

REVIEW ARTICLE

The ingenious mast cell: Contemporary insights into mast cell behavior and function

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Abstract

Mast cells are (in)famous for their role in allergic diseases, but the physiological and pathophysiological roles of this ingenious cell are still not fully understood. Mast cells are important for homeostasis and surveillance of the human system, recognizing both endogenous and exogenous agents, which induce release of a variety of mediators acting on both immune and non-immune cells, including nerve cells, fibroblasts, endothelial cells, smooth muscle cells, and epithelial cells. During recent years, clinical and experimental studies on human mast cells, as well as experiments using animal models, have resulted in many discoveries that help decipher the function of mast cells in health and disease. In this review, we focus particularly on new insights into mast cell biology, with a focus on mast cell development, recruitment, heterogeneity, and reactivity. We also highlight the development in our understanding of mast cell-driven diseases and discuss the development of novel strategies to treat such conditions.

KEYWORDS

allergy, anaphylaxis, animal models, asthma, inflammation, Mast cells, mastocytosis, urticaria

Abbreviations: BTK, Bruton's tyrosine kinase; CTMC, Connective tissue mast cells; CU, Chronic urticaria; CSU, Chronic spontaneous urticaria; H α T, Hereditary alpha tryptasemia; MC, Mast cell; MCP, Mast cell progenitor; MCAS, Mast cell activation syndrome; MMAS, Monoclonal mast cell activation syndrome; MMC, Mucosal mast cells; PMD, Piecemeal degranulation; SCF, Stem cell factor; SG, Secretory granule; SYK, Spleen associated tyrosine kinase.

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1 | INTRODUCTION

Although hematopoietic stem cells produce mast cell (MC) progenitors, mature MCs are normally absent in blood while found in almost all tissues as highly granulated cells. The stem cell factor (SCF) receptor, KIT, is one of the most critical receptors on mature MCs, as a reduction in KIT signaling leads to MC deficiency. Yet, signaling through the receptor is redundant for early development of MC progenitors in peripheral blood.¹ MCs are equipped with a great number of receptors enabling them to sense and react to a diversity of stimuli.² The most studied receptor that causes MC activation is the high-affinity IgE receptor, FcεRI. Another receptor that has received particular attention during recent years is the Mas-related G protein-coupled receptor X2 (MRGPRX2), a G protein-coupled receptor recognizing a variety of pharmacologic agents (tubocurarine, atracurium, icatibant, ciprofloxacin) causing pseudo allergic reactions.^{3,4} MRGPRX2 also serves as a receptor for substance P, components of insect venom, antimicrobial peptides, secreted eosinophil products, and other cationic peptides.^{5,6} MC expression of MRGPRX2 has been associated with neurogenic inflammation, pain, and itch⁷⁻⁹ and also to contribute to the development of allergic inflammation.¹⁰ Other receptors that induce IgE-independent MC activation include the IL-33 receptor, which is important for MCs to recognize cell injury and trauma¹¹ as well as regulating IgE-mediated responses,¹²⁻¹⁴ and pattern recognition receptors (PRRs) sensing “danger” signals, including microbes.¹⁵ When MCs sense an endogenous or exogenous agent through binding to one of their many activating receptors, they react by releasing mediators through three major pathways (Figure 1). The most rapid response is exocytosis of secretory granules (SGs) and the release of preformed mediators such as histamine, proteases, and heparin.¹⁶ This is accompanied

by the *de novo* biosynthesis of lipid mediators, predominantly eicosanoids such as prostaglandin D₂ (PGD₂), the cys-leukotrienes LTC₄, LTD₄, and LTE₄, and also other eicosanoids like thromboxane A₂ (TXA₂) and 15-HETE,¹⁷ as well as other lipid mediators such as platelet-activating factor (PAF) and sphingosine-1-phosphate (S1P).¹⁸ In addition, MCs also have the capacity to synthesize a number of cytokines, chemokines, growth factors, and interferons.¹⁹ Notably, release of *de novo*-synthesized mediators can take place without preceding degranulation (Figure 2).²⁰ Examples of such are the effect of IL-33 that induces secretion of leukotrienes and cytokines, for example,^{21,22} CD30 inducing release of only cytokines and chemokines,²³ and certain viruses, for example, respiratory syncytial virus, inducing secretion of type I interferons and chemokines^{15,24} (Figure 2). Thus, MCs can be activated and produce lipid mediators and/or cytokines in the absence of detectable degranulation (by histology or measurement of granule mediators).²⁵ Finally, MCs also secrete extracellular vesicles including exosomes. MC exosomes can transfer proteins, enzymes, RNA, and miRNA that can be taken up by other cells, either proximal to the secreting MC or located at distant sites²⁶⁻²⁹ (www.exocarta.org) (Figure 1). Notably, patients with systemic mastocytosis have increased levels of exosomes with an MC signature including constitutively activated KIT, enabling transfer of mutant proteins to other cells.³⁰

Given the broad distribution of MCs and their multifunctional role, the variety of mediators released, the symptoms associated with MC mediators (Figure 3), they have been implicated in many diseases beyond allergy.³¹⁻³³ For example, recent reviews highlight the role of MCs in cardiovascular diseases,³⁴ cancer,³⁵ airway diseases,³⁶ as well as in viral, bacterial, and fungal infections.³⁷⁻³⁹ Even if MCs commonly are discussed in the context of disease, it is important to remember that they also have a role in homeostasis, the

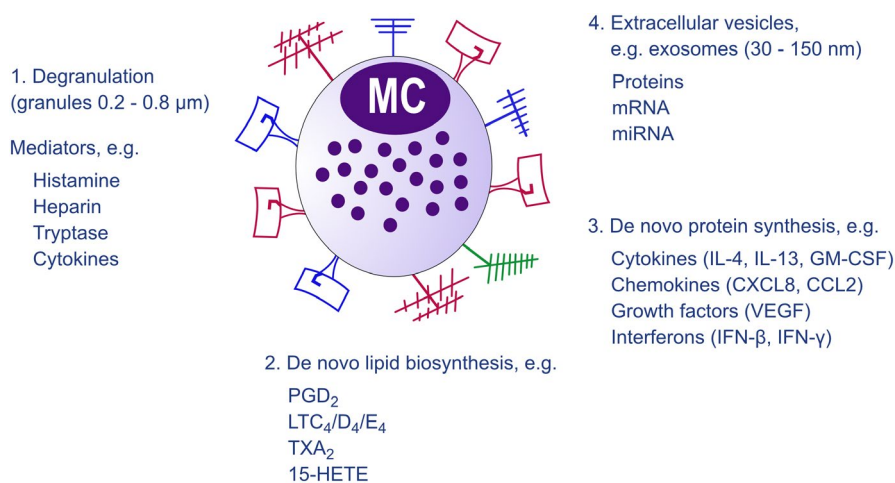


FIGURE 1 Mast cell activation pathways and release of mediators. Mast cells are endowed with a palette of receptors that can recognize endogenous and exogenous products and release different sets of mediators dependent on the receptor involved. Upon recognition mast cells react by releasing mediators through one or several pathways: (1) degranulation and release of granules containing, for example, histamine, heparin, proteases, and cytokines; (2) release of newly synthesized lipid mediators such as PGD₂, LTC₄/D₄/E₄, TXA₂ and 15-HETE; (3) release of *de novo*-synthesized cytokines, chemokines, growth factors, and interferons; (4) release of extracellular vesicles, for example, exosomes, containing proteins, mRNA and miRNA

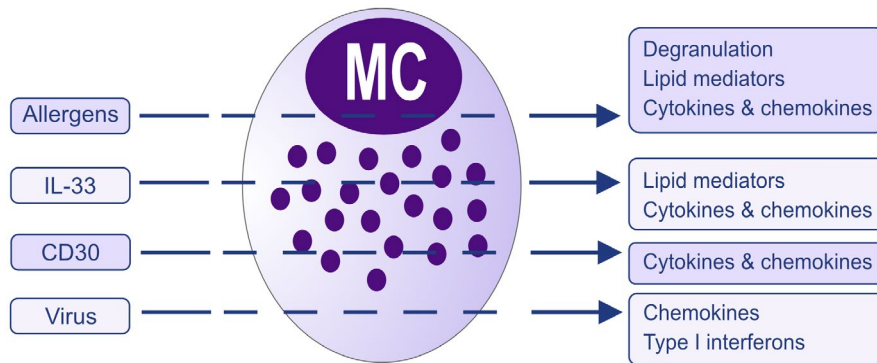
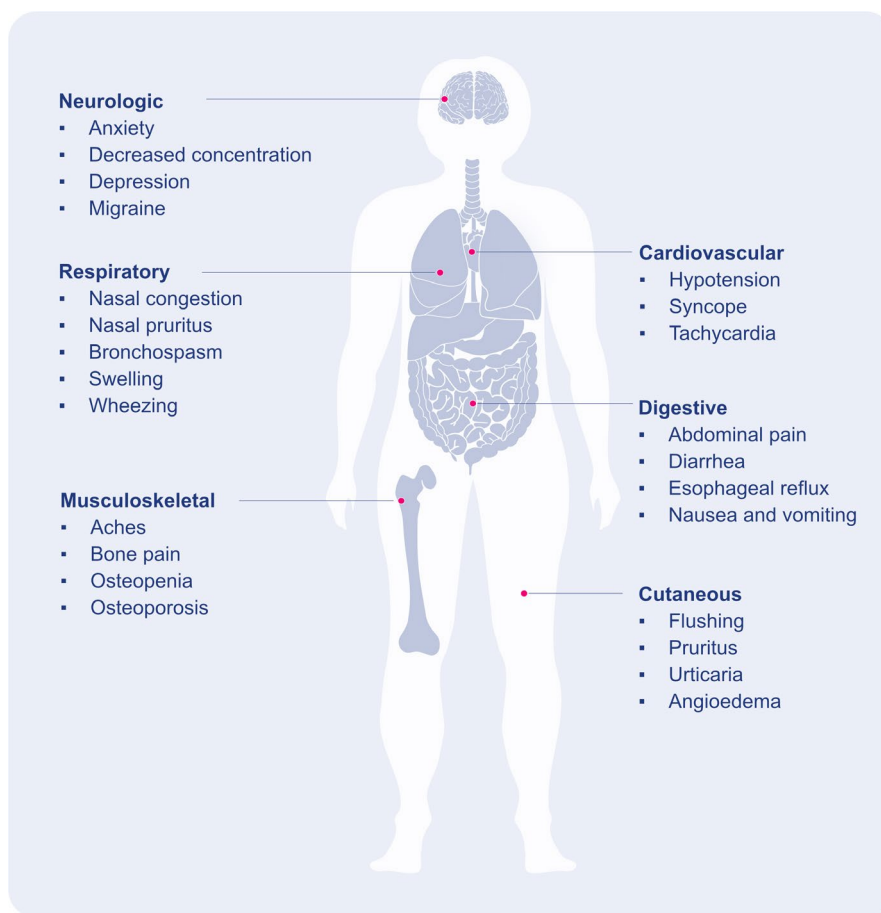


FIGURE 2 Differential release of mediators. Depending on ligand – receptor interaction mast cells react by releasing different sets of mediators, those stored in granules, newly synthesized and secreted lipid mediators, and *de novo* produced proteins. Mast cells activated with allergen binding to IgE bound to the high-affinity IgE receptor, FcεRI, induces degranulation, secretion of lipid mediators and different types of proteins, including cytokines and chemokines. In contrast, the alarmin IL-33 does not induce degranulation but causes secretion of lipid mediators, cytokines and chemokines.¹⁸⁵ The costimulatory molecule CD30 induces secretion of only cytokines and chemokines.²³ Viral infection leads to a variety of responses, depending on the type of virus encountered.¹⁵ For example, respiratory syncytial virus infection induces production of type I interferons and chemokines²⁴

FIGURE 3 Putative symptoms induced by mast cell-derived mediators. Activation of mast cells causes the release of a multitude of mediators that can act on cells or substrates in different organs and systems which might create clinically relevant symptoms as depicted in the figure



initiation of acute inflammation,⁴⁰ and in the protection against danger, whether it comes from the outside (venoms, pathogens, etc.) or from within the body (cell injury, etc.).⁴¹

In this review, we highlight some of the most recent findings regarding MC origin and development, recruitment, heterogeneity and reactivity, MC disease, new therapeutic possibilities, and animal models to study MC biology.

1.1 | The origin of mast cells

Hematopoietic cells arise in several temporally distinct waves during prenatal development. The first MCs originate from primitive erythromyeloid progenitors in the extraembryonic yolk sac.⁴²⁻⁴⁵ A second wave of MCs appears together with the first definitive hematopoietic progenitors. The first two waves mainly contribute to

connective tissue MCs (CTMC) and serosal-type MCs.⁴³ The third hematopoietic wave originates from the aorta-gonado-mesonephros region. Cells formed during this wave produce hematopoietic stem cells that exhibit MC-forming potential.⁴³ It was for a long time assumed that MCs develop from hematopoietic stem cells in the bone marrow.⁴⁶ However, it is now clear that bone marrow hematopoietic stem cells produce a fraction, but not all, MCs. Experiments also show that bone marrow-derived MCs mainly replenish the mucosal MC population postnatally.⁴³ However, there is a redundancy in the potential of the waves as bone marrow-derived MCs can reconstitute depleted skin-resident (connective tissue-type) MCs and populate the skin following inflammation.⁴⁷

1.1.1 | From hematopoietic trees to differentiation landscapes

The classic tree-like model that describes hematopoiesis assumes a stepwise loss of lineage potential with differentiation from hematopoietic stem cells to lineage-committed progenitors (Figure 4A). However, assignment of the MC differentiation trajectory to either the granulocyte-monocyte or the megakaryocyte-erythrocyte branch is a controversial topic. Studies supporting the idea that MCs belong to either branch have been presented.^{48–53} On a different angle, other investigations propose that MCs branch off early—close to hematopoietic stem cells—and differentiate along a unique trajectory.^{54,55}

Advances in high-throughput single-cell RNA sequencing and computational biology are now delineating the MC differentiation trajectory by suggesting a revision of the hematopoietic model.⁵⁶ The idea to reconstruct hematopoietic differentiation with single-cell transcriptomics is based on capturing a snapshot of single differentiating progenitors.⁵⁷ Such analysis reveals that differentiating cells traverse a continuous landscape of states, from multi- and bipotent

progenitors to lineage-committed cells (Figure 4B). A single-cell transcriptional landscape of bone marrow hematopoiesis in mouse shows that the MC developmental trajectory is positioned adjacent to the erythrocyte and basophil trajectories.^{51,58} The MC and basophil trajectories are particularly close to each other,^{58,59} which indicates the presence of a bipotent basophil-MC progenitor population, a finding that is recapitulated in single-cell fate assay experiments.^{49,58–60} Cell fate assays of mouse bone marrow progenitors also verified that basophil/MC differentiation is closely coupled with erythropoiesis.⁵¹ The combination of single-cell transcriptomics and lineage tracing provides even deeper insights into hematopoiesis with focus on MC differentiation. Tracing individually barcoded mouse hematopoietic progenitor cells during *in vitro* culture confirms a coupling between MC and basophil fates as well as between MC and erythrocyte fates.⁶¹

In human, single-cell transcriptomics analysis of bone marrow cells indicates that basophils and MCs arise from a common bipotent progenitor.⁵⁹ However, cell fate assays are yet to verify the existence of such progenitor. A link between basophil/MC progenitors and erythrocyte progenitors has also been proposed in human hematopoiesis.^{62–65} In analogy to lineage tracing experiment in mouse, tracking a somatic mutation in human hematopoiesis could potentially decipher the relationship between basophil and MC differentiation. The cellular distribution of KIT D816V mutation, a mutation present in systemic mastocytosis patients causing constitutive KIT signaling, has been studied for this purpose. No evidence supporting a close developmental relationship between MCs and basophils has been observed using this approach.⁶⁶ In fact, the results based on charting the cellular distribution of the KIT D816V mutation seem to suggest that basophils and MCs are distantly related. However, such analysis rests on a disputable assumption; presence or absence of the somatic KIT D816V mutation in a given progenitor does not influence the cell's fate potential. Specifically, it is possible that the acquired D816 V mutation primes a multi- or bipotent progenitor

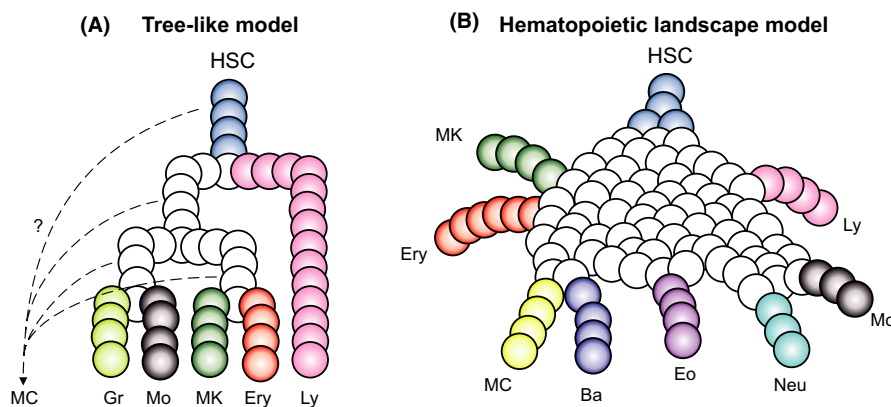


FIGURE 4 Models representing mast cell differentiation in hematopoiesis. (A) The tree-like model represents hematopoiesis as a strict series of branching events, in which cell lineage potential is lost at defined checkpoints along with differentiation from hematopoietic stem cells to lineage-committed cells. The position of the mast cell branch in this model is controversial. (B) The hematopoietic landscape model represents a continuum of single differentiating progenitors, in which there are multiple paths from hematopoietic stem cells to each lineage's entry point. Ba, basophil; Eo, eosinophil; Ery, erythrocyte; Gr, granulocyte (which commonly refers to basophils, eosinophils, and neutrophils), HSC, hematopoietic stem cell; Ly, lymphocyte; MC, mast cell; MK, megakaryocyte; Mo, monocyte; Neu, neutrophil

toward the MC fate, given that KIT signaling promotes MC differentiation.⁶⁷ This latter idea supports a close association between basophil and MC differentiation in health and explains the seemingly contradictory results in disease.

In summary, single-cell RNA sequencing has revolutionized our understanding of MC differentiation. The data reveal an overall landscape of hematopoiesis and an association between the MC, erythrocyte, and basophil granulocyte differentiation trajectories. The landscape model of hematopoiesis unifies old and new theories of the MC differentiation field and constitutes a foundation for future research.

1.2 | Mast cell heterogeneity—how different are they from each other?

MC heterogeneity was first described in the mid-60 s by differences in histochemical staining features, and the concept of connective tissue mast cells (CTMCs) and mucosal mast cells (MMCs) was born.^{68,69} In humans, different MC subpopulations have been defined by their protease content; those that express tryptase (MC_T), tryptase and chymase (MC_{TC}), and chymase only (MC_C).^{70,71} The latter was, for a long time, controversial, and the presence of chymase-only positive MCs has remained ignored and virtually unstudied. The two distinct MC subpopulations, MC_T and MC_{TC}, as well as the MMC and CTMC, differ in their localization, mediator content, and responsiveness to secretagogues.⁷²

Besides dividing MCs into subpopulations based on their localization or protease content, there are also definitions of MCs being either constitutive or inducible, inflammatory (iMC), or pro- or anti-tumorigenic (MC1 or MC2).^{35,73–75} While the division into constitutive and inducible subpopulations might be related to the prenatal origin of the MC (see above), the latter is probably dependent on changes in the microenvironment during an inflammation. It is clear that MCs in different organs differ in their receptor and mediator expression, but also within a single tissue there is a considerable heterogeneity, for example, among human lung MC_T.⁷⁶ Furthermore, the gene/protein expression within this MC_T subpopulation changes during inflammatory responses.^{75,77} A question to address is if these changes relate to different subtypes or a plasticity within the MC population.

The origin and development of different MC subpopulations have been enigmatic, but one clue was described recently as mentioned above.⁴⁵ For hematopoiesis in the adult, the question has been if there are several different MC progenitor populations in circulation, or if there is one progenitor population that has the capacity to differentiate and mature into any of the MC subtypes. In other words, is the heterogeneity driven by locally produced factors or is it driven by the recruitment of different types of designated progenitors? In a study where this question was addressed, the results suggested the existence of a common MC progenitor that gives rise to all MC subpopulations.⁷⁸ However, single-cell RNA sequencing and single-cell cultures will likely provide further proof and insights into this process.

The separation of MCs into different subpopulations based on their protease content or histochemical properties is rather simplistic. MCs show a great plasticity, and detailed analysis of protease expression in human lung MCs demonstrate a gradient in the expression of the different proteases in these cells. Transcriptome comparisons of MCs from different mouse tissues with other immune cells revealed that MCs form a distinct population well separated from all other immune cells.⁷⁹ Within the MC population, there was a substantial heterogeneity across tissue. Similarly, proteome analysis of human skin and fat MCs confirmed the unique identity of MCs among immune lineages, including the granulocytes (neutrophils, eosinophils, and basophils).⁸⁰ In this study, there were few differences in the proteome between skin and fat MCs, raising questions on the impact of the microenvironment for MC heterogeneity.⁸⁰ Analysis of single-cell RNA sequencing data of MCs from human tissues will further decipher MC heterogeneity and plasticity and might provide a clearer view about differences among MCs in different tissues, and also within the same tissue.

1.3 | Mechanisms behind directions that mast cells take during their life cycle

1.3.1 | Homing and migration

MC progenitors circulating in the blood, in humans defined as CD34⁺, KIT⁺, FcεRI⁺ cells,⁸¹ enter a specific tissue where they complete their maturation under the influence of locally produced factors. Surprisingly, the homing mechanisms for MC progenitors are still mostly unknown, except that it is a tissue-specific process.^{82–84} In addition to their basal homing, MC numbers clearly increase at sites of inflammation, such as in allergic rhinitis and asthma. This increase in MC numbers is likely a consequence of both increased proliferation, migration, and survival, as well as maturation of their progenitors recruited in response to chemoattractants.^{85,86} The fact that some chemokine receptors, such as CCR1, CXCR2, and CXCR4, are expressed on both progenitors and mature MCs suggests that MC accumulation at sites of inflammation may also involve relocation of mature MCs within a specific tissue.^{84–89}

1.3.2 | To migrate or to degranulate, that is the question

To avoid loss of their munitions before reaching their final destination at inflamed sites, mature MCs need to be regulated to migrate, but not yet degranulate⁹⁰ (Figure 5). This is a challenging requirement as some of the MC chemokines induce degranulation of basophils⁹¹ and synergize with secretagogues to potentiate MC degranulation.^{92,93} Thus, it was proposed that chemokines may either elicit distinct signals in MCs, as opposed to basophils or that MC SGs are linked to the cell cytoskeleton differently from the basophil granules.⁹⁰ Marked differences observed between

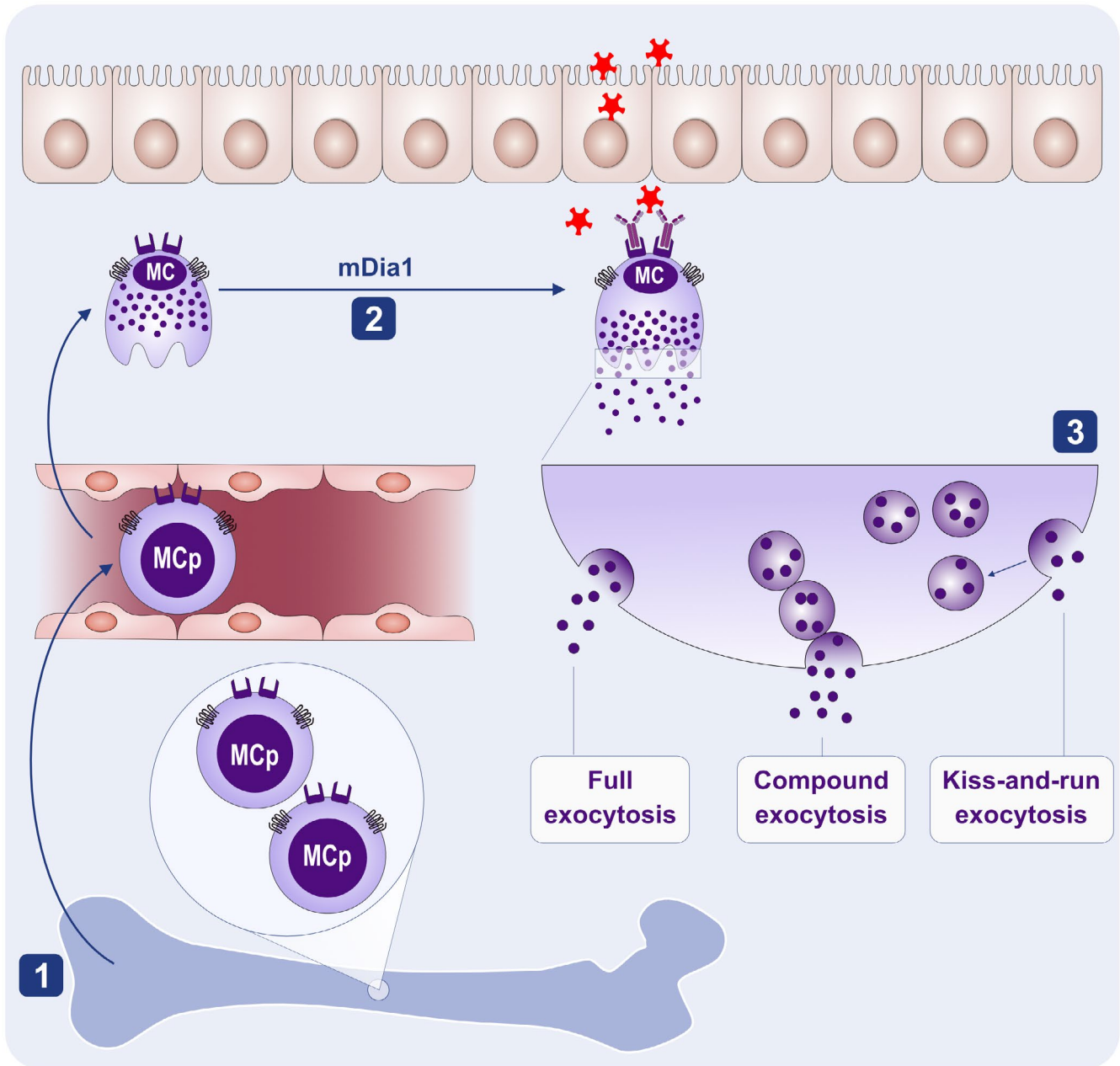


FIGURE 5 Fate decisions in the life of the mast cell. Mast cell progenitors (MCp) in the bone marrow (1) are entering the bloodstream and are recruited into the tissue (2). During this process, the cells have to avoid premature degranulation (2). In the tissue (3) MCs can degranulate in three possible modes, either by full exocytosis, compound exocytosis, or by kiss-and-run exocytosis

the actin skeleton in migrating *versus* secreting MCs support the latter possibility.⁹⁴ Analysis of actin rearrangements following chemokine stimulation of MCs revealed an accumulation of pericentral actin clusters that prevent cell flattening and converge the SGs in the cell center.⁹⁴ By contrast, reduction in the actin mesh density characterizes the secretory actin phenotype. Thus, the migratory actin phenotype immobilizes the secretory granules by trapping them in the cell center, whereas the secretory actin phenotype supports mobility and exocytosis. Diaphanous-related formin, mDia1, appears to be key player in these actin rearrangements⁹⁴ (Figure 5).

1.3.3 | Kiss-and-run, full or partial exocytosis? The next question is how to degranulate

As MCs reach their destination and encounter a secretagogue, the secretory actin phenotype overrides the migratory actin phenotype, relieving the secretory constraints.⁹⁴ MCs then enter a state in which they can undergo exocytosis (Figure 5). This can take place in three different ways: (i) individual SGs move to the plasma membrane where they dock and fuse with the membrane and release their full content; (ii) by compound exocytosis where SGs fuse with each other, forming a channel through which they release their content; or (iii) “kiss-and-run

exocytosis" where SGs only transiently fuse with the membrane and release only part of their content.⁹⁵ Choosing the mode of exocytosis bears physiological significance, as the distinct features and dynamics of the different exocytic modes are associated with unique physiological responses.⁹⁶ This notion was nicely illustrated in a recent study that investigated the MCs' response to innate stimulation (e.g., by the innate receptor MRGPRX2). Human MCs quickly mobilize discrete SGs toward the plasma membrane, resulting in very rapid secretion of individual SGs; by full or possibly also by kiss and run exocytosis.⁹⁶ By contrast, activation of MCs by antibody-dependent adaptive stimuli (e.g., IgE + Ag), resulted in the much slower exteriorization of groups of granules formed by the prior intracellular fusion of individual SGs, resulting in compound exocytosis.⁹⁶ Intriguingly, the distinct modes of exocytosis were linked with distinct physiological features. Thus, whereas the MRGPRX2-mediated trigger is brief and causes local inflammatory reactions, the IgE-stimulated reactions are more substantial and also lasted for a longer period of time.⁹⁶

Ultrastructural studies of MCs have implicated an additional mode of secretion, which is independent of SG exocytosis.⁹⁷ The latter, termed piecemeal degranulation (PMD), involves vesicle budding from the SGs and their transport and fusion with the plasma membrane. PMD has been associated mainly with MC activation under inflammatory conditions, including MC activation in pediatric cholelithiasis and biliary dyskinesia,⁹⁸ functional dyspepsia,⁹⁹ and cancer.¹⁰⁰ PMD could in principle lead to the selective release of some SG mediators, such as reported for secretion of serotonin without histamine from rat MCs.^{101,102} However, the precise mechanism of such mediator segregation awaits further investigation. At the molecular level, two factors have been identified as critical for defining the degranulation pattern. The first is the enzyme IKK β , whose activity is required for the phosphorylation of the SNARE protein SNAP23, which is essential for SG fusion during compound exocytosis.^{95,96,103} The second is the small GTPase Rab5, which plays a role in SG fusion during both their biogenesis¹⁰⁴ and compound exocytosis.¹⁰⁵ MCs may or may not release newly synthesized mediators, including lipid mediators, chemokines, and cytokines. Whether or not such release takes place is dependent on the stimulus type and may occur with or without prior release of preformed mediators.²⁰ Thus, unlike the regulation of degranulation that takes place at the level of the exocytic process, regulation of cytokine and chemokine release occurs at their transcriptional level, whereas secretion utilizes the constitutive secretory and endocytic pathways.¹⁰⁶ Mediators derived from arachidonic acid are immediately released, however, how precisely lipid mediators that are synthesized intracellularly are released is poorly understood.²⁰ Finally, MCs release exosomes, whose content is dictated by the type of trigger.¹⁰⁷

In conclusion, the underlying mechanisms that regulate MCs during their life cycle are only beginning to be clarified. They include mechanisms that ensure MC homing to destined tissues, recruitment to inflammatory areas, prevention of premature secretion, selection of the mode of exocytosis, and which lipid mediators, cytokines, or chemokines to synthesize *de novo*. Future studies will shed light on these mechanisms and the molecular entities involved.

TABLE 1 Classification of mast cell-mediated diseases^a

1. Primary (Intrinsic)
a. Mastocytosis
b. Monoclonal mast cell activation syndrome (MMAS)
c. Autosomal dominant vibratory urticaria (VU)
2. Secondary (Extrinsic)
a. Allergic disorders (FceRI mediated)
b. Mast cell activation through the high-affinity IgG receptor (CD64)
c. MRGPRX2-mediated reactions
d. Diseases associated with complement activation (C3a, C5a)
3. Idiopathic ^b
a. Anaphylaxis
b. Angioedema
c. Urticaria
d. Idiopathic mast cell activation syndrome (Idiopathic MCAS)

^aSee text for explanation. Table is conceptually based on Table 1 in reference¹⁰⁸ which classifies mast cell activation into primary or secondary. Here, focus is on human mast cell-associated diseases, examples only.

^bWhen no inciting stimulus is identified

1.4 | Mast cells in diseases

MCs are involved in the initiation and perpetuation of a number of inflammatory conditions. These conditions range from those associated with an intrinsic or primary defect in MCs due to inherited or acquired polymorphisms and mutations within the MC compartment; to diseases where MCs are activated and recruited through an extrinsic mechanism such as formation of antigen-dependent and IgE-mediated MC activation; to clinical conditions where MCs are implicated through the release of MC mediators but where the mechanism of activation and recruitment is not well understood, thus "idiopathic" (Table 1).¹⁰⁸

There are several well-characterized molecular aberrancies affecting the MC compartment. Some are associated with recognized clinical diseases due to effects on MC proliferation and survival, MC reactivity, or MC mediator production. Mastocytosis is perhaps the most widely known disease associated with a primary defect in the MC compartment. It is a clonal disease involving expansion of tissue MCs. Mastocytosis is most commonly associated with an acquired gain-of-function *KIT* p.D816V missense variant, resulting in ligand-independent MC activation. This leads to both unrestrained growth of MCs and a lowered threshold for activation. Individuals with mastocytosis may present with flushing, pruritus, gastrointestinal complaints, or systemic anaphylaxis that may occur following exposure to Hymenoptera venom or for unidentified reasons. Mastocytosis may present as cutaneous disease only, or as a systemic disease with or without cutaneous manifestations.¹⁰⁹

A group of patients with recurrent anaphylaxis has clonal MCs as demonstrated by evidence of one or two minor criteria for mastocytosis including aberrant MC morphology, CD25 expression, and/or presence of the *KIT* D816V point mutation. By consensus, such

patients are currently said to have monoclonal MC activation syndrome (MMAS).¹¹⁰ If the marrow findings are observed in the absence of evidence of systemic MC activation, the term monoclonal MC disorder of uncertain significance has been suggested.

There are now a growing number of heritable genetic conditions that lead to increased MC reactivity. One such example is manifested as a physical urticaria. A missense substitution from cysteine to tyrosine (pC492Y) in the adhesion G protein-coupled receptor E2 (ADGRE2) is present in autosomal dominant vibratory urticaria (VU) characterized by localized hives and systemic manifestations in response to a local stimulus of frictional nature.¹¹¹ ADGRE2 (CD312) belongs to a large family of adhesion GPCRs, generally with an extracellular domain facilitating interactions with proteins from the extracellular matrix. In this case, activation of MCs after a vibratory stimulus is evidenced by MC degranulation and an increase in histamine in the venous blood from the affected areas. Thus, ADGRE2 functions as a mechanoreceptor and induces cutaneous MC degranulation. Although the physiological relevance of the limited MC responses to friction in normal individuals is not completely understood, possibilities are that ADGRE2 may alert both resident and immune cells to combat potential injury and wound healing. It may also play a role in pain modulation and perhaps help sense a parasite migrating through dermal tissues.

Hereditary alpha tryptasemia (H α T) is a term used to describe a genetic trait caused by an increased TPSAB1 copy number encoding alpha-tryptase that leads to elevated basal serum tryptase levels in 4–6% of Western populations.^{112,113} Individuals with multiple duplications of alpha-tryptase are reported to have a higher risk for severe anaphylaxis. Further, the prevalence of H α T in clonal MC disease is twice that of the general population and may be a biomarker for severe mediator-related symptoms in those with mastocytosis.^{114,115} Recent mechanistic studies have demonstrated that unique enzymatic properties of alpha-tryptase containing heterotetrameric tryptases may contribute to this association.¹¹⁶ At present, H α T is thus best thought of as a disease-modifying genetic finding.

Extrinsic or secondary MC activation occurs primarily in allergic diseases, diseases associated with complement activation, and in association with activation of MCs through MRGPRX2. Symptoms may be infrequent to frequent and resultant disease sporadic or chronic depending on the activating mechanism. The immediate effects of MC degranulation, if localized to skin, include a wheal and flare reaction or, in airways, contraction of airway smooth muscle, mucus secretion, and an increase in vascular permeability. If systemic, the results may include severe hypotension and extensive vascular leakage. The early responses often transition into a late phase reaction hours later associated with an influx of circulating cell types which promote further inflammation.

The idiopathic MC category includes urticaria, angioedema, and anaphylaxis where there is no identifiable etiology, but where MC activation is documented through MC mediator release or evidence of MC degranulation in tissues involved (Table 1). The term idiopathic MC activation syndrome (Idiopathic MCAS) has been applied as a diagnosis for individuals who present with such episodic

allergic-like signs and symptoms such as flushing, urticaria, diarrhea, and wheezing involving two or more organ systems, where the etiology is unknown.¹¹⁷ Diagnostic criteria include response to anti-mediator therapy and an elevation in a validated urinary or serum marker of MC activation, such as serum tryptase with an episode. Primary and secondary MC disorders must be eliminated as possible causes of the clinical findings. However, the search should continue for the etiology of these idiopathic disorders including the possibility that MC activation may relate to a yet-to-be-identified endogenous or environmental stimulus or an intrinsic MC defect resulting in a hyperactive MC phenotype.

1.5 | The development of mast cell-targeted treatments

1.5.1 | Mast cell mediators as targets of treatment

MC-targeted treatments are primarily developed for chronic urticaria (CU), mastocytosis, and allergies, because of the critical role that MCs play in their pathogenesis.^{118,119} The evolution of MC-targeted treatments started, more than 70 years ago, with the development of drugs that inhibit the effects of individual MC mediators, first histamine, followed by prostaglandins and leukotrienes.¹²⁰ Modern antihistamines that act on the histamine 1 receptor are superior to first-generation ones in their binding affinity, specificity, and risk/benefit profiles. Antihistamines that act on the histamine 4 receptor have shown promising results, and several such compounds are currently being developed for the treatment of MC-driven diseases.¹²¹ Recently a new approach to inhibit tryptase, the major MC protease, with an anti-tryptase antibody was tested in preclinical primate studies.¹²² The therapeutic area is initially severe asthma where MCs are implicated.¹²³

However, to target one MC mediator or one of its receptors comes with an inherent limitation, that is, it prevents only the effects of one MC mediator or receptor. Activated MCs release many different mediators (acting on even more receptors) that are held to contribute to the development of signs and symptoms in patients with urticaria, mastocytosis, and other MC-mediated diseases.

1.5.2 | Treatments that inhibit mast cell activation

More recent attempts to target MCs therapeutically aim at the inhibition of activating signals and receptors (Figure 6). These include, for example, the high-affinity receptor for IgE, Fc ϵ RI, as well as the intracellular signals involved in translating receptor activation into degranulation and mediator release. Examples for the latter include Bruton's tyrosine kinase (BTK) and spleen-associated tyrosine kinase (SYK) (Figure 7). Inhibitors of BTK or SYK inhibit the degranulation of human MCs induced via Fc ϵ RI. Two BTK inhibitors, Fenebrutinib and Remibrutinib, as well as the SYK inhibitor GSK2646264, are currently under development for the treatment of patients with CU (Figure 7).

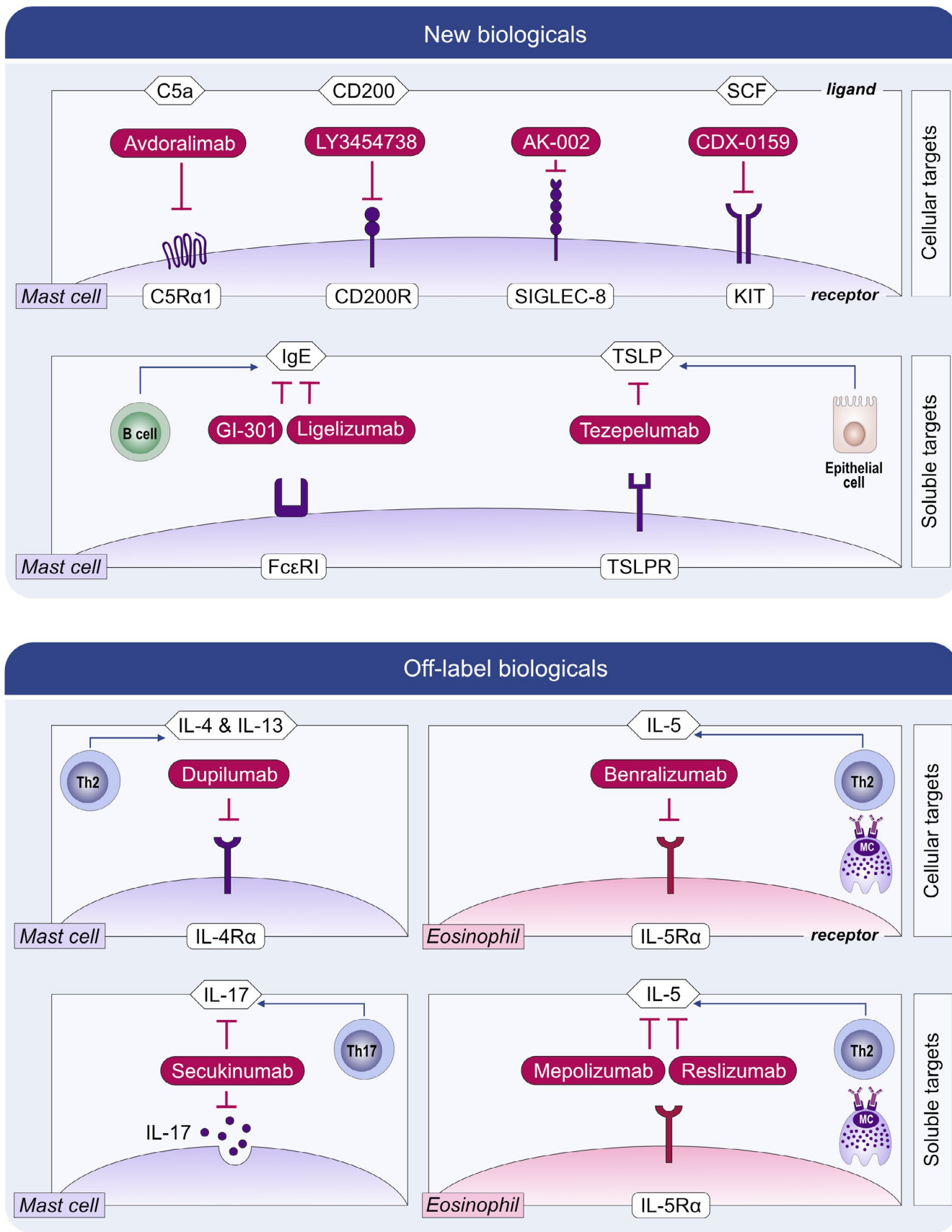


FIGURE 6 MC-targeted treatments under development. Examples of treatments currently under development that target mast cell mediators, receptors, or their signaling molecules

In chronic spontaneous urticaria (CSU), the activation of skin MCs via FcεRI, either by IgE to autoallergens or by autoantibodies to its alpha chain, is held to drive the development of signs and symptoms, itchy wheals and angioedema, in most patients.^{124–126} Treatment with omalizumab, an anti-IgE antibody, is effective in CSU¹²⁷ and prevents MC activation by reducing the levels of free IgE and FcεRI expression. Newer anti-IgEs, including ligelizumab and GI-301, with higher affinity to IgE than omalizumab, are in clinical development.¹²⁸

Several other activating signals and receptors are held to contribute to the activation and degranulation of MCs and, thereby, to the development of signs and symptoms of MC-driven diseases. These include the receptors for thymic stromal lymphopoietin (TSLP), IL-33, IL-4, IL-13, IL-5, and complement C5a as well as MRGPRX2. For all of these receptors, inhibitory compounds (or compounds that inhibit their ligands) are currently in clinical development for MC-driven diseases, primarily CU.¹²⁹

The benefit of targeting MC-activating signals, receptors, and pathways is that this approach protects from the release and, therefore, the effects of all MC mediators rather than only one. The limitation is that only one of many pathways of MC activation and degranulation is shut down. Other pathways are untouched, remain viable, and can lead to MC activation, as they often do in most MC-driven diseases.

1.5.3 | Treatments that silence mast cells

MCs express several inhibitory receptors.¹³⁰ Their ligand engagement inhibits MC activation and degranulation, thereby silencing MCs. Inhibitory MC receptors, including Siglec-8 and CD200Ra, and therapeutic antibodies that engage them are currently under development for CU (Figure 6). The Siglec-8-targeted antibody AK002 inhibits MC activation (and depletes eosinophils) and showed promising results in the treatment of omalizumab-naïve and omalizumab-refractory CSU, symptomatic dermatographism, cholinergic urticaria, and systemic mastocytosis. Several endogenous ligands for Siglec-8 have been identified. Siglec-8 preferentially binds the sialoside glycans 6'-sulfo-sialyl-Lewis X and 6'-sulfo-sialyl-N-acetyl-D-lactosamine. However, it is currently unknown how relevant they are for

the inhibition of MCs *in vivo*.^{131,132} The CD200Ra-targeted antibody LY3454738 is also under development for CU (Figure 6).

1.5.4 | Treatments that reduce mast cell numbers

The KIT receptor is the key driver of MC differentiation, migration, proliferation, and survival. The inhibition of KIT or SCF leads to MC apoptosis and reduced MC numbers. Compounds that target KIT or SCF are currently explored for the clinical development in MC-driven diseases including CU and mastocytosis.¹³³ For example, the antibody CDX-0159, which specifically binds the extracellular dimerization domain of KIT, was shown to induce profound and sustained suppression of plasma tryptase, indicative of systemic MC ablation (Figure 6). CDX-0159 is currently under development for CU. Examples for the development of oral KIT-targeted treatments include Imatinib, Nilotinib, Midostaurin, and Avapritinib (Figure 7), all of which show efficacy in mastocytosis linked to reductions in MCs and/or serum tryptase levels. To note, Imatinib and Nilotinib inhibit wild type KIT, but do not affect D816V-mutated KIT, and thus can only be used for D816V negative cases of mastocytosis. In addition, there are a number of potential targets, apart from KIT, that in experimental models have been shown to regulate MC numbers and activity.^{109,133,134}

1.6 | Animal models to study mast cell function

Numerous types of animal models, primarily in the mouse, have been utilized throughout the years to outline the contribution of MCs in diverse pathological settings. In the first generation of such models, MC deficiency in the mouse and rat was due to various mutations in *Kit*, that is, the receptor for SCF. Since SCF is an essential growth factor for MCs, defects in *Kit* result in an essentially complete absence of MCs. However, KIT is also expressed by a number of other cell types, and it has, therefore, been challenging to ascertain that consequences of *Kit* defects are indeed explained by an impact on the MC niche as opposed to off-target effects on other populations (reviewed in^{135,136}). To account for these issues, new mouse models of MC-deficiency, independent of *Kit*, have been developed (Table 2). These include mice where MC deficiency is driven by Cre

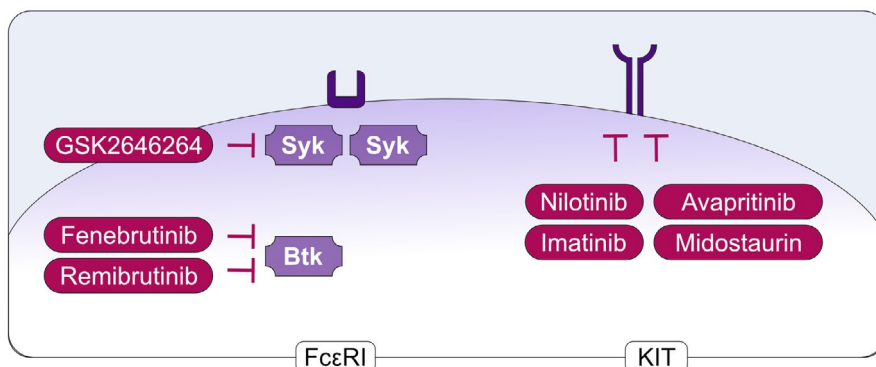


FIGURE 7 Intracellular targets to inhibit MC-activating receptors FcεRI and KIT. Small molecular inhibitors that target Syk or BTK downstream of FcεRI inhibit the downstream signaling. The KIT-inhibitors target the kinase activity of the receptor. Imatinib and Nilotinib target only wild-type KIT, while Midostaurin and Avapritinib also target D816V-mutated KIT that is commonly found in systemic mastocytosis

recombinase expression under the control of MC-specific promoters. In one strategy, Cre recombinase was driven by the promoter for *Mcpt5*, a gene specifically expressed by CTMCs. These mice can then be crossed with *R26^{DTA}* mice, leading to constitutive MC deficiency due to MC-specific expression of diphtheria toxin (DT).¹³⁷ Alternatively, the mice can be crossed with the *iDTR* line, leading to MC-specific expression of the DT receptor; treatment of these mice with DT will thus lead to conditional depletion of MCs.¹³⁷ In another approach, MC deficiency was accomplished by inserting Cre under the control of the promoter for *Cpa3*, a gene expressed predominantly by MCs.¹³⁸ This leads to constitutive MC depletion, apparently due to Cre-mediated genotoxicity, but also to a substantial reduction of basophils, the latter in agreement with studies showing that basophils express low levels of *Cpa3*. The *Cpa3* promoter was also exploited to generate a mouse strain in which the Cre-LoxP recombination system was used for deletion of the gene coding for the anti-apoptotic factor *Mcl-1*. This led to an essentially complete absence of MCs but also to a major reduction in basophils.¹³⁹ MC depletion has also been accomplished in a model where the DT receptor gene was expressed under the control of an MC-specific IL-4 enhancer element.¹⁴⁰ Another strategy was to insert the DT receptor and bright red td-Tomato fluorescent protein genes into the gene coding for the β chain of *Fc ϵ RI*, which is expressed by basophils and MCs. This approach can be used for the depletion of MCs and basophils and also as an elegant tool to visualize MCs/basophils in vivo.¹⁴¹ More recently, a mouse line with reduced numbers of MMCs (CTMCs were not affected) was generated by expressing Cre under the control of the baboon- α -chymase gene and crossing these to mice with a floxed allele of *Mcl-1*.¹⁴²

By using these *Kit*-independent models of MC deficiency, important insight into the biological function of MCs has been obtained. As expected, the use of *Kit*-independent mouse models for MC deficiency has firmly confirmed the essential role of MCs in allergic responses.^{138,143} Moreover, recent studies have shown that MCs can have a role in melanoma dissemination,¹⁴⁴ cutaneous lymphoma,¹⁴⁵ collagen-induced arthritis,¹⁴⁶ bone fracture-associated inflammation,¹⁴⁷ and bone healing.¹⁴⁸ It was also demonstrated that MCs aggravate osteoarthritis¹⁴⁹ and can mediate the detrimental impact of smoke components on asthmatic features.¹⁵⁰ Further, it has been demonstrated that MCs have a beneficial role in controlling bacterial clearance and promoting wound healing after *Pseudomonas aeruginosa* infection,¹⁵¹ whereas a detrimental impact of MCs was seen in skin infection by *Sporothrix schenckii*.¹⁵²

However, it is important to note that the use of these novel mouse models for MC deficiency has challenged some previous findings where a contribution of MCs in various pathologies has been implied. For example, recent findings based on *Kit*-independent mouse models for MC deficiency have questioned the role of MCs in certain models for autoimmune diseases¹³⁸ and obesity,¹⁵³ as well as the proposed adjuvant activities of MCs.¹⁴⁶ Hence, a more nuanced view of how MCs are involved in pathological settings is currently emerging.

In addition to the various mouse models described above, recent efforts have resulted in the generation of mice in which the MC niche is populated by human MCs. This was accomplished by transplanting human hematopoietic stem cells into NOD-scid IL2R- $\gamma^{-/-}$ mice, and then promoting MC growth by administering

TABLE 2 KIT-independent constitutive and inducible mouse models of MC deficiency

Model, designation	Principle	Type of MC affected	Basophils affected	Ref
Constitutive				
Mcpt5-Cre; R-DTA	Cre expression under the control of the <i>Mcpt5</i> promoter; Cre-driven expression of DT	CTMCs	No	137
<i>Cpa3</i> ^{Cre+} ("Cre-Master")	Cre expression under the control of the <i>Cpa3</i> promoter	CTMCs + MMCs	Yes (~60% reduction)	138
<i>Cpa3</i> -Cre; <i>Mcl-1</i> ^{fl/fl} ("Hello Kitty")	<i>Mcl-1</i> deletion under the control of the <i>Cpa3</i> promoter	CTMCs + MMCs	Yes (~60–80% reduction)	139
<i>Chm</i> -Cre; <i>Mcl-1</i> ^{fl/fl}	<i>Mcl-1</i> deletion under the control of the baboon- α -chymase gene	MMCs reduced; CTMCs normal	Not determined	142
Inducible				
Mas-TRECK	DT receptor expressed under the control of an MC-specific IL-4 enhancer element	CTMCs; MMCs not determined	Transient depletion; recovery of basophil populations 12 days after DT administration	140
Mcpt5-Cre; <i>iDTR</i>	DT receptor expressed under the control of the <i>Mcpt5</i> promoter	CTMCs	No	137
Red mast cell and basophil (RMB) mouse	DT receptor and bright red td-Tomato fluorescent protein expressed under the control the β chain of <i>FcϵRI</i> (<i>Ms4a2</i>)	CTMCs; MMCs not determined	Transient depletion; recovery of basophil populations 12 days after DT administration	141

Abbreviations: CTMC, Connective tissue-type MC; DT, Diphtheria toxin; MMC, Mucosal-type MC.

plasmids expressing human SCF, GM-CSF, and IL-3. In these mice (denoted "humice" or NSG-SGM3), mature human MCs (co-expressing KIT and FcεRI) were detected in multiple tissues. These "humice" have so far mainly been used to study the role of MCs in anaphylaxis and cutaneous drug reactions,¹⁵⁴⁻¹⁵⁶ but also in the evaluation of new therapies, for example, using a BTK inhibitor.¹⁵⁷ Moreover, functional human MCs could be developed from the bone marrow of these mice. Clearly, this humanized model has the potential to be used as a highly valuable tool to study human MC function. Another approach for studying the function of MCs is to evaluate mice deficient in various MC mediators, including the MC-restricted proteases, serglycin, and histamine (reviewed in^{16,123,158}).

2 | CONCLUSION

MC biology and their function in health and disease have been a fascinating subject for many researchers over the years. Many seminal findings have been made since the discovery of MCs in the late 19th century (some of them given in Box 1), shedding light on the function of this ingenious cell. Nevertheless, there are many fundamental questions that still are awaiting an answer (some listed in Box 2). With the rapid developments in methodology, systems biology, etc., in combination with more relevant animal models, experimental human studies, and clinical investigations, we can foresee a rapid development in MC research in the coming years that will not only give insights about their biology but also a better understanding on their role in different diseases.

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CONFLICT OF INTEREST

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BOX 1 Major milestone discoveries in the field of mast cell biology

- 1863 Friedrich von Recklinghausen identify granulated cells in unstained connective tissues from different species.
- 1878 Identification and description of MCs by Paul Ehrlich¹⁵⁹
- 1937 Heparin is present in MCs^{160,161}
- 1949 Description of systemic mastocytosis¹⁶²
- 1953 MCs contain histamine¹⁶³
- 1956 Demonstration of the involvement of MCs in anaphylaxis¹⁶⁴
- 1966 Description of MC heterogeneity, that is, mucosal MCs and connective tissue MCs^{68,69}
- 1966 & 1967 Identification and characterization of IgE¹⁶⁵⁻¹⁶⁷
- 1970 & 1972 Slow reacting substance of anaphylaxis (SRS-A), later shown to be leukotrienes, was demonstrated to be released after IgE-receptor activation^{168,169}
- 1977 MCs develop from bone marrow cells⁴⁶
- 1981 Identification of tryptase as the predominant MC protease^{170,171}
- 1982 Prostaglandin D₂ shown to be released from MCs¹⁷²
- 1987 MCs can express and secrete cytokines^{173,174}
- 1989 Characterization of the high-affinity IgE-receptor^{175,176}
- 1989 The central nervous system affects MC reactivity¹⁷⁷
- 1990 Identification, cloning, and characterization of SCF¹⁷⁸
- 1992 Demonstration that SCF is the main growth and maturation factor for human MCs^{67,179-181}
- 1995 Identification of the D816V KIT mutation in systemic mastocytosis¹⁸²
- 2004 & 2006 MC proteases detoxify endogenous peptides and venoms^{183,184}
- 2015 Identification of MRGPRX2 as a receptor causing pseudoallergic reactions³
- 2018 Insight into the prenatal development of MCs^{43,44}

REFERENCES

1. Dahlin JS, Ekoff M, Grootens J, et al. KIT signaling is dispensable for human mast cell progenitor development. *Blood*. 2017;130(16):1785-1794.
2. Olivera A, Beaven MA, Metcalfe DD. Mast cells signal their importance in health and disease. *J Allergy Clin Immunol*. 2018;142(2):381-393.
3. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519(7542):237-241.
4. Elst J, Sabato V, Faber MA, et al. MRGPRX2 and immediate drug hypersensitivity: insights from cultured human mast cells. *J Invest Allergol Clin Immunol*. 2020; 31: Online ahead of print.

BOX 2 Future research perspectives

- To determine if MCs from different hematopoietic waves exhibit distinct functions.
 - To determine the developmental relationship between the MC trajectory and other myeloerythroid lineages. Is it consistent in health and disease?
 - To identify mechanisms behind an increase in MCs at a site of inflammation: local proliferation, survival, and/or progenitor recruitment to the site of inflammation? What chemotactic factors drive MC progenitor recruitment in vivo?
 - To get a better understanding of MC heterogeneity in different tissues and to define the mechanisms that regulate MC plasticity.
 - To understand the mechanisms for differential release of MC mediators.
 - To decipher the contribution of MCs and their mediators in diseases beyond primary MC diseases and allergy.
 - To understand mast cell activation syndrome (MCAS). What are the mechanisms? How can it be diagnosed and treated?
 - Development of drugs that selectively target MCs.
 - Development of new KIT-independent MC deficient models (mouse, but also other species such as rat, ferret, and guinea pig that might be better for specific diseases), in which MC functions and contributions to health and disease can be specifically investigated.
5. Subramanian H, Gupta K, Ali H. Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. *J Allergy Clin Immunol*. 2016;138(3):700-710.
 6. Kühn K, Kolkhir P, Babina M, et al. Mas-related G protein-coupled receptor X2 and its activators in dermatological allergies. *J Allergy Clin Immunol*. 2021;147:456-469.
 7. Green DP, Limjunyawong N, Gour N, Pundir P, Dong X. A mast-cell-specific receptor mediates neurogenic inflammation and pain. *Neuron*. 2019;101(3):412-420.
 8. Meixiong J, Anderson M, Limjunyawong N, et al. Activation of mast-cell-expressed mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity*. 2019;50(5):1163-1171.
 9. Dondalska A, Ronnberg E, Ma H, et al. Amelioration of compound 48/80-mediated itch and LL-37-induced inflammation by a single-stranded oligonucleotide. *Front Immunol*. 2020;11:559589.
 10. Serhan N, Basso L, Sibilano R, et al. House dust mites activate nociceptor-mast cell clusters to drive type 2 skin inflammation. *Nat Immunol*. 2019;20(11):1435-1443.
 11. Lunderius-Andersson C, Enoksson M, Nilsson G. Mast cells respond to cell injury through the recognition of IL-33. *Front Immunol*. 2012;3:120-130.
 12. Ohno T, Morita H, Arae K, Matsumoto K, Nakae S. Interleukin-33 in allergy. *Allergy*. 2012;67(10):1203-1214.
 13. Babina M, Wang Z, Franke K, Guhl S, Artuc M, Zuberbier T. Yin-yang of IL-33 in human skin mast cells: reduced degranulation, but

- augmented histamine synthesis through p38 activation. *J Invest Dermatol*. 2019;139(7):1516-1525.
14. Ronnberg E, Ghaib A, Ceriol C, et al. Divergent effects of acute and prolonged interleukin 33 exposure on mast cell IgE-mediated functions. *Front Immunol*. 2019;10:1361.
 15. Marshall JS, Portales-Cervantes L, Leong E. Mast cell responses to viruses and pathogen products. *Int J Mol Sci*. 2019;20(17):4241.
 16. Wernersson S, Pejler G. Mast cell secretory granules: armed for battle. *Nat Rev Immunol*. 2014;14(7):478-494.
 17. Boyce JA. Mast cells and eicosanoid mediators: a system of reciprocal paracrine and autocrine regulation. *Immunol Rev*. 2007;217:168-185.
 18. Kulinski JM, Munoz-Cano R, Olivera A. Sphingosine-1-phosphate and other lipid mediators generated by mast cells as critical players in allergy and mast cell function. *Eur J Pharmacol*. 2016;778:56-67.
 19. Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol Rev*. 2018;282(1):121-150.
 20. Moon TC, Befus AD, Kulka M. Mast cell mediators: their differential release and the secretory pathways involved. *Front Immunol*. 2014;5:569.
 21. Enoksson M, Lyberg K, Moller-Westerberg C, Fallon PG, Nilsson G, Lunderius-Andersson C. Mast cells as sensors of cell injury through IL-33 recognition. *J Immunol*. 2011;186(4):2523-2528.
 22. Pan D, Buchheit KM, Samuchiwal SK, et al. COX-1 mediates IL-33-induced extracellular signal-regulated kinase activation in mast cells: Implications for aspirin sensitivity. *J Allergy Clin Immunol*. 2019;143(3):1047-1057.
 23. Fischer M, Harvima IT, Carvalho RFS, et al. Mast cell CD30 ligand is up-regulated in cutaneous inflammation and mediates degranulation-independent chemokine secretion. *J Clin Invest*. 2006;116:2748-2756.
 24. Al-Afif A, Alyazidi R, Oldford SA, et al. Respiratory syncytial virus infection of primary human mast cells induces the selective production of type I interferons, CXCL10, and CCL4. *J Allergy Clin Immunol*. 2015;136(5):1346-1354.
 25. Theoharides TC, Kempuraj D, Tagen M, Conti P, Kalogeromitros D. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol Rev*. 2007;217:65-78.
 26. Toyoshima S, Sakamoto-Sasaki T, Kurosawa Y, et al. miR103a-3p in extracellular vesicles from FcepsilonRI-aggregated human mast cells enhances IL-5 production by group 2 innate lymphoid cells. *J Allergy Clin Immunol*. 2021;147(5):1878-1891.
 27. Skokos D, Le Panse S, Villa I, et al. Mast cell-dependent B and T lymphocyte activation is mediated by the secretion of immunologically active exosomes. *J Immunol*. 2001;166(2):868-876.
 28. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007;9(6):654-659.
 29. Lecce M, Molfetta R, Milito ND, Santoni A, Paolini R. FcepsilonRI signaling in the modulation of allergic response: role of mast cell-derived exosomes. *Int J Mol Sci*. 2020;21(15):5464.
 30. Kim DK, Cho YE, Komarow HD, et al. Mastocytosis-derived extracellular vesicles exhibit a mast cell signature, transfer KIT to stellate cells, and promote their activation. *Proc Natl Acad Sci USA*. 2018;115(45):E10692-E10701.
 31. Siebenhaar F, Redegeld FA, Bischoff SC, Gibbs BF, Maurer M. Mast cells as drivers of disease and therapeutic targets. *Trends Immunol*. 2018;39(2):151-162.
 32. Wilcock A, Bahri R, Bulfone-Paus S, Arkwright PD. Mast cell disorders: From infancy to maturity. *Allergy*. 2019;74(1):53-63.
 33. Galli SJ, Gaudenzio N, Tsai M. Mast cells in inflammation and disease: recent progress and ongoing concerns. *Annu Rev Immunol*. 2020;38:49-77.

34. Varricchi G, Marone G, Kovanen PT. Cardiac mast cells: underappreciated immune cells in cardiovascular homeostasis and disease. *Trends Immunol.* 2020;41(8):734-746.
35. Varricchi G, de Paulis A, Marone G, Galli SJ. Future Needs in Mast Cell Biology. *Int J Mol Sci.* 2019;20(18):4397.
36. Virk H, Arthur G, Bradding P. Mast cells and their activation in lung disease. *Transl Res.* 2016;174:60-76.
37. Piliponsky AM, Acharya M, Shubin NJ. Mast cells in viral, bacterial, and fungal infection immunity. *Int J Mol Sci.* 2019;20(12):2851.
38. Jiao Q, Luo Y, Scheffel J, Zhao Z, Maurer M. The complex role of mast cells in fungal infections. *Exp Dermatol.* 2019;28(7):749-755.
39. Rathore AP, St John AL. Protective and pathogenic roles for mast cells during viral infections. *Curr Opin Immunol.* 2020;66:74-81.
40. Nathan C. Points of control in inflammation. *Nature.* 2002;420:846-852.
41. Dudeck A, Koberle M, Goldmann O, et al. Mast cells as protectors of health. *J Allergy Clin Immunol.* 2019;144(4S):S4-S18.
42. Sonoda T, Hayashi C, Kitamura Y. Presence of mast cell precursors in the yolk sac of mice. *Dev Biol.* 1983;97(1):89-94.
43. Li Z, Liu S, Xu J, et al. Adult connective tissue-resident mast cells originate from late erythro-myeloid progenitors. *Immunity.* 2018;49(4):640-653.
44. Gentek R, Ghigo C, Hoeffel G, et al. Hemogenic Endothelial fate mapping reveals dual developmental origin of mast cells. *Immunity.* 2018;48(6):1160-1171.
45. Nilsson G, Dahlin JS. New insights into the origin of mast cells. *Allergy.* 2019;74(4):844-845.
46. Kitamura Y, Shimada M, Hatanaka K, Miyano Y. Development of mast cells from grafted bone marrow cells in irradiated mice. *Nature.* 1977;268(5619):442-443.
47. Weitzmann A, Naumann R, Dudeck A, Zerjatke T, Gerbaulet A, Roers A. Mast cells occupy stable clonal territories in adult steady-state skin. *J Invest Dermatol.* 2020;140(12):2433-2441.
48. 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(7):2333-2342.
49. Arinobu Y, Iwasaki H, Gurish MF, et al. Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. *Proc Natl Acad Sci USA.* 2005;102(50):18105-18110.
50. Franco CB, Chen CC, Drukker M, Weissman IL, Galli SJ. Distinguishing mast cell and granulocyte differentiation at the single-cell level. *Cell Stem Cell.* 2010;6(4):361-368.
51. Tusi BK, Wolock SL, Weinreb C, et al. Population snapshots predict early haematopoietic and erythroid hierarchies. *Nature.* 2018;555(7694):54-60.
52. Ahmed N, Kunz L, Hoppe PS, et al. A Novel GATA2 protein reporter mouse reveals hematopoietic progenitor cell types. *Stem Cell Reports.* 2020;15(2):326-339.
53. Inclan-Rico JM, Hernandez CM, Henry EK, et al. Trichinella spiralis-induced mastocytosis and erythropoiesis are simultaneously supported by a bipotent mast cell/erythrocyte precursor cell. *PLoS Pathog.* 2020;16(5):e1008579.
54. Chen CC, Grimbaldston MA, Tsai M, Weissman IL, Galli SJ. Identification of mast cell progenitors in adult mice. *Proc Natl Acad Sci USA.* 2005;102(32):11408-11413.
55. Motakis E, Guhl S, Ishizu Y, et al. Redefinition of the human mast cell transcriptome by deep-CAGE sequencing. *Blood.* 2014;123(17):e58-e67.
56. Grootens J, Ungerstedt JS, Nilsson G, Dahlin JS. Deciphering the differentiation trajectory from hematopoietic stem cells to mast cells. *Blood Adv.* 2018;2(17):2273-2281.
57. Laurenti E, Gottgens B. From haematopoietic stem cells to complex differentiation landscapes. *Nature* 2018;553(7689):418-426.
58. Dahlin JS, Hamey FK, Pijuan-Sala B, et al. A single-cell hematopoietic landscape resolves 8 lineage trajectories and defects in Kit mutant mice. *Blood.* 2018;131(21):e1-e11.
59. Hamey FK, Lau WWY, Kucinski I, et al. Single-cell molecular profiling provides a high-resolution map of basophil and mast cell development. *Allergy.* 2021;76(6):1731-1742.
60. Qi X, Hong J, Chaves L, et al. Antagonistic regulation by the transcription factors C/EBPalpha and MITF specifies basophil and mast cell fates. *Immunity.* 2013;39(1):97-110.
61. Weinreb C, Rodriguez-Fraticelli A, Camargo FD, Klein AM. Lineage tracing on transcriptional landscapes links state to fate during differentiation. *Science* 2020;367(6479):eaaw3381.
62. Grootens J, Ungerstedt JS, Wu C, Hamberg Levedahl K, Nilsson G, Dahlin JS. CD203c distinguishes the erythroid and mast cell-basophil differentiation trajectories among human FcepsilonRI(+) bone marrow progenitors. *Allergy.* 2020;75(1):211-214.
63. Drissen R, Thongjuea S, Theilgaard-Monch K, Nerlov C. Identification of two distinct pathways of human myelopoiesis. *Sci Immunol.* 2019;4(35):eaau7148.
64. Bian Z, Gong Y, Huang T, et al. Deciphering human macrophage development at single-cell resolution. *Nature.* 2020;582(7813):571-576.
65. Popescu DM, Botting RA, Stephenson E, et al. Decoding human fetal liver haematopoiesis. *Nature.* 2019;574(7778):365-371.
66. Kocabas CN, Yavuz AS, Lipsky PE, Metcalfe DD, Akin C. Analysis of the lineage relationship between mast cells and basophils using the c-kit D816V mutation as a biologic signature. *J Allergy Clin Immunol.* 2005;115(6):1155-1161.
67. Irani AA, Nilsson G, Miettinen U, et al. Recombinant human stem cell factor stimulates differentiation of mast cells from dispersed human fetal liver cells. *Blood.* 1992;80(3009):3009-3021.
68. Enerbäck L. Mast cells in rat gastrointestinal mucosa. i. effects of fixation. *Acta Pathol Microbiol Scand.* 1966;66:289-302.
69. Enerbäck L. Mast cells in rat gastrointestinal mucosa. II. Dye-binding and metachromatic properties. *Acta Pathol Microbiol Scand.* 1966;66:302-312.
70. Irani AA, Schechter NM, Craig SS, DeBlois G, Schwartz LB. Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci USA.* 1986;83(4464):4464-4468.
71. Weidner N, Austen KF. Ultrastructural and Immunohistochemical Characterization Of Normal Mast Cells At Multiple Body Sites. *J Invest Dermatol.* 1991;96(3):S26-S31.
72. Lowman MA, Rees PH, Benyon RC, Church MK. Human mast cell heterogeneity: Histamine release from mast cells dispersed from skin, lung adenoids, tonsils, and colon in response to IgE-dependent and nonimmunologic stimuli. *J Allergy Clin Immunol.* 1988;81(590):590-597.
73. Bankova LG, Dwyer DF, Liu AY, Austen KF, Gurish MF. Maturation of mast cell progenitors to mucosal mast cells during allergic pulmonary inflammation in mice. *Mucosal Immunol.* 2015;8(3):596-606.
74. Derakhshan T, Samuchiwal SK, Hallen N, et al. Lineage-specific regulation of inducible and constitutive mast cells in allergic airway inflammation. *J Exp Med.* 2021;218(1):e20200321.
75. Dwyer DF, Ordovas-Montanes J, Allon SJ, et al. Human airway mast cells proliferate and acquire distinct inflammation-driven phenotypes during type 2 inflammation. *Sci Immunol.* 2021;6(56):eabb7221.
76. Andersson CK, Mori M, Bjermer L, Lofdahl CG, Erjefalt JS. Novel site-specific mast cell subpopulations in the human lung. *Thorax.* 2009;64:297-305.
77. Andersson CK, Mori M, Bjermer L, Lofdahl CG, Erjefalt JS. Alterations in lung mast cell populations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010;181(3):206-217.

78. Maaninka K, Lappalainen J, Kovanen PT. Human mast cells arise from a common circulating progenitor. *J Allergy Clin Immunol*. 2013;132(2):463-469.
79. Dwyer DF, Barrett NA, Austen KF, The Immunological Genome Project Consortium. Expression profiling of constitutive mast cells reveals a unique identity within the immune system. *Nat Immunol*. 2016;17(7):878-887.
80. Plum T, Wang X, Rettel M, Krijgsveld J, Feyerabend TB, Rodewald HR. Human mast cell proteome reveals unique lineage, putative functions, and structural basis for cell ablation. *Immunity*. 2020;52(2):404-416.
81. Dahlin JS, Malinowski A, Ohrvik H, et al. Lin- CD34hi CD117int/hl FcεsilonRI+ cells in human blood constitute a rare population of mast cell progenitors. *Blood*. 2016;127(4):383-391.
82. Gurish MF, Tao H, Abonia JP, et al. Intestinal mast cell progenitors require CD49dβ7 (α4β7 integrin) for tissue-specific homing. *J Exp Med*. 2001;194(9):1243-1252.
83. Hallgren J, Gurish MF. Mast cell progenitor trafficking and maturation. *Adv Exp Med Biol*. 2011;716:14-28.
84. Salomonsson M, Dahlin JS, Ungerstedt J, Hallgren J. Localization-Specific Expression of CCR1 and CCR5 by Mast Cell Progenitors. *Front Immunol*. 2020;11:321.
85. Juremalm M, Nilsson G. Chemokine receptor expression by mast cells. *Chem Immunol Allergy*. 2005;87:130-144.
86. Halova I, Draberova L, Draber P. Mast cell chemotaxis-chemoattractants and signaling pathways. *Front Immunol*. 2012;3:119.
87. Nilsson G, Mikovits J, Metcalfe DD, Taub DD. Mast cell migratory response to IL-8 is mediated through interaction with chemokine receptor CXCR2/IL-8RB. *Blood*. 1999;93:2791-2797.
88. Juremalm M, Hjertson M, Olsson N, Harvima I, Nilsson K, Nilsson G. The chemokine receptor CXCR4 is expressed within the mast cell lineage and its ligand SDF-1α acts as a mast cell chemotaxin. *Eur J Immunol*. 2000;30:3614-3622.
89. Juremalm M, Olsson N, Nilsson G. Selective CCL5/RANTES-induced mast cell migration through interactions with chemokine receptors CCR1 and CCR4. *Biochem Biophys Res Commun*. 2002;297(3):480-485.
90. Taub D, Dastyk J, Inamura N, et al. Bone marrow-derived murine mast cells migrate, but do not degranulate, in response to chemokines. *J Immunol*. 1995;154:2393-2402.
91. Bischoff SC, Krieger M, Brunner T, et al. RANTES and related chemokines activate human basophil granulocytes through different G protein-coupled receptors. *Eur J Immunol*. 1993;23:761-767.
92. Toda M, Dawson M, Nakamura T, et al. Impact of engagement of FcεRI and CC chemokine receptor 1 on mast cell activation and motility. *J Boil Chem*. 2004;279(46):48443-48448.
93. Nguyen M, Solle M, Audoly LP, et al. Receptors and signaling mechanisms required for prostaglandin E2-mediated regulation of mast cell degranulation and IL-6 production. *J Immunol*. 2002;169(8):4586-4593.
94. Klein O, Krier-Burris RA, Lazki-Hagenbach P, et al. Mammalian diaphanous-related formin 1 (mDia1) coordinates mast cell migration and secretion through its actin-nucleating activity. *J Allergy Clin Immunol*. 2019;144(4):1074-1090.
95. Pickett JA, Edwardson JM. Compound exocytosis: mechanisms and functional significance. *Traffic*. 2006;7(2):109-116.
96. Gaudenzio N, Sibilano R, Marichal T, et al. Different activation signals induce distinct mast cell degranulation strategies. *J Clin Invest*. 2016;126(10):3981-3998.
97. Dvorak AM. Ultrastructural studies of human basophils and mast cells. *J Histochem Cytochem*. 2005;53(9):1043-1070.
98. Friesen CA, Neilan N, Daniel JF, et al. Mast cell activation and clinical outcome in pediatric cholelithiasis and biliary dyskinesia. *BMC Res Notes*. 2011;4:322.
99. Vanheel H, Vicario M, Boesmans W, et al. Activation of eosinophils and mast cells in functional dyspepsia: an ultrastructural evaluation. *Sci Rep*. 2018;8(1):5383.
100. Crivellato E, Nico B, Vacca A, Ribatti D. Ultrastructural analysis of mast cell recovery after secretion by piecemeal degranulation in B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2003;44(3):517-521.
101. Theoharides TC, Bondy PK, Tsakalos ND, Askenase PW. Differential release of serotonin and histamine from mast cells. *Nature*. 1982;297(5863):229-231.
102. Theoharides TC, Kops SK, Bondy PK, Askenase PW. Differential release of serotonin without comparable histamine under diverse conditions in the rat mast cell. *Biochem Pharmacol*. 1985;34(9):1389-1398.
103. Hepp R, Puri N, Hohenstein AC, Crawford GL, Whiteheart SW, Roche PA. Phosphorylation of SNAP-23 regulates exocytosis from mast cells. *The Journal of biological chemistry*. 2005;280(8):6610-6620.
104. Azouz NP, Zur N, Efergan A, et al. Rab5 is a novel regulator of mast cell secretory granules: impact on size, cargo, and exocytosis. *J Immunol*. 2014;192(9):4043-4053.
105. Klein O, Roded A, Zur N, et al. Rab5 is critical for SNAP23 regulated granule-granule fusion during compound exocytosis. *Sci Rep*. 2017;7(1):15315.
106. Blank U, Madera-Salcedo IK, Danelli L, et al. Vesicular trafficking and signaling for cytokine and chemokine secretion in mast cells. *Front Immunol*. 2014;5:453.
107. Vukman KV, Forsonits A, Oszvald A, Toth EA, Buzas EI. Mast cell secretome: soluble and vesicular components. *Semin Cell Dev Biol*. 2017;67:65-73.
108. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. *J Allergy Clin Immunol*. 2010;126(6):1099-1104.
109. Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. *Cancer Res*. 2017;77(6):1261-1270.
110. Metcalfe DD, Gotlib J, et al. Systemic mastocytosis. In: Greer JP, Arber DA, Applebaum FR, (Eds.). *Wintrobe's Clinical Hematology*. 14th ed. Philadelphia: Wolters Kluwer; 2019: pp 1793-1808.
111. Boyden SE, Desai A, Cruse G, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med*. 2016;374(7):656-663.
112. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*. 2016;48(12):1564-1569.
113. Robey RC, Wilcock A, Bonin H, et al. Hereditary alpha-tryptasemia: uk prevalence and variability in disease expression. *J Allergy Clin Immunol Pract*. 2020;8(10):3549-3556.
114. Lyons JJ, Chovanec J, O'Connell MP, et al. Heritable risk for severe anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. *J Allergy Clin Immunol*. 2021;147:622-632.
115. Greiner G, Sprinzl B, Gorska A, et al. Hereditary alpha tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. *Blood*. 2021;137(2):238-247.
116. Le QT, Lyons JJ, Naranjo AN, et al. Impact of naturally forming human alpha/beta-tryptase heterotetramers in the pathogenesis of hereditary alpha-tryptasemia. *J Exp Med*. 2019;216(10):2348-2361.
117. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract*. 2019;7(4):1125-1133.
118. Hallgren J, Hellman L, Maurer M, et al. Novel aspects of mast cell and basophil function: Highlights from the 9th meeting of the European Mast cell and Basophil Research Network (EMBRN)-a Marcus Wallenberg Symposium. *Allergy*. 2020;75(3):707-708.

119. Harvima IT, Levi-Schaffer F, Draber P, et al. Molecular targets on mast cells and basophils for novel therapies. *J Allergy Clin Immunol.* 2014;134(3):530-544.
120. Church MK, Maurer M. Antihistamines. *Chem Immunol Allergy.* 2014;100:302-310.
121. Thurmond RL, Venable J, Savall B, et al. Clinical development of histamine H4 receptor antagonists. *Handb Exp Pharmacol.* 2017;241:301-320.
122. Maun HR, Jackman JK, Choy DF, et al. An allosteric anti-tryptase antibody for the treatment of mast cell-mediated severe asthma. *Cell.* 2019;179(2):417-431.
123. Pejler G. The emerging role of mast cell proteases in asthma. *Eur Respir J.* 2019;54(4):1900685.
124. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-mediated autoimmunity. *Front Immunol.* 2018;9:689.
125. Maurer M, Eyerich K, Eyerich S, et al. Urticaria: Collegium Internationale Allergologicum (CIA) Update 2020. *Int Arch Allergy Immunol.* 2020;181(5):321-333.
126. Altrichter S, Zampeli V, Ellrich A, Zhang K, Church MK, Maurer M. IgM and IgA in addition to IgG autoantibodies against Fc ϵ 2.35 are frequent and associated with disease markers of chronic spontaneous urticaria. *Allergy.* 2020;75(12):3208-3215.
127. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med.* 2013;368(10):924-935.
128. Maurer M, Gimenez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med.* 2019;381(14):1321-1332.
129. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. *Ann Allergy Asthma Immunol.* 2020;124(1):2-12.
130. Bulfone-Paus S, Nilsson G, Draber P, Blank U, Levi-Schaffer F. Positive and negative signals in mast cell activation. *Trends Immunol.* 2017;38(9):657-667.
131. Schleimer RP, Schnaar RL, Bochner BS. Regulation of airway inflammation by siglec-8 and siglec-9 sialoglycan ligand expression. *Curr Opin Allergy Clin Immunol.* 2016;16(1):24-30.
132. Gonzalez-Gil A, Li TA, Porell RN, et al. Isolation, identification, and characterization of the human airway ligand for the eosinophil and mast cell immunoinhibitory receptor siglec-8. *J Allergy Clin Immunol.* 2021;147(4):1442-1452.
133. Valent P, Akin C, Hartmann K, et al. Mast cells, a unique hematologic lineage and cell system: from Paul Ehrlich to precision medicine. *Theranostics.* 2020;10(23):10743-10768.
134. Mueller N, Wicklein D, Eisenwort G, et al. CD44 is a RAS/STAT5-regulated invasion receptor that triggers disease expansion in advanced mastocytosis. *Blood.* 2018;132(18):1936-1950.
135. Rodewald HR, Feyerabend TB. Widespread immunological functions of mast cells: fact or fiction? *Immunity.* 2012;37(1):13-24.
136. Reber LL, Marichal T, Galli SJ. New models for analyzing mast cell functions in vivo. *Trends Immunol.* 2012;33(12):613-625.
137. 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(6):973-984.
138. Feyerabend TB, Weiser A, Tietz A, et al. Cre-mediated cell ablation contests mast cell contribution in models of antibody- and T cell-mediated autoimmunity. *Immunity.* 2011;35(5):832-844.
139. Lilla JN, Chen CC, Mukai K, et al. Reduced mast cell and basophil numbers and function in Cpa3-Cre; Mcl-1fl/fl mice. *Blood.* 2011;118(26):6930-6938.
140. Otsuka A, Kubo M, Honda T, et al. Requirement of interaction between mast cells and skin dendritic cells to establish contact hypersensitivity. *PLoS One.* 2011;6(9):e25538.
141. Dahdah A, Gautier G, Attout T, et al. Mast cells aggravate sepsis by inhibiting peritoneal macrophage phagocytosis. *J Clin Invest.* 2014;124(10):4577-4589.
142. Luo Y, Meyer N, Jiao Q, et al. Chymase-Cre; Mcl-1(fl/fl) mice exhibit reduced numbers of mucosal mast cells. *Front Immunol.* 2019;10:2399.
143. Hoppe A, Katsoulis-Dimitriou K, Edler HJ, Dudeck J, Drube S, Dudeck A. Mast cells initiate the vascular response to contact allergens by sensing cell stress. *J Allergy Clin Immunol.* 2020;145(5):1476-1479.
144. Ohrvik H, Grujic M, Waern I, et al. Mast cells promote melanoma colonization of lungs. *Oncotarget.* 2016;7(42):68990-69001.
145. Rabenhorst A, Schlaak M, Heukamp LC, et al. Mast cells play a protumorigenic role in primary cutaneous lymphoma. *Blood.* 2012;120(10):2042-2054.
146. Schubert N, Dudeck J, Liu P, et al. Mast cell promotion of T cell-driven antigen-induced arthritis despite being dispensable for antibody-induced arthritis in which T cells are bypassed. *Arthritis Rheumatol.* 2015;67(4):903-913.
147. Kroner J, Kovtun A, Kemmler J, et al. Mast cells are critical regulators of bone fracture-induced inflammation and osteoclast formation and activity. *J Bone Miner Res.* 2017;32(12):2431-2444.
148. Ramirez-Garcia Luna JL, Chan D, Samberg R, et al. Defective bone repair in mast cell-deficient Cpa3Cre/+ mice. *PLoS One.* 2017;12(3):e0174396.
149. Wang Q, Lepus CM, Raghu H, et al. IgE-mediated mast cell activation promotes inflammation and cartilage destruction in osteoarthritis. *Elife.* 2019;8:e39905.
150. Yu M, Mukai K, Tsai M, Galli SJ. Thirdhand smoke component can exacerbate a mouse asthma model through mast cells. *J Allergy Clin Immunol.* 2018;142(5):1618-1627.
151. Zimmermann C, Troeltzsch D, Gimenez-Rivera VA, et al. Mast cells are critical for controlling the bacterial burden and the healing of infected wounds. *Proc Natl Acad Sci USA.* 2019;116(41):20500-20504.
152. Jiao Q, Luo Y, Scheffel J, et al. Skin mast cells contribute to *Sporothrix schenckii* infection. *Front Immunol.* 2020;11:469.
153. Gutierrez DA, Muralidhar S, Feyerabend TB, Herzig S, Rodewald HR. Hematopoietic kit deficiency, rather than lack of mast cells, protects mice from obesity and insulin resistance. *Cell Metab.* 2015;21(5):678-691.
154. 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(5):797-807.
155. 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(3):769-779.
156. 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(1):314-322.
157. Dispenza MC, Krier-Burris RA, Chhiba KD, Udem BJ, Robida PA, Bochner BS. Bruton's tyrosine kinase inhibition effectively protects against human IgE-mediated anaphylaxis. *J Clin Invest.* 2020;130(9):4759-4770.
158. Pejler G. Novel insight into the in vivo function of mast cell chymase: lessons from knockouts and inhibitors. *J Innate Immun.* 2020;12(5):357-372.
159. Ehrlich P. *Beiträge zur Theorie und Praxis der Histologischen Färbung.* Leipzig: Leipzig University; 1878.
160. Jorpes JE, Holmgren H, Wilander O. Über das Vorkommen von Heparin in den Gefäßwänden und in den Augen. *Ztschr mikr-anat Forsch.* 1937;42:279-301.
161. Holmgren H, Wilander O. Beitrag zur Kenntnis der Chemie und Funktion der Ehrlichschen Mastzellen. *Ztschr mikr-anat Forsch.* 1937;42:242-278.
162. Ellis JM. Urticaria pigmentosa; a report of a case with autopsy. *Arch Pathol (Chic).* 1949;48(5):426-435.
163. Riley JF, West GB. The presence of histamine in tissue mast cells. *J Physiol (London).* 1953;120:528-537.

164. Mota I, Vugman I. Effects of anaphylactic shock and compound 48/80 on the mast cells of the guinea pig lung. *Nature*. 1956;177(4505):427-429.
165. Ishizaka K, Ishizaka T, Hornbrook MM. Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity with gamma-E-globulin antibody. *J Immunol*. 1966;97(6):840-853.
166. Johansson SG, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology*. 1967;13(4):381-394.
167. Bennich HH, Ishizaka K, Johansson SG, Rowe DS, Stanworth DR, Terry WD. Immunoglobulin E: a new class of human immunoglobulin. *Immunology*. 1968;15(3):323-324.
168. Ishizaka T, Ishizaka K, Orange RP, Austen KF. The capacity of human immunoglobulin E to mediate the release of histamine and slow reacting substance of anaphylaxis (SRS-A) from monkey lung. *J Immunol*. 1970;104(2):335-343.
169. Ishizaka T, Ishizaka K, Tomioka H. Release of histamine and slow reacting substance of anaphylaxis (SRS-A) by IgE-anti-IgE reactions on monkey mast cells. *J Immunol*. 1972;108(2):513-520.
170. Schwartz LB, Lewis RA, Austen KF. Tryptase from human pulmonary mast cells: Purification and characterization. *J Biol Chem*. 1981;256(11939):11939-11943.
171. Schwartz LB, Lewis RA, Seldin D, Austen KF. Acid hydrolases and tryptase from secretory granules of dispersed human lung mast cells. *J Immunol*. 1981;126:1290-1294.
172. Lewis RA, Soter NA, Diamond PT, et al. Prostaglandin D2 generation after sactivation of rat and human mast cells with anti-IgE. *J Immunol*. 1982;129(4):1627-1631.
173. Brown MA, Pierce JH, Watson CJ, Falco J, Ihle JN, Paul WE. B cell stimulatory factor-1/interleukin-4 mRNA is expressed by normal and transformed mast cells. *Cell*. 1987;50:809-818.
174. Young J-E, Liu C-C, Butler G, Cohn ZA, Galli SJ. Identification, purification, and characterization of a mast cell-associated cytolytic factor related to tumor necrosis factor. *Proc Natl Acad Sci USA*. 1987;84:9175-9179.
175. Blank U, Ra C, Miller L, White K, Metzger H, Kinet JP. Complete structure and expression in transfected cells of high affinity IgE receptor. *Nature*. 1989;337(6203):187-189.
176. Miller L, Blank U, Metzger H, Kinet JP. Expression of high-affinity binding of human immunoglobulin E by transfected cells. *Science*. 1989;244(4902):334-337.
177. MacQueen G, Marshall J, Perdue M, Siegel S, Bienenstock J. Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. *Science*. 1989;243(4887):83-85.
178. Witte ON. Steel locus defines new multipotent growth factor. *Cell*. 1990;63(1):5-6.
179. Kirshenbaum AS, Goff JP, Kessler SW, Mican JM, Zsebo KM, Metcalfe DD. Effect of IL-3 and stem cell factor on the appearance of human basophils and mast cells from CD34+ pluripotent progenitor cells. *J Immunol*. 1992;148:772-777.
180. Valent P, Spanblöchl E, Sperr WR, et al. Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor/kit ligand in long-term culture. *Blood*. 1992;80(2237):2237-2245.
181. Mitsui H, Furitsu T, Dvorak AM, et al. Development of human mast cells from umbilical cord blood cells by recombinant human and murine c-kit ligand. *Proc Natl Acad Sci USA*. 1993;90(735):735-739.
182. Nagata H, Worobec AS, Oh CK, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc Natl Acad Sci USA*. 1995;92:10560-10564.
183. Maurer M, Wedemeyer J, Metz M, et al. Mast cells promote homeostasis by limiting endothelin-1-induced toxicity. *Nature*. 2004;432(7016):512-516.
184. Metz M, Piliponsky AM, Chen CC, et al. Mast cells can enhance resistance to snake and honeybee venoms. *Science*. 2006;313(5786):526-530.
185. Saluja R, Zoltowska A, Ketelaar ME, Nilsson G. IL-33 and Thymic Stromal Lymphopoietin in mast cell functions. *Eur J Pharmacol*. 2016;778:68-76.

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