receptor [171]. Targeting MCs via c-kit (receptor for SCF) could also be an option (see "*Strategies to reduce MC survival*"). Another unique feature of MCs is their abundant cytoplasmic secretory granules. The granules contain exceptionally large amounts of various bioactive compounds, including proteases [19, 75, 76]. Conceptually, the escape of such proteases into the cytosolic compartment could cause apoptosis by proteolytic activation of pro-apoptotic compounds and/or degradation of anti-apoptotic proteins.

Interestingly, MC granules have striking similarities with lysosomes and are therefore also denoted "secretory lysosomes" [172]. For example, both compartments have an acidic pH, similar membrane composition and contain typical lysosomal enzymes such as cysteine- and aspartic acid cathepsins, arylsulfatase A, β-glucuronidase, and β-hexosaminidase [19, 172, 173]. Based on such similarities, it is reasonable to assume that compounds capable of inducing lysosome permeabilization, that is, "lysosomotropic agents" (see under "*Strategies to induce MC apoptosis*"), also cause granule permeabilization in MCs. This would cause the release of potent granule enzymes, for example, proteases, into the cytosol where they potentially may induce apoptosis. Moreover, since MCs have a much higher content of protease-rich granules than any other cell type in the body, it is conceivable that strategies to induce apoptosis through granule permeabilization could be selectively cytotoxic for MCs. In support of this notion, it was shown that the prototype lysosomotropic agent L-leucyl-L-leucine methyl ester (LLME) induces apoptosis in murine cultured MCs by causing permeabilization of the granule membrane (Fig. 2) [174]. Moreover, it was demonstrated that LLME showed selectivity for MCs versus several other cell types [175, 176].

Interestingly, mouse MCs lacking serglycin were considerably less sensitive to LLME than were wild-type (WT) cells [174]. Since serglycin is restricted to the secretory granules of MCs [177], this finding thus provides strong support for an involvement of the secretory granules in the cell death responses towards LLME. It was also noted that the type of cell death differed dramatically in WT versus serglycin$^{-/-}$ MCs, with WT cells undergoing apoptosis whereas the serglycin$^{-/-}$ cells died preferentially by necrosis [178]. Since serglycin acts as a scaffold for the storage of several potent proteases [177], a likely explanation for these findings might be that the apoptosis-promoting effect of serglycin is due to downstream effects of any of the proteases that are dependent on serglycin for storage, rather than through direct apoptosis-promoting functions of serglycin. Indeed, it was shown that the absence of Mcpt6 (a serglycin-dependent protease [177]) phenocopied the effects of serglycin-deficiency in terms of effects on apoptosis/necrosis [178].

These findings suggest that MCs are highly sensitive to cell death induced by granule permeabilization caused by lysosomotropic agents, introducing the possibility of evaluating lysosomotropic agents as potential therapeutics to selectively deplete harmful MC populations. However, LLME is not approved for usage in vivo in humans, and it has therefore been important to identify lysosomotropic agents that are more readily adaptable for clinical purposes. One such candidate is siramesine. Siramesine was originally developed as a sigma-2 agonist for treatment of anxiety [179]. It was reported to be safe for use in humans but was inefficient for the intended purpose. On the other hand, it was later shown that it possessed lysosomotropic activity on certain cancer cell types [180], and it was therefore reasoned that it could have the ability to induce secretory granule permeabilization and cell death also in MCs. Indeed, it was shown that siramesine potently induced apoptotic cell death in MCs [181]. Moreover, it was shown that siramesine selectively depleted MC populations, both in vivo in mouse models and in human ex vivo settings [176, 181, 182].

In further attempts to identify lysosomotropic agents with optimal cytotoxic effects on MCs, it was shown that mefloquine, an approved anti-malaria drug, was strongly cytotoxic for both mouse and human MCs, causing apoptotic cell death [183]. As for LLME and siramesine, mefloquine was shown to cause membrane permeabilization in various types of MCs, leading to apoptotic cell death. Further, it was shown that mefloquine-induced cell death was dependent on ROS [183]. It was also demonstrated that mefloquine, similar to siramesine, shows selective cytotoxic effects on MCs [183, 184]. In attempts to further clarify the mechanism by which mefloquine induces MC death, it was revealed that the ROS production in response to mefloquine occurs in the secretory granules, and that the ROS production was dependent on iron bound to serglycin present in granules. ROS production was also partially dependent on granzyme B, and it was

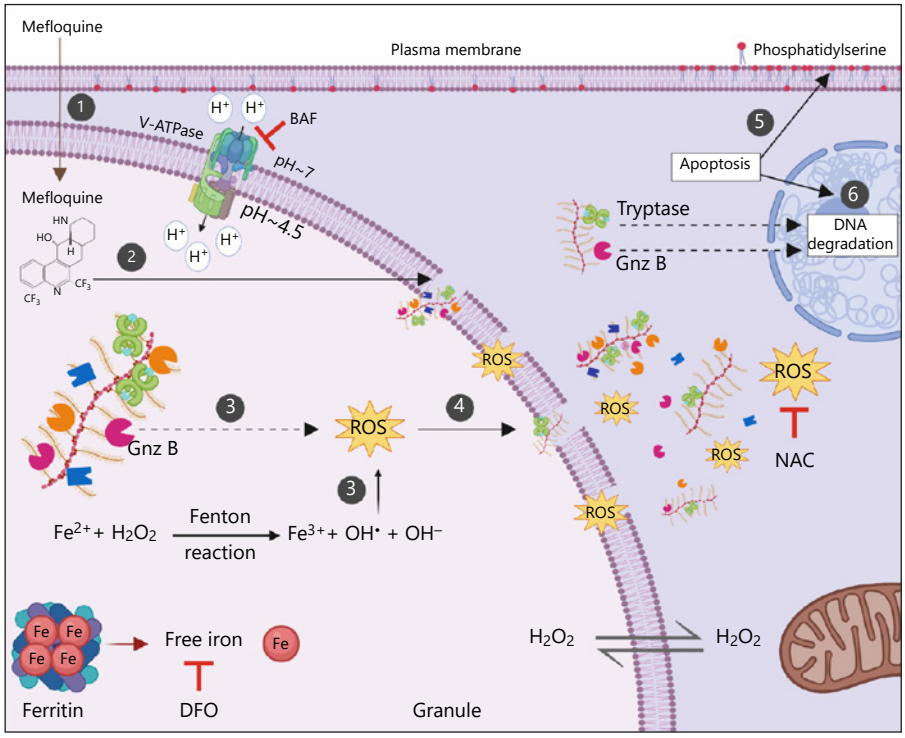

Fig. 3. Suggested mechanism by which lysosomotropic agents (here exemplified by mefloquine) induce granule membrane permeabilization and apoptosis in MCs. (1) Accumulation of mefloquine inside the granules. Mefloquine, a weakly basic compound, can in its unprotonated form passively diffuse through the MC plasma and granule membranes. In the acidic interior of granules, mefloquine becomes protonated and can no longer pass through the membrane, thus accumulating inside the granules. (2) Granule membrane permeabilization. When the mefloquine concentration reaches a certain threshold, mefloquine acquires detergent-like properties and induces granule membrane damage and permeabilization. (3) Induction of oxidative stress within granules. Hydrogen peroxide (H_2O_2) freely diffuses into the granules. In the granules, the acidic pH and the presence of free iron promote the oxidation of iron and the generation of ROS such as hydroxyl radicals ($HO^{\bullet}$) via Fenton-type reactions. The electrostatic interaction between negatively charged serglycin and cationic iron likely participates in maintaining the iron pool within MC granules, thus contributing to the generation of ROS. The generated ROS cause further destabilization of granule membranes leading to the release of many granule components into the cytosol. Granzyme B also participates in induction of ROS production upon exposure to mefloquine. (4) Release of granule contents into the cytosol. Due to the granule permeabilization, granule contents (e.g., fully active proteases in complex with serglycin, ROS and iron) enter the cytosol. (5, 6) Induction of apoptosis. Mefloquine-induced granule permeabilization and the subsequent translocation of the granule contents to the cytosol induce apoptosis manifested by phosphatidylserine externalization and DNA degradation. The MC proteases, such as tryptase and granzyme B, may participate in apoptosis in response to mefloquine. BAF, bafilomycin-A1; DFO, deferoxamine mesylate; Gnz B, granzyme B; NAC, *N*-acetylcysteine; ROS, reactive oxygen species.

shown that the cytotoxic effects of mefloquine on MCs were strictly dependent on an acidic pH in the granules [185]. A proposed model for how lysosomotropic agents can promote MC apoptosis is depicted in Figure 3. Importantly, since mefloquine is an approved drug for usage in humans, it may be relatively feasible to adapt it for clinical purposes under circumstances where selective depletion of MCs may have a therapeutic potential.

Concluding Remarks and Future Perspectives

The current consensus is that MCs contribute importantly to the manifestations of many debilitating human diseases including asthma, and there is therefore a current demand for strategies to block or dampen their harmful effects. As described here, multiple regimes to accomplish this have been developed or are under development, and many such strategies are currently being exploited in the clinic. However, it is important to empha-

size that MCs from different species and from different tissues show considerable heterogeneity in terms of gene expression profile, granular content and morphological criteria. Thereby, an important consideration is that MCs of different phenotype can be differently sensitive to individual treatment options. This issue certainly warrants further investigations to firmly establish the applicability of the various available anti-MC therapies. Another general consideration is that most of the currently available strategies to limit MC activities are not MC-selective. For example, the pathogenic cytokines secreted by MCs are also expressed by multiple other cell types, and their targeting will thus not selectively interfere with MC-dependent effects of the corresponding cytokines/chemokines. Further, compounds known as "MC stabilizers" show only moderate selectivity for MCs, and anti-IgE therapy will target, not only MCs, but also other cells expressing FcεRI (e.g., basophils). Hence, effects seen for such therapeutic regimens may not be exclusively due to effects on the MC niche, which may affect the interpretation of the data as to whether MCs play a prominent role in the respective condition. In other strategies, MCs are targeted with a higher extent of selectivity, as exemplified by strategies targeting MC-restricted mediators such as chymase and tryptase. In addition, an emerging concept is to selectively induce MC apoptosis, at least locally. As described herein, there are multiple emerging strategies for the latter purpose, although these efforts are still at the pre-clinical stage. We foresee that such strategies will be developed in the future, and will aid in our attempts to therapeutically intervene with the detrimental impact of MCs in human diseases.

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Conflict of Interest Statement

The authors report no conflict of interest in relation to this work.

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Author Contributions

A.P. and G.P. conceived of this article; A.P. prepared the illustrations; A.P. drafted the manuscript; G.P. contributed to the writing of the article.

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