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Novel Insights into Mast Cell Biology
Review

Mast Cells as Drivers of Disease and Therapeutic Targets

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Mast cells (MCs) contribute to the pathogenesis of a multitude of diseases that include MC-driven disorders such as urticaria, type I allergies, and mastocytosis as well as autoimmune and other inflammatory disorders and malignant tumors. Here, we review and discuss the results of studies that identified and characterized how MCs contribute to disease and, importantly, what strategies may be used to target MCs and MC effects therapeutically. Specifically, we discuss the most common approaches for investigating the role and relevance of MCs in various diseases. We also review current therapeutic approaches aimed at modulating MC numbers, inhibiting MCs and/or preventing MC activation, modulating MC signal transduction and protection from the effects of MC mediators.

MCs as Local Sentinels

MCs are derived from committed hematopoietic lineage cells in the bone marrow. These $CD34^+$ progenitor cells circulate in the blood and migrate into peripheral tissues, where they further differentiate into mature MCs under the influence of various tissue-specific factors such as extracellular matrix proteins, adhesion molecules, cytokines, and chemokines. MCs can be found in virtually all tissues including the brain. Their numbers are especially high in the skin and mucosal tissues, interfaces with the outside environment. MCs express a substantial number of activating and inhibitory receptors, which both eventually fine tune the level of mast cell activation [1,2]. The most well-known pathway of activation involves IgE/FcεRI signaling, but MCs can also be triggered via Toll-like receptors (TLRs), complement, neuropeptides, cytokines, and many other stimuli [3]. Upon activation, MCs can rapidly release their preformed granule-stored mediators such as histamine, serotonin, tumor necrosis factor (TNF)-α, proteoglycans and various proteases, and can also release *de novo* synthesized lipid mediators, cytokines, and chemokines. Many of these mediators attract or activate other immune, endothelial, epithelial, neuronal, and stromal cells, highlighting the important role of MCs in the network of cells involved in innate and adaptive immune responses. Of note, the strategic localization of MCs in close proximity to blood vessels, neurons, and lymphatic vessels gives them the ability to relay local inflammatory signals to distant target cells and tissues.

Studying the Roles of MCs

How We Can Learn from Mice about the Roles of MCs in Health and Disease

To study the role of MCs in the pathogenesis of diseases, MC-deficient mouse strains have been used. The majority of these studies used mice with a mutation in *KIT*, e.g. $KIT^{W}KIT^{W}/^{W-v}$ or $KIT^{W}KIT^{W-sh}/^{W-sh}$ mice, which blocks the development of MCs in all tissues. The lack of MCs in these mice can be restored by the injection of bone marrow cells or bone marrow-cultured MCs from normal littermates. Most tissues can be replenished with MCs in these so called MC knock-in animals [4], but their tissue MC numbers may differ from normal animals,

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MCs are strategically localized in close proximity to blood vessels, neurons, and lymphatic vessels, which gives them the ability to relay local inflammatory signals to distant target cells and tissues.

Beside activation via IgE, MCs can be triggered by many other stimuli including TLR ligands, complement, and neuropeptides.

MC numbers at sites of inflammation are frequently increased and this could be a driving mechanism, a bystander effect or a compensatory mechanism as an attempt by the host to control and terminate disease.

The development of more effective and specific MC-altering drugs is urgently required, and existing treatment strategies should be reinvestigated to determine their potential effects on MCs.

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and some organs (e.g., brain) can be difficult to reconstitute [5]. The use of these models has confirmed the crucial role of MCs in allergic diseases, and suggests their involvement in a plethora of other immune responses such as: tolerance induction after implanting tissue grafts [6,7]; protection against bacterial and viral infections [8,9]; protection against bee and snake venom [10–13]; promotion or reduction of tumor growth and development; and development of vascular, autoimmune, metabolic, and neurological diseases. In recent years, KIT-independent MC-deficient mouse models, for example, Cpa3Cre, Cre-Master, and Mcpt5-Cre mice have been developed. The use of these mice, as compared to KIT-dependent MC-deficient mice, has led to similar results in some disease models and different results in others [14]. For instance, studies in Mcpt5-Cre mice showed that MCs are key promoters of contact allergy responses, while in the same study KIT-dependent MC-deficient mice showed an enhanced late phase contact hypersensitivity response [15]. In $KIT^{W}/^{W-v}$ or $KIT^{W-sh}/^{W-}$sh mice [16–18] and KIT-independent Mas-Treck and Mcpt5-Cre mice [18,19], MCs were shown to enhance inflammation. However, in fibroblast growth factor receptor 1-deficient mice crossed with Cre-Master MC-deficient mice, no or only a minor role for MCs was observed in chronic inflammation [20]. The reasons for this dissimilarity are currently unclear and under investigation, but may involve MC-independent effects of KIT. Another approach to investigate the role of MCs in the pathogenesis of disease is to use specific inhibitors of MC activation and mediators in murine models of disease.

How to Study the Role of Human MCs in Health and Disease

How MCs contribute to health and disease in humans is more challenging to investigate. As of yet, no human individuals who lack MCs have been reported. Also, there are no

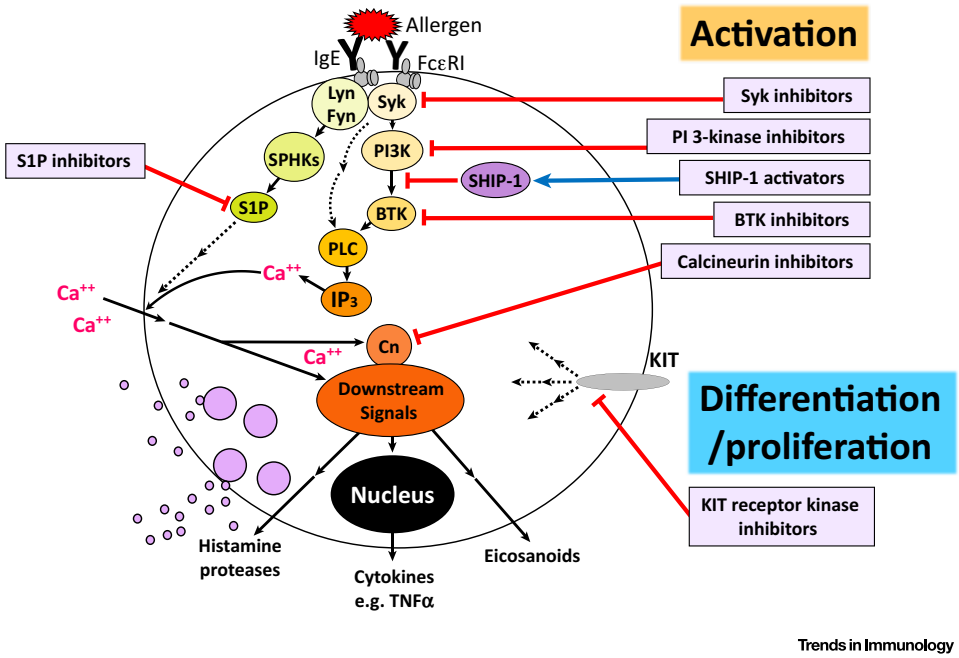

Figure 1. Simplified Overview of Therapeutic Strategies Targeting Signaling in Order to Prevent Activation (in Terms of Subsequent Mediator Release to Allergen Provocation), Chemotaxis, or Differentiation of Mast Cells. ⊣ Denotes inhibition, arrows activation (dotted arrows indirect activation). Abbreviations: Syk, spleen tyrosine kinase; PI3K, phosphatidylinositol 3-kinase; BTK, Bruton's tyrosine kinase; CN, calcineurin; IP3, inositol trisphosphate; PLC, phospholipase C; S1P, sphingosine-1-phosphate; SHIP-1, Src homology 2 (SH2) domain-containing inositol 5′ phosphatase 1; SPHKs, sphingosine kinases.

pharmacological tools available that allow for the selective depletion of MCs in humans. Finally, few inhibitors of MC activation and MC mediators are available, and none is specific for MCs. The notion that MCs contribute to human diseases, therefore, relies largely on circumstantial evidence, from preclinical models or the investigation of patients. One of these circumstantial lines of evidence is the change of MC numbers observed in many diseases. When MCs are studied in patients, an increase in MC numbers at sites of disease manifestation is often regarded as an indication that MCs contribute to the pathogenesis. For example, allergic diseases such as atopic dermatitis, allergic rhinitis, and asthma are characterized by increased MC numbers in affected organs. In this case, this increase in MC numbers is complemented by functional data from mice and human models, which, together, support the notion that allergies are MC mediated. In other human diseases, such as autoinflammatory [21] and autoimmune diseases [22,23], cancers [12], cardiovascular diseases [24], and in rejected organ transplants [25], where increased numbers of MCs are frequently observed in affected organs or tissues, the case is less clear.

In principle, increased MC numbers could be a driving mechanism, a bystander effect, or a compensatory mechanism as an attempt by the host to control and terminate disease. Thus, the increase of MCs that is observed in many disorders by itself does not prove that MCs are involved in their pathogenesis. For this, further evidence from multiple regression analyses of correlations of MC numbers with disease activity, exacerbation, progression, and remission, as well as functional studies are needed [26].

Much can be learned about the role of MCs in the pathogenesis of diseases by studying human MCs *in vitro* and *ex vivo* and through preclinical human *in vivo* models. Such models include the use of MC-specific activators in healthy humans and the investigation of lesions in patients with inducible MC-dependent diseases. For example, the effects of MCs and their activation (and those of MC-targeted treatments) can be investigated by inducing the degranulation of cutaneous MCs and monitoring subsequent skin responses and the elicitation of MC-mediated signs and symptoms such as wheals, reflex erythema and itch as well as angioedema. Common approaches to induce the degranulation of skin MCs involve intracutaneous injections or skin prick testing of codeine, allergens, or substance P [27]. Similar approaches may be used to investigate the responses of MCs in the airways, the eye, and the gut [28–30]. In addition, MC-driven diseases with inducible symptoms, such as chronic inducible urticaria (e.g., cold urticaria) and cutaneous mastocytosis (Darier's sign), can also be very useful to investigate the pathogenic effects of skin MCs and their response to treatment strategies aimed at reducing MC activation or MC numbers [31]. Notably, in inducible urticaria patients, focal stimulation of MCs by appropriate provocation testing with relevant triggers (such as cold in cold urticaria) can be used to assess the effects of local or systemic treatment with therapies that modulate MC activation [32].

Mastocytosis is a clonal MC disorder accompanied with systemic or local increases in MC numbers. Diagnosis is based on MC accumulation in the skin and/or in extracutaneous tissues and the demonstration of a clonal expansion of mostly morphologically altered MCs, that is, detection of Kit mutation, spindle-shaped MCs and aberrant expression of CD25 [33]. Activation of cutaneous MCs can be stimulated locally by standardized mechanical provocation (Darier's sign) and monitoring of wheal-and-flare responses. This approach has been used successfully to investigate the effects of therapeutic MC-targeted intervention, for example, topical treatment with miltefosine and clobetasol [31]. Also, skin biopsies could be used to isolate and culture patients' mast cells *in vitro* to further characterize molecular pathways [34].

MCs as Therapeutic Targets

Recent studies have identified and characterized multiple therapeutic strategies that target MCs. The aims of these approaches include, but are not limited to, the alteration of MC numbers, the downregulation or inhibition of MC activation, shutting down their signal transduction, and the prevention of the effects of their mediators.

Therapeutic Approaches Aimed at Reducing MC Numbers

Reducing MC numbers is a promising treatment approach in mastocytosis and other diseases in which MC numbers are increased. Tissue MC numbers can be reduced by the targeted induction of apoptosis or by blocking the effects of tissue factors that promote MC progenitor recruitment, MC migration, differentiation, or survival. Stem cell factor (SCF), which signals through the KIT receptor (CD117) expressed on MCs, is considered to be the most important factor for regulating tissue MC numbers under physiological conditions [8,35,36]. Its role in the accumulation of MCs in pathological conditions is less clear, and various other mediators and signals appear to contribute to MC hyperplasia by promoting MC recruitment and differentiation as well as survival at sites of disease manifestation.

For example, in murine models of disease, several mediators of MC progenitor recruitment [chemokine CC receptor (CCR)2, 3, and 5; chemokine CC ligand (CCL)2 and chemokine CXC receptor (CXCR)2; and interleukin (IL)-4] are considered to be important for the accumulation of MCs in affected organs [37]. Interestingly, the trafficking of human MC precursors and mature MCs caused by the chemokine CXC ligand (CXCL)12 has been shown to be markedly enhanced by histamine acting through the H4 receptor expressed on these cells [38]. This suggests that histamine derived from activated MCs can increase local MC accumulation via H4 receptor activation, which may be prevented by H4 receptor antagonists that are currently undergoing clinical development [39]. Also, the Notch signaling pathway and IL-9 reportedly promote mucosal MC hyperplasia in the gastrointestinal tract and the lung in murine models of disease [40,41]. Recently, MCs in the skin of eczema patients have been reported to be increased and to show increased expression of substance P (SP) and its receptor, neurokinin (NK)-1. SP, via its effects on NK-1, can induce the accumulation of MCs in the murine peritoneum [42]. Other neurogenic signals, such as nerve growth factor, have also been demonstrated to induce MC hyperplasia in rodents [43]. Finally, cannabinoid (CB)1 receptors and their ligands may regulate tissue MC numbers. Recent studies have shown that tonic CB1 stimulation by locally synthesized endocannabinoids controls the maturation of resident skin and airway MC progenitors thus underlining the potential of CB1 stimulation as a future strategy for MC-dependent diseases [44,45].

As of now, it is largely unclear how relevant these or other factors are for the accumulation of MCs in humans. A better understanding of the signals and mechanisms that lead to MC hyperplasia in human tissue is needed for the development of targeted therapies. This may come from profiling sites of disease manifestation for the expression of signals that promote MC accumulation or by analyzing the effects of targeted therapies on MC numbers. For example, anti-IL-5 treatment, in pediatric patients with eosinophilic esophagitis, has recently been reported to markedly reduce MC hyperplasia [46].

At present, however, the investigation and use of MC-reducing therapies is virtually limited to mastocytosis. In mastocytosis, somatic activating *KIT*-mutations (predominantly KitD816V) drive the accumulation of MCs in various tissues including the skin, bone marrow, and gastrointestinal tract. In contrast to aggressive forms of mastocytosis including MC leukemia, in which symptoms and disease burden are mainly driven by tissue infiltration of MCs and

subsequent organ dysfunction, symptoms of indolent systemic mastocytosis (ISM) are derived by an increased release of MC mediators, including histamine, leukotrienes, and prostaglandins. Although MC-reducing therapies are commonly used, especially in aggressive forms of mastocytosis [47], no specific treatment options are presently available to do this. Mastocytosis patients with skin manifestations, for example, are often treated with a topical glucocorticosteroid for several weeks, sometimes in combination with UV therapy. Repeated applications of a potent glucocorticosteroid to the skin of allergic patients have been reported to reduce cutaneous MC numbers [48], but also have various other effects. Systemic cytoreductive therapies such as cladribine and tyrosine kinase inhibitors (TKIs) are used in patients with aggressive forms of mastocytosis to reduce MCs numbers. Cladribine has been reported to reduce MCs in patients with advanced mastocytosis; however, its mode of action is unspecific und not yet understood in detail [49,50].

The TKI imatinib is the first immunological anticancer drug successfully used in the clinics for the treatment of CML (targeting BCR-ABL1) and gastrointestinal stromal tumors (targeting KIT and other molecules) [51]. Imatinib is also FDA-approved for the treatment of adult patients with aggressive systemic mastocytosis, who do not exhibit the KitD816V mutation. It reduces MC numbers in CML and in mastocytosis patients [52] and also has other effects on MCs, such as inhibition of activation [53]. The use of imatinib in mastocytosis, especially in ISM, is limited due to the fact that the common presence of the KitD816V mutation in mastocytosis results in resistance to imatinib treatment. Also, imatinib has effects on cells other than MCs and therefore causes several adverse effects, which may be of particular relevance in the long-term treatment of ISM patients. Recently, other TKIs such as masitinib and midostaurin have been investigated in mastocytosis, and midostaurin has been demonstrated to effectively reduce MC numbers in aggressive systemic mastocytosis, although it does not result in complete disease remission in all patients [54]. The novel multi-kinase inhibitor, DCC-2618, which has been shown to inhibit the growth of neoplastic MCs and leukemic monocytes, blasts and eosinophils *in vitro*, has entered clinical investigation [55].

Two current developments may result in more specific approaches for reducing MC numbers in patients with mastocytosis. (1) BLU-285 is a selective and potent inhibitor of KitD816V presently in preclinical development [56]. KitD816V drives the accumulation of MCs in mastocytosis, and selective inhibitors such as BLU-285 may allow for a more specific way to reduce MC numbers with less effects on other cells [57]. (2) Siglec-8 is one of several inhibitory receptors recently identified on human MCs [58]. Activation of Siglec-8 and other inhibitory receptors can inhibit the degranulation of MCs, possibly by engaging inhibitory signaling through their immunoreceptor tyrosine-based inhibition motifs (ITIMs). More importantly, targeting of Siglec-8, which is almost exclusively expressed by MCs (and eosinophils and basophils), may allow for specifically reducing MC numbers in mastocytosis and other MC-driven diseases [59]. A Siglec-8-specific antibody, which can kill MCs by antibody-dependent cell-mediated cytotoxicity *in vitro*, is currently under clinical development for the treatment of patients with mastocytosis.

Therapeutic Approaches Aimed at Inhibiting MCs and/or Preventing MC Activation?

MCs express a substantial number of activating and inhibitory receptors, which can be exploited to develop drugs to interfere with MC activation (Figure 1). Presently, several drugs, which are believed to have MC stabilizing effects, are used in the clinic to treat MC-driven disorders, mostly allergic diseases. These include cromolyn sodium, nedocromil, lodoxamide, and antagonists for the histamine receptor H1 such as azelastine, ketotifen, olopatidine, bilastine, desloratadine, rupatadine, and epinastine [60]. The mechanisms of action of these

drugs on MCs are not well defined, and their MC inhibiting effects are moderate or negligible; in fact, some of these drugs, do not inhibit human MCs effectively or do so only at high concentrations and locally.

Human MCs may be inhibited *in vivo* by targeting various pathways (Table 1) [60,61]. For some of these targets, drugs are being developed and are currently in various phases of clinical testing [62]. For others, compounds have recently been approved for the treatment of patients. For example, TKIs that affect KIT kinase activity such as imatinib, nilotinib, sunitinib, ibrutinib, and dasatinib have been developed for the treatment of leukemia, and some are now approved for the treatment of aggressive mastocytosis [60]. Preventing the sensitization of the FcεRI and promoting its downregulation by blocking the binding of IgE with the anti-IgE monoclonal omalizumab is a successful approach to inhibit MC activation in chronic urticaria, and omalizumab was approved for the treatment of chronic spontaneous urticaria in 2014 [63,64]. Other biologicals such as designed ankyrin repeat proteins, DARPins bi53_79 and E2_79, have also shown to be promising inhibitors of IgE-mediated MC activation. These drugs are still in preclinical development [65].

MCs can be activated by many other means, independently of IgE and its receptor. Therefore, blocking IgE-induced activation is not a suitable strategy for the treatment of all MC-driven diseases. At this point, no MC-specific drugs are available and there is a definite need for further research that identifies and defines unique MC-specific targets and molecules that can be used to engage them [66]. In addition, it is of great importance to further define predictive and prognostic biomarkers to monitor the effects of therapies on MC activation.

Therapeutic Strategies Aimed at MC Signal Transduction

Targeting MC intracellular signaling pathways responsible for the release of the substantial arsenal of proinflammatory mediators is highly desirable, also because this strategy circumvents the need for polypharmacy to block the effects of individual mediators. Many therapeutic approaches aimed at targeting IgE-dependent MCs signaling do so at the level of blocking early stimulatory signals, which is theoretically more effective than attempting to block signals further downstream due to marked signal amplification (and diversification). Effective inhibitors of early allergen (IgE)-mediated signaling include inhibitors of the spleen tyrosine kinase (Syk), phosphatidylinositol 3-kinase (PI3K), and Bruton's tyrosine kinase (BTK), all of which are currently being trialed for MC-driven diseases (e.g., in allergic rhinitis, rheumatoid arthritis, and chronic urticaria), and can block the release of all mediator types from MCs [61].

A novel approach to terminate MC activation at the level of signal transduction is to activate inhibitory signals such as the phosphatase SHIP-1 [Src homology 2 (SH2) domain-containing inositol 5′ phosphatase 1], which dephosphorylates the stimulatory product of PI3K activation, phosphatidylinositol 3,4,5-triphosphate to phosphatidylinositol 4,5-bisphosphate. PI3K not only plays a role in IgE-dependent MC activation, but is also important for KIT-mediated (and other stimulatory receptor) signals. Either inhibiting the enzyme directly or blocking its effects by stimulating SHIP-1 could be a useful therapeutic strategy for diverse MC-driven diseases. Indeed, clinical trials in allergic asthma and rhinitis using PI3K inhibitors (e.g., CAL-101 and CAL-263) and the SHIP-1 activator AQX-1125 are at an advanced stage [67–69].

A further essential step in MC activation is the release of intracellular calcium, which regulates calcium channels permitting a substantial influx of calcium ions into the cells. Many existing anti-allergic drugs such as β agonists and phosphodiesterase inhibitors exhibit their inhibitory effects by ultimately blocking calcium mobilization (via increasing cyclic AMP and activating

Table 1. Therapeutic Targets to Inhibit MC Activation

Signaling pathway	Compound	Mode of action	Clinical stage and current clinical indication	Refs
Syk kinase	Pyrimidines: R406, R112, BAY61-3606, PRT062607	Inhibition of IgE-receptor signaling	Preclinical and clinical phase (R112 allergic rhinitis failed)	[61,62,66,80]
	Acridones: ER27317	Inhibition of IgE-receptor signaling	Preclinical	
	Isoquinolinones: U63A05	Inhibition of IgE-receptor signaling	Preclinical	
	Flavonoids: homoisoflavone	Inhibition of IgE-receptor signaling	Preclinical	
PKC	Balanol, riluzole, staurosporin, enzastaurin, ruboxistaurin, UCN-01, bryostatin	Inhibitors of pan-PKC activity or activity of selective PKC isozymes	Clinical phase (cancer, diabetic retino/nephro/neuropathy)	[81]
PI3K	IC87114, CAL-101/GS1101 (idelalisib), CAL-263,	Inhibitors of δ isoform of PI3K	FDA approved (hematological malignancies)	
	IPI-145 (duvelisib)	Inhibitors of δ and γ isoform of PI3K	Clinical phase (hematological malignancies)	
	Buparlisib	Pan PI3K inhibitor	Clinical phase (breast cancer)	[61,80,81]
BTK	Ibrutinib, dasatinib, AVL-292/CC-292, GDC-0834, CGI1746, RN486, RN983, CNX774, spebrutinib, GS 4059	Inhibition of Btk activity	Clinical development and/or FDA approved (e.g., chronic lymphocytic leukemia; MALT lymphoma; mantle-cell lymphoma; Waldenstrom's macroglobulinemia	[61,82]
Janus kinase	WHI131	Inhibition of JAK3 and possibly PI3 kinase	Clinical phase (hematological malignancies)	[80]
IgE and FcεR1				
Neutralizing anti-IgE mAb	Omalizumab	Preventing binding of IgE to FcεRI	FDA approved	[83]
Neutrolizing anti-IgE mAB	Ligelizumab	Preventing binding of IgE to FceRI	Clinical phase (asthma, urticaria)	[111,112]
Anti-IgE darpins	Darpin	Preventing binding of IgE to FcεRI	Preclinical phase	[65,84]
Gene targeting of FcεR1beta	Antisense technology	Exon skipping	Preclinical phase	[85]
MC mediators				
Histamine	Ketotifen, olopatadine, azelastine, epinastine	Histamine (H1) receptor antagonists and MC stabilization	FDA approved	[61,62,80]
Leukotrienes	Montelukast, zafirlukast	CysLT1 antagonist blocking the action of LTC4, LTD4 and LCE4	FDA approved	[61]
Prostaglandins	S-555739, OC000459, QAV680	PD2/CRT2 receptor antagonists	Clinical phase (some failed)	[61,86]
	Laropiprant	DP1 antagonist	Withdrawn from market	
	AMG853	Dual DP1-DP2 antagonist	Clinical phase (discontinued)	
TNF-α	Infliximab, adalimumab, certolizumab pegol, and golimumab	Neutralizing TNF-alpha by binding	FDA approved	[87–90]
	Etanercept	Circulating receptor fusion protein neutralizing TNF-α by binding	FDA approved	
Tryptase	APC-366, APC-2059, MOL6131, JNJ-27390467, RWJ-58643	Inhibition of beta-Tryptase activity	Preclinical and clinical phase (discontinued)	[62]
Chymase	SUN C8077, SUN13834, ONO-WH-236	Inhibition of chymase activity	Preclinical and clinical phase (discontinued)	[62]
Chymase/cathepsin G	JNJ-10311795	Dual inhibition of chymase/cathepsin G activity	Preclinical phase	[91,92]

Table 1. (continued)

Signaling pathway	Compound	Mode of action	Clinical stage and current clinical indication	Refs
Various activating targets				
C3a	Anti-C3 protease	Enzymatic complement inhibitor	Clinical phase (discontinued)	[93,94]
	SB290157	C3a receptor inhibitor	Preclinical phase	
C5a	LFG316, ARC1905 pegylated RNA aptamer	Bind to C5 and prevent cleavage into C5a and C5b	Clinical phase (paroxysmal nocturnal hemoglobinuria)	
	Eculizimab, pexelizumab	Anti-C5 antibody	FDA approved (paroxysmal nocturnal hemoglobinuria); clinical phase (pexelizumab: development stopped)	
SP	RPR-100893, CP-96345, CP-99994, L-741671, L-742694, GR-205171, GR-205171, LY-303870, T-2328, aprepitant, rolapitant, NEPA	NK1 receptor antagonists	Clinical phase and FDA approved (nausea)	[95]
MRGPRX2	Not available			[96–98]
H4R	JNJ17777120, JNJ28307474, JNJ39758979, torefant, PF-3893787, ZPL-3893787, UR-63325, NCT022958865, NCT01823016	Antagonists of the H4-receptor	Clinical phase (pruritus, atopic dermatitis, rhinitis, asthma, psoriasis, RA)	[99]
ST2	Not available	ST2 is the receptor for IL-33 causing mast cell activation		[100–102]
KIT	Imatinib, nilotinib, ponatinib, midostaurin	Inhibitors of kinase activity KIT	FDA approved (e.g. leukemia, mastocytosis)	[115–118]
KIT	Masitinib, BLU-285 and DCC-2618	Inhibitors of kinase activity KIT	Clinical phase (e.g. mastocytosis, GIST)	[113,114]
TrkA	LOXO101	Inhibition of NGF action (growth, differentiation, degranulation)	FDA recognition as breakthrough therapy (unresectable or metastatic solid tumors)	[103,104]
Ig-free light chains	F991	F991 prevents mast cell activation via Ig free light chains	Preclinical phase	[105–107]
CD63	Not available	Activation marker of mast cells and basophils		[108,109]
Inhibitory receptors				
Siglec-8/Siglec-F	AK002	Anti-siglec-8 antibody AK002	Clinical phase (mastocytosis)	[110]
CD300	Not available	Inhibitory receptor on mast cells		
FcγRIIb	Anti-IgE DARPin-Fc fusion protein	Coligation of FcεRI and FcγRIIb	Preclinical	[84]
GPR35	Lodoxamide, cromolyn sodium	Possibly via activation of inhibitory pathways via GPR35	FDA approved	[80,81]

protein kinase; PKA). These agents effectively block MC responses, but their full potential is rarely reached because of numerous adverse effects, which limit their systemic use. A possible alternative route to blocking calcium entry is by inhibiting the effects of sphingosine-1-phosphate, which increases cytosolic calcium levels leading to further calcium influx into mast cells. It also plays a role in MC migration and may, therefore, limit MC numbers [70].

Downstream of calcium mobilization, calcineurin plays a crucial role in mediator release from MCs [71]. Calcineurin inhibitors (e.g., ascomycin and cyclosporine A) have long been used in the treatment of severe MC-related diseases. A further downstream signal target is p38

mitogen-activated protein kinase (p38 MAPK); an inhibitor of which (AZD7624) is currently undergoing clinical trials for corticosteroid resistant asthma.

The problem with all signal transduction inhibitors used for treating MC disorders is the widespread expression of the signaling enzymes they target in a variety of different cell types, resulting in a high risk of adverse drug reactions. A degree of selectivity may be still be obtained by targeting early IgE-dependent signaling components, which, if the thresholds of signal transduction are low, may permit the use of lower doses of inhibitors that would otherwise have too many ubiquitous effects. However, there are still too few comparative studies regarding allergic effector cells to prove this hypothesis. The use of nanotechnologies to specifically target MCs with signal transduction modulators may help to overcome the issue of ubiquitous intracellular signal enzyme expression. For example, we have recently provided proof-of-principle that gold nanoparticles containing ascomycin (coupled to glutathione as a prodrug and also containing targeting antibodies) can substantially increase the potency of ascomycin at inhibiting IgE-dependent histamine release from basophils by the specific delivery of the drug to these cells [72]. However, it is yet unclear whether this technology will be sufficiently robust and safe for clinical use. Certain nanomaterials themselves have anti-inflammatory properties, such as the fullerenes, which inhibit Syk phosphorylation and IgE-mediated degranulation of human MCs and basophils [63,73]. However, since fullerenes can cause lung fibrosis, it is questionable whether these materials could be used therapeutically.

Therapeutic Approaches Aimed at Inhibition of the Effects of MC Mediators

MCs produce and release a large set of diverse biologically active mediators such as histamine, proteoglycans, proteases, cytokines, chemokines, lipid mediators, and growth factors [74]. Interestingly, MCs can differentially release their mediators in response to distinct activating signals [75].

Many MC mediators such as histamine, leukotrienes, prostaglandins, and cytokines are effectively neutralized by available drugs.

Over the past few years, MC proteases such as chymase, tryptase, and carboxypeptidase A have received increased attention [76]. Proteases are known to mediate various biological activities, including the activation and deactivation of effector peptides. For example, MC proteases have been shown to limit the activity of endothelin-1, an endogenous toxic peptide that contributes to the morbidity and mortality of severe infection and sepsis [9], and have also been demonstrated to degrade and detoxify several animal venoms [13]. MC chymase converts angiotensin I to angiotensin II and activates transforming growth factor-β and matrix metalloproteinase-9, all of which are involved in cardiovascular remodeling [77]. As of yet, no specific MC protease inhibitors are approved drugs.

In most cases, MC effects are not due to a single mediator acting on a single target. Novel developments, therefore, aim to neutralize more than one MC mediator, for example histamine and platelet activating factor [78], or to inhibit the effects of MC mediators on more than one target, for example histamine effects on both H1 and H3 receptors [79].

Concluding Remarks

Much has been learned about the role of MCs in the pathogenesis of various disorders, but further research is needed to better define their role in homeostasis as well as in promoting and limiting disease. In particular, future research using nonhuman models of disease, preclinical human models, and investigations of patients will need to better characterize the role and

contribution of MCs to the pathogenesis of chronic inflammatory diseases (see Outstanding Questions). We have also learned a lot about the biology of MCs and how to alter MC functions and their effects in contributing to disease including increased numbers of MCs and their release of mediators. The first targeted treatments aimed at neutralizing these pathogenic effects of MC are already in clinical practice and new ones are being investigated in ongoing clinical trials. On the down side, it is yet unclear how disease promoting versus homeostatic functions of MCs can be targeted differentially. The development of more effective MC-altering drugs is urgently required, and existing treatment strategies should be reinvestigated to determine their potential effects on MCs.

Outstanding Questions

Other than IgE/allergen in allergic diseases, what are the activators of MCs in different diseases, and what benefits are there to targeting different aspects of MC activation in different diseases?

What mediators are involved in the different effects that MCs have in different responses, and how is their differential release regulated?

How would treatment approaches that block MC differentiation, migration, signaling, mediator release or proliferation differ in their effects and efficacy in different diseases?

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