



Understanding human mast cells: lesson from therapies for allergic and non-allergic diseases

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Abstract | Mast cells have crucial roles in allergic and other inflammatory diseases. Preclinical approaches provide circumstantial evidence for mast cell involvement in many diseases, but these studies have major limitations — for example, there is still a lack of suitable mouse models for some mast cell-driven diseases such as urticaria. Some approaches for studying mast cells are invasive or can induce severe reactions, and very few mediators or receptors are specific for mast cells. Recently, several drugs that target human mast cells have been developed. These include monoclonal antibodies and small molecules that can specifically inhibit mast cell degranulation via key receptors (such as FcεRI), that block specific signal transduction pathways involved in mast cell activation (for example, BTK), that silence mast cells via inhibitory receptors (such as Siglec-8) or that reduce mast cell numbers and prevent their differentiation by acting on the mast/stem cell growth factor receptor KIT. In this Review, we discuss the existing and emerging therapies that target mast cells, and we consider how these treatments can help us to understand mast cell functions in disease.

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Mast cells are tissue-resident haematopoietic cells that were first visualized by Paul Ehrlich in 1877 (REF.¹). As local tissue sentinels, mast cells play a crucial role in host defence against certain parasites, bacteria and venoms. They can detect potential threats and respond to them due to several key features, namely their strategic location at barrier tissues, such as the skin and the mucosa of the gut and airways; their high level of heterogeneity and plasticity; their survival for months or years within the tissue; and their expression of a wide range of receptors and production of a broad array of mediators with different biological activities^{2–4} (see Supplementary Tables 1 and 2).

In innate immune responses to microorganisms, mast cells can respond without prior experience of the infection. For example, they are directly activated through Toll-like receptors (TLRs) and release products that have direct bactericidal activity⁵, enhance host defence mechanisms⁶ and kill pathogens via different mechanisms⁷. Similarly, in response to venomous toxins, mast cells can be directly activated to release proteases that degrade, and thus detoxify, the respective toxins⁸. Mast cells also contribute to adaptive immune responses by binding antibodies through Fc receptors. Mast cells can be ‘pre-armed’ with antibodies against venoms⁹ and bacteria, which enables them to respond rapidly

to subsequent exposures to these challenges¹⁰. Taken together, these features indicate an important and diverse role for mast cells in responding to external threats.

However, the capacity to mount an immediate response and to release a plethora of potent immune mediators makes mast cells among the most potentially dangerous cells of the human body. Activation of mast cells can lead to chronic inflammation and pathogenic tissue remodelling¹¹. Moreover, pathological activation of mast cells can lead to rapid death via anaphylactic shock. When mast cell activities are not directed at protecting us from threats, they typically hurt us and make us sick. This is ‘the dark side’ of the mast cell and contributes to a wide range of diseases. The key question is which diseases. This is not an easy question to answer. Currently, all of the evidence that supports a pathogenic role of human mast cells in any disease is circumstantial and indirect. The recent development and use of mast cell-targeted treatments should change this. The effects and efficacy of these treatments, in diseases where mast cells are held to be important, will help us to identify those diseases in which mast cells are drivers and those in which they are bystanders. Such studies will further our understanding of how mast cells contribute to the pathogenesis of disease and provide novel treatment options for patients. Because of this, it is important to

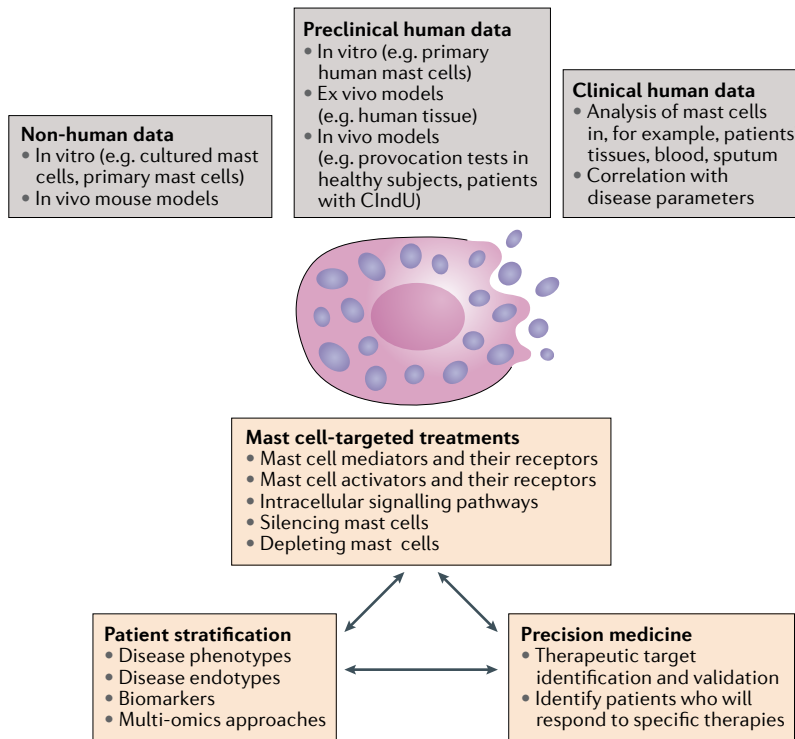


Fig. 1 | Approaches for characterizing the functions of human mast cells in disease. Mast cells play a crucial role in the development of bona fide mast cell-driven diseases such as urticaria, mastocytosis and many allergic diseases, and are thought to be involved in other inflammatory diseases and cancer. Several approaches are used to study the role and relevance of mast cells in human disease, from animal models to preclinical and clinical studies on human disease, to the use of mast cell-targeted treatments. Mast cell-targeted treatments significantly contribute to the evidence obtained from other approaches by linking the effects of blocking mast cell mediators, inhibiting activating receptors on mast cells, neutralizing mast cell-activating signals, silencing mast cells and reducing mast cell numbers to the decrease of symptoms in patients with mast cell-mediated diseases. Additionally, mast cell-targeted therapies help define disease endotypes and their biomarkers and contribute to the development of personalized (precision) medicine. CIndU, chronic inducible urticaria.

know, firstly, how the contribution of mast cells to diseases can be assessed; secondly, which diseases can be treated with mast cell-targeted therapies; and thirdly, what mast cell-targeted treatments we have. In this Review, we address these three key questions and discuss how the answers to each can help us to understand human mast cells and to develop treatments for mast cell-driven diseases.

Approaches to studying mast cells in disease

To determine whether mast cells contribute to the pathogenesis of any given disease, one can study the effects of their absence on the risk for developing that disease and on its course. This, however, is challenging to do in humans. Although genetic deficiencies in mast cell-derived mediators, such as α -tryptase¹², or mast cell-associated transcription factors, such as GATA2 (REF.¹³), have been described, no humans deficient in mast cells have been reported. In addition, we currently lack pharmacological means of depleting mast cells in humans, although there are promising emerging drugs in development. Hence, all of the evidence

for a role of mast cells in human disease is circumstantial, albeit overwhelmingly suggestive of a role for mast cells in many diseases. Below, we discuss the four main approaches that can currently be used to investigate mast cell functions in human disease. These range from animal models to preclinical and clinical studies on human disease, to the use of mast cell-targeted treatment (FIG. 1).

Approach 1: non-human models. Murine mast cells and in vivo mouse models are attractive and extremely valuable tools for exploring the pathogenic roles of mast cells as mouse and human mast cells share many features. For example, the secretory granules of mouse and human mast cells contain similar mediators, such as histamine and tryptase. Also, both species show IgE-mediated mast cell degranulation, and type I hypersensitivity reactions triggered by mast cells are similar in mice and humans. However, specific differences exist. For example, murine and human mast cells differ in their secretory responses upon TLR ligation¹⁴ and their FcεRI expression upon stimulation with IL-4 (REF.¹⁵). Furthermore, murine mast cells produce a broader array of proteases than human mast cells and are classified as connective-tissue mast cells and mucosal mast cells based on their pattern of protease expression as well as their localization and phenotype. By contrast, human mast cells are mainly classified based on their expression levels of two proteases as tryptase⁺, chymase⁺ or tryptase⁺chymase⁺ mast cell subsets^{4,16}.

KIT-dependent (*Kit* mutant) and KIT-independent mast cell-deficient mouse models have been used to identify mast cell functions (reviewed by Galli et al.¹⁷). The former, that is C57BL/6-*Kit*^{W-sh}/*Kit*^{W-sh} (*Kit*^{W-sh}) and WBB6F₁-*Kit*^W/*Kit*^{W-v} (*Kit*^W/*Kit*^{W-v}) mice, lack mast cells due to hypomorphic expression of KIT, which is the receptor for stem cell factor (SCF). SCF signalling through KIT is crucial for mast cell differentiation and survival. The disadvantage of these models is the fact that other KIT-expressing haematopoietic and non-haematopoietic cells such as melanocytes are also affected. Whereas *Kit*^W/*Kit*^{W-v} mice are anaemic, have reduced basophils and neutrophils and are sterile, *Kit*^{W-sh} mice do not show these features but, rather, have increased numbers of basophils and neutrophils.

New mouse models with constitutive mast cell deficiency have been developed during the past decade that are unrelated to *Kit* abnormalities. They rely mostly on the expression of Cre-recombinase (Cre) under the control of mast cell-specific promoters. These mice demonstrated lack of mucosal mast cells (*Chm-Cre*; *Mcl-I*^{fl/fl})¹⁸ or connective tissue mast cells (*Mcpt5-Cre*; *R-DTA*, *Mcpt5-Cre*; *Gata2*^{fl/fl}), or both (*Cpa3*^{Cre/+}, *Cpa3-Cre*; *Mcl-I*^{fl/fl}), reduced or undetectable IgE-mediated responses and abnormalities in the function and numbers of basophils (*Cpa3*^{Cre/+}, *Cpa3-Cre*; *Mcl-I*^{fl/fl})¹⁷.

As an additional limitation, mouse models with constitutive mast cell deficiency — including KIT-dependent mice — may show different biological responses when compared with mice in which mast cells are selectively and inducibly depleted. With regards to the latter, depletion of mast cells was induced by injection of diphtheria

Type I hypersensitivity
An IgE and mast cell-mediated allergic reaction in response to environmental antigens (allergens) in sensitized individuals.

β -Hexosaminidase

A mediator stored in mast cell granules, the release of which is measured in mast cell supernatants in vitro in order to determine the degree of cell activation and degranulation upon stimulation with various substances, such as drugs or neuropeptides.

toxin in transgenic mice expressing diphtheria toxin receptor (DTR) under the control of mast cell-specific IL-4 enhancer element ('Mas-TRECK' mice), the *Mcpt5* promoter (*Mcpt5-Cre;iDTR*) or the β -chain of Fc ϵ RI (red mast cell and basophil mouse (RMB)). Potential limitations of these models include the presence of mucosal mast cells (seen in *Mcpt5-Cre;iDTR* systems) and transient reduction in basophil numbers and function (seen in RMB and Mas-TRECK mice)^{17,19}.

Both KIT-dependent and KIT-independent mouse models have demonstrated essential functions of mast cells in IgE-mediated allergic reactions¹⁷, but the role of mast cells in asthma, cutaneous contact hypersensitivity and non-allergic diseases is still a matter of debate (reviewed in REFS^{17,20}). Some findings from studies on autoimmune diseases, type 2 diabetes and cancer in KIT-dependent models of mast cell-deficiency were not reproducible in KIT-independent mouse models^{21–23}. For example, a metabolic analysis of KIT-dependent *Kit^W/Kit^{W-v}* and KIT-independent *Cpa3^{Cre/+}* mice showed that haematopoietic cells other than mast cells are relevant for obesity development²³. Furthermore, *Cpa3^{Cre/+}* mice were susceptible to autoimmune arthritis, in contrast to *Kit^W/Kit^{W-v}* mice that were protected from the disease²¹. Additionally, there is still a lack of mouse models for some diseases that are held to be mast cell-dependent, such as urticaria, which limits the use of mice for studies of the contribution of mast cells in human diseases.

The use of double or triple-transgenic mice expressing fluorescence signals and intravital two-photon microscopy has allowed for the visualization of mast cell responses in vivo, but this method is expensive and time-consuming. New non-genetic approaches to visualize mast cell secretory granules include the use of real-time confocal microscopy in vitro and non-invasive two-photon microscopy in living mice (reviewed by Gaudenzio et al.²⁴).

A humanized mouse model (also called 'humice' or NSG-SGM3) is another valuable approach used in mast cell research for investigating IgE-mediated and Mas-related G-protein-coupled receptor member X2 (MRGPRX2)-mediated anaphylaxis, cutaneous drug reactions²⁵ and new treatments such as BTK inhibition²⁶. These mice can be generated by transplantation of human haematopoietic stem cells into NOD-SCID-*Il2rg^{-/-}* mice and by hydrodynamic injection of plasmids that express human granulocyte-macrophage colony-stimulating factor and IL-3 and promote the growth of mast cells²⁵. This model also allows for the correlation of in vitro (with bone marrow-derived mast cells) and in vivo observations²⁵, but some limitations exist. For example, certain mouse cytokines do not fully support the development of certain immune cell subsets, and long-term expression of human cytokines in a humanized mouse model is challenging because of the possibility of non-physiological effects, for example anaemia^{25,27}.

Approach 2: preclinical human models. In vitro stimulation of human mast cells with specific activators enables the investigation of their degranulation and cytokine production²⁸. This can be assessed by measuring their

release of mediators such as β -hexosaminidase or histamine, eicosanoids such as leukotriene C₄ and prostaglandin D₂ (PGD₂), and cytokines such as IL-1 β , IL-6, IL-13 and TNF. For example, the stimulation of human mast cells with substance P and other mast cell activators^{29,30} helped characterize the mast cell receptor MRGPRX2 as a driver of IgE-independent mast cell-mediated hypersensitivity reactions³⁰ and as a potentially pathogenic pathway in chronic urticaria³¹.

Ex vivo models for assessing mast cell functions make use of human tissue — for instance, skin derived from plastic surgery — and employ different activation and sampling assays, such as skin microdialysis. Ex vivo skin microdialysis allows for the recovery of soluble endogenous molecules such as histamine or cytokines from the extracellular compartment of excised human skin in real time (reviewed by Baumann et al.³²). The intradermal injection of substance P and compound 48/80, which are MRGPRX2 agonists, in human skin explants induced histamine release as assessed by microdialysis sampling³³. Additionally, numbers of mast cells and their activation status and receptor expression can be evaluated in healthy and diseased skin by immunohistochemistry or immunofluorescence staining of skin obtained by biopsy (reviewed by Ribatti³⁴).

In vivo techniques used for preclinical studies in humans include intradermal injection or skin prick testing with various substances, for example, codeine, drugs and allergens, to induce the degranulation of skin mast cells in patients and in healthy humans, with subsequent assessment of wheals, reflex erythema and itch. Three antidepressants with MRGPRX2-activating properties were able to induce wheal and flare reactions following intradermal injections in healthy volunteers²⁹. Likewise, allergen challenge tests are used to study the IgE-mediated responses of mast cells in the airways, the conjunctiva and the gut. Notably, the early-phase response after the first dose of nasal challenge with Timothy grass pollen strongly correlated with the number of submucosal mast cells³⁵.

Another method is the examination of inducible mast cell-dependent lesions, for example in patients with chronic inducible urticaria (CIndU) or mastocytosis with involvement of the skin. In patients with cold urticaria, a decrease in critical temperature thresholds for developing wheals assessed by cold provocation test was observed in response to desloratadine, an antihistamine³⁶. Furthermore, in vivo skin microdialysis helped monitor effects of another antihistamine, bilastine, showing a decrease in histamine, IL-6 and IL-8 assessed 1–3 h after cold challenge in patients with cold urticaria³⁷. Recently, non-invasive staining-free two-photon fluorescence lifetime imaging, a novel in vivo method, has been introduced for the visualization of dermal mast cells in healthy people and in patients with allergy and mastocytosis³⁸.

Regarding the limitations of this approach, mast cells are tissue-resident cells, and high numbers and purity of primary human mast cells are hard to obtain but are necessary for in vitro and ex vivo studies. Moreover, in vivo skin microdialysis, biopsy and intradermal testing are invasive procedures, and severe adverse reactions can

Canakinumab

A recombinant, human anti-IL-1 β mAb, approved by the FDA (US Food and Drug Administration) for the treatment of periodic fever syndromes and active systemic juvenile idiopathic arthritis.

develop in patients who are allergic and in patients with CINDU after provocation tests.

Approach 3: correlating mast cells with clinical disease.

Mast cell numbers, activators, mediators, receptors and degranulation status can be assessed in affected organs, blood and/or urine of patients with different diseases (reviewed by Baumann et al.³⁹ and Metcalfe et al.⁴⁰). Correlation of these parameters with disease duration, activity, exacerbation, progression and remission suggests that mast cells may play a role in the pathogenesis of the disease studied. Specifically, mast cell-associated blood biomarkers are extensively measured in IgE-mediated allergic diseases (total and allergen-specific IgE, histamine, methylhistamine, prostaglandin metabolites, total tryptase) and mastocytosis (total tryptase). Recently described hereditary α -tryptasaemia associated with increased *TPSAB1* copy number can provide greater insights into mast cell functions, linking the elevated basal serum tryptase with multisystem complaints and their potential therapy⁴¹. Arachidonic acid metabolites such as cysteinyl leukotrienes (for example, LTE₄) and prostaglandins (for example, PGD₂) are assessed in allergic asthma⁴², aspirin-exacerbated respiratory disease, anaphylaxis, systemic mastocytosis⁴³ and other conditions^{39,40}. Furthermore, histamine can be measured in bronchoalveolar lavage fluid in patients with allergic asthma⁴⁴. Finally, mast cells or mast cell mediators in the lesional skin of patients with cutaneous diseases, for example urticaria or mastocytosis, stained using immunohistochemistry or immunofluorescence, can be upregulated and/or correlated with disease severity and other parameters³¹.

However, a hypothesis-based approach focusing mainly on one or few mast cell-related biomarkers, in other words on individual 'omics' data, is limited by the fact that there are very few mediators and receptors that are produced and expressed exclusively by mast cells. Thus, elevated levels of mediators in biological fluids do not necessarily reflect their secretion by mast cells alone. Also, many inflammatory processes can lead to mast cell accumulation and degranulation, and increased mast cell numbers may be a bystander effect, rather than an indicator of functional importance and active pathogenic involvement of mast cells. Recent developments in multi-omics approaches can identify the role of mast cells in human disease and better classify distinct disease phenotypes and endotypes associated with mast cells. These technologies include genomics, epigenomics, transcriptomics, proteomics, metabolomics and other methods for endotype profiling and biomarker screening in an unbiased manner. A high number of analytes, including proteins, genes and metabolites, can be measured simultaneously on a single specimen, and complex, non-linear associations in multi-omics in large-scale biological databases can be assessed using machine learning methods (reviewed by Mersha et al.⁴⁵). However, some methods such as transcriptomics are expensive and time-consuming. There are limitations in sample biomass and sample access, and the possibility of background contamination exists. Moreover, the presence of specific biomolecules can differ depending

on sample type; for example, urine fits ideally for metabolomics analysis but has a limited number of proteins, RNA and DNA in comparison with blood.

Approach 4: mast cell-targeted treatments. Mast cell-targeted treatments can significantly contribute to characterizing the role and relevance of mast cells in a particular human disease. These approaches link the blockage or inhibition of mast cell mediators or activating receptors to a decrease of symptoms in mast cell-driven diseases, as discussed below.

Mast cells produce and release many mediators, more than any other human cell. Histamine is one of them and is mainly derived from mast cells. Thus, inhibition of the signs and symptoms of a disease by antihistamines suggests a role for mast cells, and allergic diseases and urticaria are well-recognized examples of this⁴⁶. The picture is less clear when the mediators targeted are also produced by cells other than mast cells, for example IL-4 and IL-5. Therapeutic approaches aimed at mast cell mediators can also help us to understand where these mediators are not essential. Lack of canakinumab efficacy in chronic spontaneous urticaria (CSU), for example, suggests that mast cells do not critically contribute to the pathogenesis of this disease by the release of IL-1 β (REF.⁴⁷). Taken together, blocking mast cell-derived mediators can help us to understand how mast cells contribute to human disease, but cannot teach us which diseases mast cells are critical pathogenic drivers of, as most mast cell mediators are also produced and released by other cells.

Many mast cell-activating receptors and pathways are unique for mast cells or expressed by few other cells. Blocking them can help define the role of mast cells in diseases. For example, the anti-IgE antibodies omalizumab and ligelizumab and the BTK inhibitor fenebrutinib indicated the importance of the IgE-Fc ϵ RI pathway of mast cell activation in CSU^{48–50}. However, an absence of clinical benefit following treatment with inhibitors of mast cell activation does not necessarily rule out their involvement in a disease as they may be activated by pathways other than the one that is blocked.

Drugs targeting inhibitory receptors on mast cells are powerful tools to help us understand their roles in disease, and recent studies with liletrinemab — which engages the mast cell inhibitory receptor sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) — provided proof of concept for this^{51–53}. Silencing mast cells via Siglec-8 engagement was beneficial in numerous allergic and non-allergic settings including CSU, clearly pointing to a pathogenic role of mast cells in these diseases. However, as Siglec-8 is also expressed by eosinophils, the clinical benefit of this treatment may relate to the combined effects on both cell types⁵².

The most convincing argument for a role of mast cells in a disease is when the disease enters remission following mast cell depletion. Several selective mast cell-depleting treatment strategies are currently under development. However, it is important to keep in mind that non-selective mast cell depletion can also affect physiological roles of mast cells and other immune cells, which, for example, could increase the risk for opportunistic infections including sepsis. Despite this caveat,

Bullous pemphigoid

A chronic autoimmune skin disease characterized by the production of autoantibodies against hemidesmosomal antigens, leading to the formation of subepidermal blisters.

mast cell-targeted treatments can teach us about the role of mast cells in human disease and, specifically, where mast cells are critical disease drivers, where mast cells are pathogenically relevant but not critical, where they are bystanders and where they provide protection from getting sick or help control disease progression.

In which diseases can we target mast cells?

Bona fide mast cell-driven diseases. A large body of evidence supports the notion that urticaria, mastocytosis and mast cell activation syndrome are bona fide mast cell-driven diseases^{3,11,20,54} (BOX 1). Furthermore, several lines of evidence provided by extensive use of the approaches described above strongly indicate a fundamental role of mast cells in type I hypersensitivity diseases^{11,20}. For example, anaphylactic responses after passive sensitization with specific IgE were abrogated in both KIT-dependent and KIT-independent mast cell-deficient mouse models^{17,21}. Increased numbers of mast cells were found in the airway smooth muscle of patients with allergic asthma⁵⁵ and the nasal epithelium of patients with perennial allergic rhinitis⁵⁶, as well as in lesions of atopic dermatitis skin⁵⁷. In patients with asthma, mast cells infiltrating the smooth muscle layer displayed signs of activation and degranulation when imaged by electron microscopy⁵⁸. Similarly, levels of mast cell mediators such as histamine, tryptase, leukotrienes and prostaglandins were elevated in bronchoalveolar lavage from patients with atopic asthma and patients with allergic rhinitis⁴⁴. Airway hyperresponsiveness and asthma severity correlated with increased mast cell numbers in the bundles of airway smooth muscle⁵⁵ and tryptase in sputum, bronchoalveolar lavage

fluid and/or blood^{59,60}. In this regard, mast cell activation in severe asthma is likely more important than any increase seen in overall mast cell numbers as mast cell activation is insensitive to corticosteroid treatment⁶⁰. Recently, injection of food antigens into the rectosigmoid mucosa of patients with irritable bowel syndrome led to local oedema and mast cell activation⁶¹. Therefore, patients with urticaria, mastocytosis, mast cell activating syndrome and type I hypersensitivity diseases can be expected to benefit from mast cell-targeted treatments and these diseases are ideally suited to obtain proof of concept that such treatments work.

Probable mast cell-associated diseases. There is also evidence to support a role for mast cells in other chronic inflammatory diseases and cancer. For example, high numbers of mast cells and elevated levels of mast cell-derived mediators are seen in the tissues and blood of patients with multiple sclerosis⁶², rheumatoid arthritis⁶³, bullous pemphigoid⁶⁴ and various types of cancer (reviewed in REF.⁶⁵), and correlate with the intensity of inflammation in some of these diseases⁶⁶. Also, studies in *Kit* mutant mice suggested that mast cells drive pathology in autoimmune diseases (reviewed in REF.²⁰), although the results were inconsistent between different mouse strains^{67,68} and were not reproduced using KIT-independent mast cell-deficient mice in certain models, for example in models of type 1 diabetes⁶⁹. Furthermore, KIT-dependent mouse models showed mixed results with regards to mast cell functions in cancer — mast cells were shown to have tumour-promoting effects in some studies and protective effects in others (reviewed in REF.⁷⁰). Meanwhile, KIT-independent mast cell-deficient mouse models suggested that mast cells do not drive tumour growth²². In solid tumours, mast cell density was associated with poor or good prognosis⁶⁵, and the contribution of mast cells to cancer progression may differ between different types of cancer, organs affected and stages of cancer development.

The take-away message is that the use of mast cell-targeted treatments may provide benefit to patients with these diseases and can help better define the role and relevance of mast cells in their pathogenesis. Importantly, mast cell activity is highly dependent on the environment the cells are located in. For example, mast cells within tumour cell islets were associated with improved survival in non-small cell lung cancer, whereas those in the tumour stroma were not⁷¹. This is a challenge for the development of mast cell therapeutics as a drug that works in one environment may not work in another. In the following section, we focus on the drugs that have been developed or are in development for the treatment of what we consider to be bona fide mast cell-driven diseases, namely urticaria, mastocytosis and mast cell activation syndrome. We also review the evidence for the efficacy of these treatments in allergic diseases where relevant to our focus on mast cells.

Therapies targeting mast cells

The use of mast cell-targeted treatments is the most powerful approach for characterizing mast cell functions in human disease. We have already learned much

Box 1 | Bona fide mast cell-driven diseases**Urticaria**

Urticaria presents with itchy wheals or angioedema, or both. It is considered a mast cell-driven disease with secondary pathogenic contributions of other cells, such as eosinophils and basophils. Chronic urticaria persists longer than 6 weeks and is classified as chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)⁵⁴. In the latter disease, symptoms are triggered by a specific and definite factor, for example cold (in cold urticaria), pressure (in delayed pressure urticaria) or physical exercise (in cholinergic urticaria).

Mastocytosis

Mastocytosis is characterized by increased numbers and accumulation of neoplastic mast cells in different organs with symptoms of mast cell mediator release, for example pruritus and anaphylaxis. Mastocytosis is classified as cutaneous mastocytosis, systemic mastocytosis and mast cell sarcoma¹⁵². *KIT* mutations, mostly D816V, are the key drivers of the proliferation and maturation of mast cell progenitors in the bone marrow. In indolent systemic mastocytosis (ISM), mast cell accumulation is usually limited to the sites of physiological mast cell presence — that is, bone marrow, skin and gastrointestinal tract — and organ function is not affected. Advanced forms of systemic mastocytosis — for example, mast cell leukaemia — are associated with secondary and tertiary mutations, for example in *TET2* and *JAK2*, in addition to *KIT* mutations. Mast cells accumulate in organ systems where they are usually absent or minor — for example, lymph nodes, bones, spleen and liver — leading to organ dysfunction and poor prognosis.

Mast cell activation syndrome

Mast cell activation syndrome is a debilitating heterogeneous chronic mast cell-mediated disorder. It is diagnosed in patients who present with multiple mast cell mediator-induced symptoms but in whom differential diagnosis including systemic mastocytosis has been excluded. The reasons for mast cell activation and the exact pathomechanisms of mast cell activation syndrome are still poorly investigated.

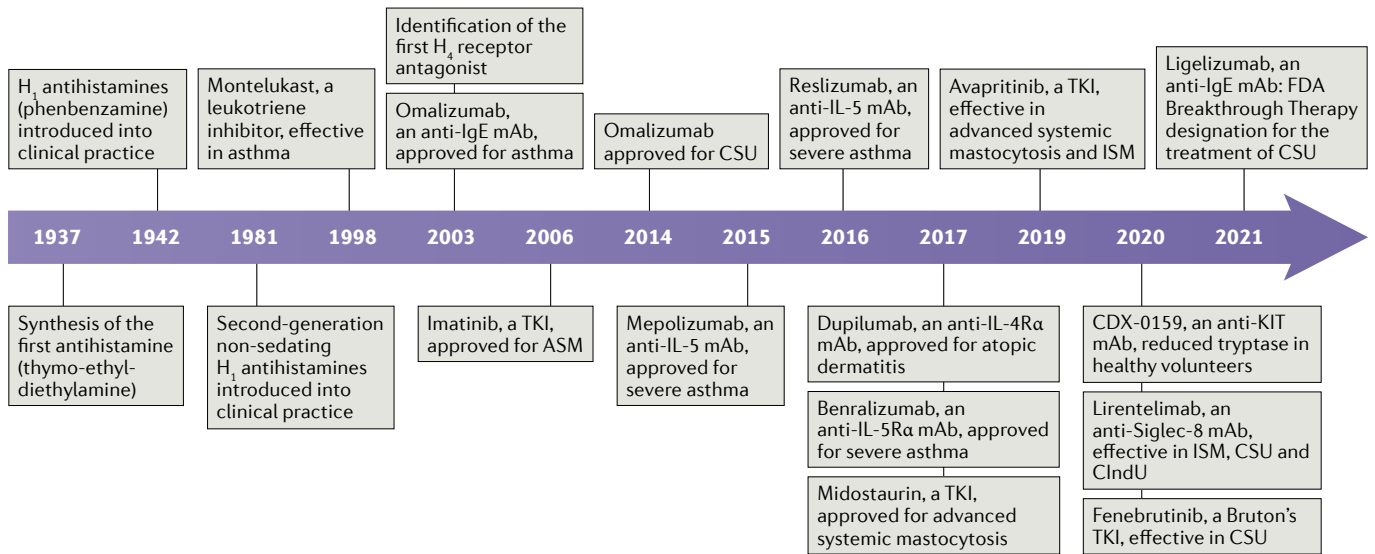


Fig. 2 | Timeline for the development of mast cell-targeted treatments. Timeline visualizes the development of mast cell-targeted treatments, which has been very slow over the years but has recently exploded, with most novel therapies developed very recently and still under development. ASM, aggressive systemic mastocytosis; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; FDA, US Food and Drug Administration; H₁, histamine H1 receptor; ISM, indolent systemic mastocytosis; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; TKI, tyrosine kinase inhibitor.

about human mast cells, especially their role in CSU, from existing mast cell-targeted treatments. Novel mast cell-directed therapies are under development and some of them are being used in clinical trials today (FIG. 2; TABLE 1). Below, we provide an overview of both current and future therapies that target mast cells.

Targeting histamine and its receptors. Mast cells are the major tissue source of histamine, which activates its primary receptor, the H₁ receptor, to elicit a broad range of responses that cause the symptoms related to allergic and other inflammatory diseases, including urticaria. Since their discovery, H₁ antihistamines have been the mainstay of treatment for many mast cell-driven diseases^{46,54,72} (FIG. 3a). However, clinical guidelines discourage the use of first-generation H₁ antihistamines and speak in favour of using safer second-generation H₁ antihistamines as the first line of treatment for chronic urticaria⁵⁴. The H₄ receptor was identified at the beginning of the millennium⁷³. Several H₄ receptor antagonists (for example, JNJ39758979, ZPL-3893787 and toreforant) exhibit anti-inflammatory and antipruritic effects in murine models of pruritus and allergic diseases. Some of them have been tested in clinical trials for allergic and non-allergic inflammatory diseases with mixed results^{74–76}. Studies of H₄ receptor antagonists in mast cell-driven diseases are needed to further clarify the role and relevance of mast cells and histamine-mediated effects linked to H₄ receptor activation.

Targeting tryptase. Tetrameric β -tryptase is the predominant enzymatically active mast cell protease that was increased in asthma independently of type 2 inflammation and associated with lesser omalizumab response⁵⁹. MTPS9579A (RG6173), a mAb that selectively inhibits

tryptase activity, is in a phase II trial as an add-on therapy in patients with uncontrolled moderate to severe asthma (TABLE 1). Two other selective anti-tryptase mAbs, E104 and 31A.v11, are in development and showed promising effects in preclinical studies dissociating tetrameric β -tryptase into inactive monomers and inactivating the enzyme^{59,77}.

Targeting lipid mediators: prostaglandins and leukotrienes. Mast cells are a major source of PGD₂, a lipid mediator that has been implicated in urticaria and allergy via its action on CRTh2, a chemoattractant receptor homologous molecule expressed on T helper 2 cells (T_H2 cells). In patients with antihistamine-resistant CSU, AZD1981 (a selective CRTh2 antagonist) had a safe profile, reduced weekly itch scores more than wheals and inhibited PGD₂-mediated eosinophil shape change⁷⁸. Several CRTh2 antagonists, including timapiprant (OC-459), AZD1981, BI671800, fevipiprant and setipiprant, showed mixed results in the treatment of patients with asthma and allergic rhinitis, with several studies reporting no or low clinical efficacy. For example, fevipiprant failed to show significant benefit in phase III trials in patients with severe asthma⁷⁹, whereas another CRTh2 antagonist, GB001, showed some benefit in limiting asthma exacerbations⁸⁰.

Leukotriene inhibitors such as montelukast, zafirlukast, pranlukast and zileuton have been used with variable efficacy in urticaria and allergic diseases. Montelukast is an FDA (US Food and Drug Administration)-approved drug for the treatment of asthma and allergic rhinitis. In both conditions, it is held to be a less effective treatment compared with corticosteroids (inhaled or intranasal)^{72,81}. The level of evidence for the efficacy of montelukast in CSU, CIndU and atopic dermatitis is low^{54,82}. In 2020, the FDA reported

Table 1 | Selected mast cell-targeted treatments in development

Drug	Target	Type	Disease	Phase	ClinicalTrials.gov identifier
Targeting mast cell mediators and their receptors					
MTPS9579A	Tryptase	mAb	Asthma	II	NCT04092582
Dupilumab	IL-4Rα	mAb	CSU	II–III	NCT03749135, NCT04180488
			CIndU	II–III	NCT03749148, NCT04681729
			Chronic prurigo	III	NCT04202679
			Chronic eczema	II	NCT03861455
			ACD	IV	NCT03935971
			Bullous pemphigoid	II–III	NCT04206553
			Cow's milk allergy	II	NCT04148352
			Peanut allergy	II	NCT03793608
			AKC	II	NCT04296864
Benralizumab	IL-5Rα	mAb	CSU	II	NCT04612725
			Atopic dermatitis	II	NCT03563066
Mepolizumab	IL-5	mAb	CSU	I	NCT03494881
Tralokinumab	IL-13	mAb	Atopic dermatitis	III	NCT03761537
Lebrikizumab	IL-13	mAb	Atopic dermatitis	III	NCT04250337, NCT04146363, NCT04178967, NCT04250350
Nemolizumab	IL-31Rα	mAb	Atopic dermatitis	III	NCT03989349
			Chronic prurigo	III	NCT04204616
Vixarelimab	IL-31 (via OSMRβ)	mAb	Pruritus, chronic prurigo, CSU, psoriasis	II	NCT03816891, NCT03858634
Targeting mast cell activators, their receptors and signal transduction					
Ligelizumab	FcεRI (via IgE)	mAb	CSU	III	NCT03580356, NCT03580369, NCT04210843, NCT03907878
UB-221	FcεRI (via IgE)	mAb	CSU	I	NCT03632291, NCT04175704
UCB8600	FcεRI (via IgE)	mAb	CSU	I	NCT04444466
Etokimab	IL-33	mAb	Atopic dermatitis	II	NCT03533751
Tezepelumab	TSLP	mAb	Asthma	III	NCT04048343, NCT03927157, NCT03347279, NCT03406078
CSJ117	TSLP	Antibody fragment	Asthma	II	NCT04410523
Astegolimab	ST2	mAb	Asthma	II	NCT02918019
			Atopic dermatitis	II	NCT03747575
Avdoralimab	C5aR	mAb	Bullous pemphigoid	II	NCT04563923
Fenebrutinib	BTK	SMI	CSU	II	NCT03137069
Remibrutinib	BTK	SMI	CSU	II	NCT03926611, NCT04109313
GSK2646264	SYK	SMI	CSU, CIndU	I	NCT02424799
Targeting inhibitory receptors					
LY3454738	CD200R	mAb	CSU	II	NCT04159701
			Atopic dermatitis	I	NCT03750643
Lirentelimab	Siglec-8	mAb	CSU, CIndU	II	NCT03436797
			Allergic conjunctivitis, AKC	I	NCT03379311
			ISM	I	NCT02808793
Targeting at reducing mast cell numbers					
CDX-0159	KIT	mAb	CSU	I	NCT04538794
			CIndU	I	NCT04548869
Masitinib	Tyrosine kinase	SMI	Asthma	III	NCT03771040, NCT01449162
Avapritinib	Tyrosine kinase	SMI	Advanced systemic mastocytosis, ISM	I–II	NCT02561988, NCT03580655, NCT03731260

ACD, allergic contact dermatitis; AKC, atopic keratoconjunctivitis; C5aR, complement C5a receptor; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; ISM, indolent systemic mastocytosis; OSMR β , oncostatin M receptor- β ; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; SMI, small-molecule inhibitor; SYK, spleen tyrosine kinase; TSLP, thymic stromal lymphopoietin.

serious neuropsychiatric events in patients taking montelukast and recommended montelukast as a reserve drug for treatment of allergic rhinitis.

Targeting cytokines and their receptors. IL-4 and IL-5 are type 2 cytokines that can be produced by human mast cells⁸³ and these cytokines influence the biological

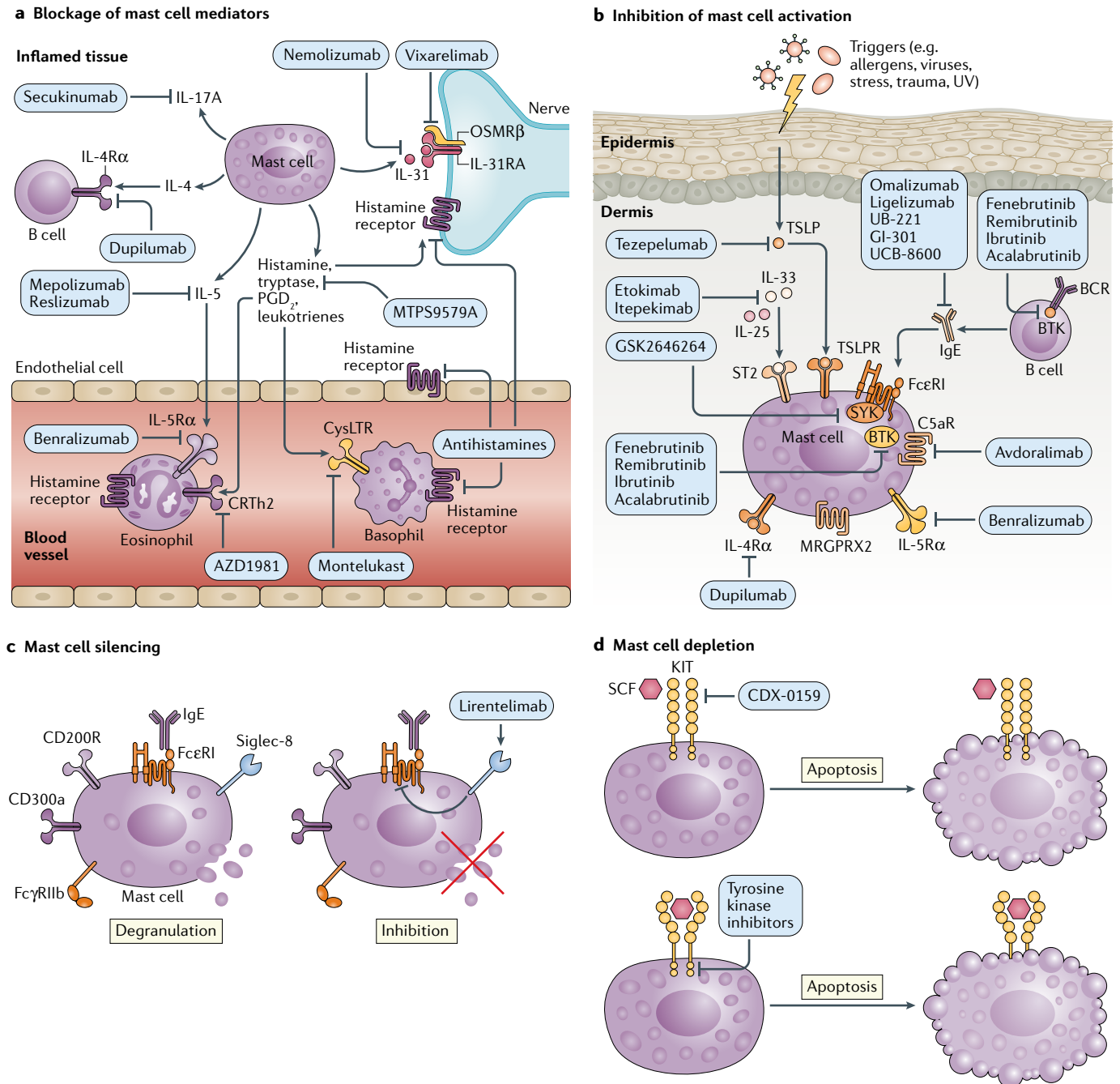


Fig. 3 | Current targets and relevant mast cell-targeted treatments under development. **a** | Activated mast cells can release a plethora of preformed and de novo synthesized mediators¹¹, which activate receptors on target cells. Drugs that block these mediators or their receptors can abrogate mast cell-associated effects. **b** | Diverse pathways of mast cell activation drive the development of the signs and symptoms of mast cell-mediated diseases and can be therapeutically targeted. Alarmins such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 are emerging targets as they activate mast cells. Allergen or autoallergen cross-linking of FcεRI-bound IgE can be blocked through use of anti-IgE therapies. FcεRI-mediated signalling through spleen tyrosine kinase (SYK) and BTK drives mast cell degranulation and production of mediators. Additional

benefit of BTK inhibition may come from effects on B cell receptor (BCR) signalling and decreased production of disease-relevant autoantibodies in autoimmune chronic spontaneous urticaria (CSU) and other diseases. Other promising therapeutic targets include complement C5a receptor (C5aR) (REF.¹²⁸) and Mas-related G-protein-coupled receptor X2 (MRGPRX2)^{29,31}. **c** | Mast cell activation and degranulation can be blocked via sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) and other inhibitory receptors⁵². **d** | Depletion of mast cells can be achieved with therapies aimed at the stem cell factor (SCF)–KIT interaction or KIT signalling. CRTh2, chemoattractant receptor homologous molecule expressed on T helper 2 cells (T_H2 cells); CysLTR, cysteinyl leukotriene receptors; OSMRβ, oncostatin M receptor-β; PGD₂, prostaglandin D₂.

Table 2 | Selected FDA-approved mast cell-targeted biological treatments and kinase inhibitors

Drug and indication	Age (years)	Recommended dose	Comments
Omalizumab, an anti-IgE mAb			
Antihistamine-resistant CSU	≥12	150 or 300 mg SC every 4 weeks	Add-on to H ₁ antihistamines
Moderate to severe persistent asthma	≥6	75–375 mg SC every 2 or 4 weeks ^a	Proved allergy ^b ; not controlled with ICS
Dupilumab, an anti-IL-4Rα mAb			
Moderate to severe atopic dermatitis	≥18	Initial dose 600 mg SC, followed by 300 mg every other week	Not controlled with topical treatment or when those therapies are not advisable
Moderate to severe eosinophilic asthma or oral corticosteroid-dependent asthma	≥12	Initial dose 400 or 600 mg followed by 200 or 300 mg, respectively, given every other week	Add-on maintenance treatment
Reslizumab, an anti-IL-5 mAb			
Severe eosinophilic asthma	≥18	3 mg/kg once every 4 weeks IV over 20–50 min	Add-on maintenance treatment
Mepolizumab, an anti-IL-5 mAb			
Severe eosinophilic asthma	≥12	100 mg SC once every 4 weeks	Add-on maintenance treatment
Eosinophilic granulomatosis with polyangiitis	≥18	300 mg as three separate 100 mg injections SC once every 4 weeks	–
Benralizumab, an anti-IL-5Rα mAb			
Severe asthma with an eosinophilic phenotype	≥12	30 mg SC every 4 weeks for the first three doses, followed by once every 8 weeks	Add-on maintenance treatment
Secukinumab, an anti-IL-17A mAb			
Moderate to severe plaque psoriasis	≥18	300 mg SC at weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks	In candidates for systemic therapy or phototherapy
Active psoriatic arthritis	≥18	Differs	–
Active ankylosing spondylitis	≥18	Differs	–
Midostaurin, a kinase inhibitor			
ASM, SM-AHN or mast cell leukaemia	≥18	100 mg orally twice daily with food	–
Acute myeloid leukaemia	≥18	50 mg orally twice daily with food	FLT3 mutation-positive; in combination with other treatment
Imatinib mesylate, a kinase inhibitor			
ASM	≥18	100 mg/day or 400 mg/day orally	Without the <i>KIT</i> D816V mutation or with <i>KIT</i> mutational status unknown
Other indications	All ages	Differs	For example, chronic myeloid leukaemia
Avapritinib, a kinase inhibitor			
Unresectable or metastatic gastrointestinal stromal tumour	≥18	300 mg orally once daily	Presence of <i>PDGFRA</i> exon 18 mutation

ASM, aggressive systemic mastocytosis; CSU, chronic spontaneous urticaria; FDA, US Food and Drug Administration; H₁, histamine H₁ receptor; ICS, inhaled corticosteroids; IV, intravenous infusion; SC, subcutaneous injection; SM-AHN, systemic mastocytosis with associated haematological neoplasm. ^aDose and dosing frequency determined by baseline serum total IgE level and body weight. ^bPositive skin test or in vitro reactivity to a perennial aeroallergen.

functions of mast cells and other type 2 immune cells, including eosinophils, by regulating cellular responses such as cell differentiation, growth and cytokine production. Dupilumab, a mAb, acts as a dual inhibitor of IL-4 and IL-13 signalling through blockade of their shared IL-4 receptor-α subunit. It is approved for the

treatment of atopic dermatitis^{84,85}, asthma⁸⁶ and chronic rhinosinusitis with nasal polyps (TABLE 2). Preliminary reports also demonstrated that it can be effective in other IL-4/IL-13-mediated diseases, such as CSU and chronic prurigo^{87,88}. The anti-IL-13 mAbs lebrikizumab⁸⁹ and tralokinumab⁹⁰ showed inconsistent effects for treatment

of asthma in phase III studies, but early and sustained symptom control and a favourable safety profile in phase II studies in adults with moderate to severe atopic dermatitis^{91,92}.

The anti-IL-5 mAbs reslizumab⁹³ and mepolizumab⁹⁴ and the anti-IL-5 receptor- α mAb benralizumab⁹⁵ are used as add-on therapy for the treatment of severe eosinophilic asthma⁸¹ (TABLE 2). All three drugs decrease the frequency of asthma exacerbations and markedly deplete blood eosinophils, with less relevant improvement in lung function^{93,96,97}. Recently, benralizumab demonstrated promising effects in patients with CSU⁹⁸.

Mast cells are reported to be a major source of IL-17A (through uptake and/or production of IL-17A) in patients with inflammatory diseases, including asthma, CSU and cancer^{99–101}. In CSU, secukinumab, an anti-IL-17A mAb, reduced disease activity, although it was slow in onset¹⁰¹. In one randomized controlled trial (RCT) in patients with asthma, brodalumab, a human anti-IL-17 receptor mAb, showed lack of efficacy¹⁰².

IL-31 is produced by mast cells and other cells, and its levels are elevated in pruritic skin diseases. In phase II trials, nemolizumab, a mAb to IL-31R α , led to significant improvement of pruritus and skin lesions in patients with atopic dermatitis^{103–105} and prurigo nodularis¹⁰⁶, although gastrointestinal and musculoskeletal side effects have been reported. Vixarelimab is an anti-oncostatin M receptor- β (anti-OSMR β) mAb, which inhibits IL-31 signalling. It is being evaluated in patients with CSU, chronic prurigo and other pruritic diseases.

When targeting cytokines to inhibit mast cell activity, it is important to note that although mast cells are an important source of certain cytokines such as IL-17A, their production of other cytokines may be relatively low compared with other cells. For example, T_H2 cells rather than mast cells are thought to be the major sources of IL-5 and IL-13 in many allergic-type diseases. Nevertheless, clinical trials are underway to evaluate the efficacy of cytokine-targeting therapies in various bona fide mast cell-driven diseases (TABLE 1).

Targeting Fc ϵ RI and IgE. Fc ϵ RI, the high-affinity IgE receptor, is involved in urticaria, asthma and allergic responses¹¹. Omalizumab is the first highly effective anti-IgE mAb approved for the treatment of moderate and severe asthma¹⁰⁷ and antihistamine-resistant CSU⁴⁸ (FIG. 3b; TABLE 2). It binds to free IgE, decreases free IgE levels and inhibits the IgE–Fc ϵ RI interaction by preventing binding of IgE to Fc ϵ RI on the surface of mast cells and basophils, and by indirectly downregulating Fc ϵ RI expression. Furthermore, omalizumab improved symptoms in patients with CSU with IgE autoantibodies against thyroperoxidase, suggesting that these autoantibodies are involved in disease pathogenesis in a subpopulation of patients with CSU¹⁰⁸. In addition to CSU and asthma, omalizumab has been reported to be effective in other mast cell-mediated conditions including CIndU, atopic dermatitis, mastocytosis, food allergy, allergic rhinitis and urticarial vasculitis (partly reviewed in REF.¹⁰⁹). In idiopathic anaphylaxis, however, the effects of omalizumab were shown to be modest¹¹⁰.

Ligelizumab, a next-generation humanized anti-IgE mAb, has 40-fold to 50-fold higher affinity for the C ϵ 3 domain of IgE compared with omalizumab and may affect IgE production by B cells¹¹¹. In a phase IIb RCT, a higher number of patients with CSU benefited from ligelizumab therapy as compared with omalizumab or placebo⁴⁹. Ligelizumab had a rapid onset of action and dose-dependent efficacy and showed a longer time to relapse after the last injection than omalizumab, that is 10 weeks versus 4 weeks. Currently, ligelizumab is being studied in phase III trials in adults and adolescents with CSU. In January 2021, ligelizumab received FDA Breakthrough Therapy designation for use in patients with CSU who show an inadequate response to H₁ antihistamines. However, in asthma, phase II clinical trials of ligelizumab failed to meet the primary objective and were discontinued (NCT02075008, NCT02336425). As compared with omalizumab, ligelizumab is a less potent inhibitor of IgE–CD23 interactions, the pathway that might be more important in asthma than in CSU¹¹¹.

Several other promising compounds and approaches targeting Fc ϵ RI and/or IgE are being investigated (TABLE 1). Compared with omalizumab, GI-301 — a long-acting IgE trap–Fc fusion protein — and the anti-IgE mAb UB-221 exhibited higher and more durable binding to IgE. Dual treatment with omalizumab and omalizumab-resistant IgE–Fc fragment (IgE–R419N–Fc3–4 mutant) induced stronger inhibition of basophil activation than either agent alone¹¹². Antisense oligonucleotide-mediated exon skipping of the β -subunit of Fc ϵ RI β eliminated Fc ϵ RI expression and function in mast cells. Importantly, this therapy is very selective and restricted to mast cells and basophils, which are the cells that exclusively express Fc ϵ RI β ¹¹³.

Targeting type 2 cytokines and their receptors. Alarmins, thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 act on downstream cellular targets, including mast cells, to initiate the release of a broad range of cytokines involved in atopy (FIG. 3b). Tezepelumab (AMG-157/MEDI9929), a human anti-TSLP mAb, decreased asthma exacerbation rates¹¹⁴ and showed statistically non-significant improvements of atopic dermatitis over placebo¹¹⁵. Further studies of anti-TSLP drugs are under way (TABLE 1). Etokimab (ANB020), an anti-IL-33 mAb, demonstrated the potential to desensitize participants who are allergic to peanuts¹¹⁶ and showed a rapid and sustained improvement in adult patients with moderate to severe atopic dermatitis¹¹⁷, but failed to meet its primary end point in a phase IIb study in atopic dermatitis. Another anti-IL-33 mAb, itepekimab (REGN3500), improved lung function in patients with asthma when compared with placebo but was less effective in comparison with dupilumab in a phase II proof-of-concept trial. A novel IL-33 antagonist, IL-33trap, exhibited anti-inflammatory effects in a mouse model of acute allergic airway inflammation at the time of allergen challenge¹¹⁸. The anti-IL-33 receptor (ST2) mAb astegolimab is being investigated in asthma and atopic dermatitis in phase II clinical trials (TABLE 1). Neutralizing antibodies to IL-25 have also shown some beneficial effects in a mouse model of allergic asthma¹¹⁹.

Targeting other mast cell receptors. MRGPRX2 is crucial for IgE-independent mediator release by mast cells. This receptor is also unique in that it can be activated by a broad range of exogenous and endogenous substances including cysteine proteases, neuropeptides and some drugs^{29,31,120}. Interestingly, activation of the MRGPRX2 mouse orthologue, Mrgprb2 (REF.³⁰), led to release of more tryptase and less histamine from mast cells compared with IgE–FcεRI stimulation¹²¹. Pathological MRGPRX2 activation is poorly understood but may be linked primarily to genetic polymorphisms and mutations in the *MRGPRX2* gene. These may influence the receptor's structure and affinity for agonists, for example, by altering ligand-binding properties or by inducing stronger intracellular signalling. Gain-of-function and loss-of-function missense single-nucleotide polymorphisms in *MRGPRX2* have been reported¹²². Additionally, increased MRGPRX2 expression in tissue can explain why only some patients experience exacerbated reactions to certain drugs or other MRGPRX2 ligands in chronic diseases. For example, the number of MRGPRX2-positive skin mast cells was found to be higher in patients with chronic urticaria than in healthy subjects³¹. In addition, higher MRGPRX2 expression levels might predispose to a greater response to MRGPRX2 agonists, such as substance P. Indeed, patients with chronic urticaria showed enhanced and longer-lasting wheal reactions after intradermal injection of substance P compared with healthy controls¹²³. Novel MRGPRX2 antagonists have shown beneficial effects in preclinical models of mast cell-driven pathology^{124,125}. Furthermore, intradermal injection of photosensitizer-coupled anti-MRGPRX2 antibodies in human skin explants enabled 70–90% depletion of skin-resident mast cells following exposure to 660-nm wavelength light without any reduction of bystander macrophages¹²⁶.

Two other mast cell-expressed receptors that are being investigated are complement C5a receptor (C5aR; also known as CD88) and cell adhesion molecule 1 (CADM1). C5aR is expressed by skin mast cells¹²⁷ but not by other mast cells, and its interaction with C5a has been proposed to drive the symptoms of CSU¹²⁸ and other autoimmune diseases, for example rheumatoid arthritis. Avdoralimab, a C5aR-blocking mAb, is being investigated in patients with autoimmune CSU (EudraCT Number: 2020-002510-40) and bullous pemphigoid (TABLE 1). CADM1 is used by mast cells to interact with other cells, for example fibroblasts and airway smooth muscle cells, and this adhesion molecule is crucial for the normal function of KIT (reviewed in REF.¹²⁹). Although anti-human CADM1 mAbs are in development as a potential therapy for cancer, their effects on mast cells have not yet been investigated.

Targeting intracellular signalling pathways. There are promising drugs that can target intracellular signal transduction from the plasma membrane receptors to cytoplasmic effectors and block mast cell activation and degranulation. In mast cells, several cytoplasmic signalling proteins are potential targets, including spleen tyrosine kinase (SYK) and BTK (FIG. 3b).

GSK2646264, a SYK inhibitor, administered topically or directly to the dermis blocked histamine release from skin mast cells¹³⁰ in situ and showed a clinically meaningful reduction in the critical temperature threshold in some patients with cold urticaria¹³¹. In rodent models, other SYK inhibitors such as fostamatinib, LAS189386, TAS05567, BAY61-3606 and aerosolized SYK antisense oligodeoxynucleotides inhibited mast cell degranulation, asthmatic and/or anaphylactic responses, and/or IgE-mediated ear swelling. In an RCT, an intranasal SYK inhibitor R112 improved symptoms in patients with seasonal rhinitis¹³².

Fenebrutinib is a potent, highly selective, reversible, oral BTK inhibitor, which inhibits FcεRI signalling in mast cells and basophils and B cell receptor (BCR) signalling, thus disrupting antibody production. Fenebrutinib rapidly decreased disease activity in patients with refractory CSU and circulating IgG anti-FcεRI autoantibodies in patients with autoimmune CSU. Fenebrutinib was well tolerated, although reversible liver enzymes abnormalities have been reported⁵⁰. Other BTK inhibitors are in development for the treatment of mast cell-driven diseases, including remibrutinib for CSU, ibrutinib for food allergy¹³³ and acalabrutinib for anaphylaxis²⁶.

Silencing mast cells. Mast cells express inhibitory receptors such as Siglec-8, CD200R, CD300a and FcγRIIb, which block mast cell activation upon interaction with ligands of the inhibitory receptors (reviewed in REF.¹³⁴) (FIG. 3c). As eosinophils also express Siglec-8, anti-Siglec-8 antibody treatment showed combined effects, inhibition of mast cell-mediated anaphylaxis in humanized mice and IgE-dependent and IgE-independent activation of human mast cells in lung tissues as well as depletion of eosinophils in dissociated human lung tissue and the sputum of patients with asthma^{51–53}. The anti-Siglec-8 mAb lirentelimab (AK002) has been recently investigated in patients with indolent systemic mastocytosis (ISM), omalizumab-naïve and omalizumab-refractory CSU, CIndU and other diseases. For example, a press release reported lirentelimab efficacy in 55% of patients with omalizumab-refractory CSU. Lirentelimab reduced blood eosinophil counts and gastrointestinal mast cell numbers in patients with eosinophilic gastrointestinal diseases, suggesting that mast cells also may be implicated in the pathogenesis of these conditions¹³⁵.

LY3454738, a CD200R agonist, is currently under development for atopic dermatitis and CSU (TABLE 1). In preclinical studies, bispecific antibodies that cross-link either IgE¹³⁶ or KIT¹³⁷ and CD300a, and co-aggregate FcεRI with FcγRIIb¹³⁸, abrogated FcεRI/IgE-induced or KIT-induced signalling. A novel bispecific anti-IgE DARPIn (designed ankyrin repeat protein)–Fc fusion protein was able to aggregate FcεRI-bound IgE with FcγRIIb and blocked IgE–FcεRI interactions faster and more efficiently than omalizumab, and led to the dissociation of preformed ligand–receptor complexes^{139,140}.

Depleting mast cells. A reduction of tissue mast cell numbers can be achieved by the induction of apoptosis, via neutralization of the effects of tissue factors,

Box 2 | Major advances in understanding of human mast cells functions in disease we have learned from mast cell-targeted treatments

- Antihistamines: mast cells are the major source of histamine in tissues and significantly contribute to urticaria, mastocytosis and allergic diseases via secretion of this mediator.
- Anti-IgE therapies: the IgE–FcεRI pathway of mast cell activation is crucial in urticaria and allergic diseases. FcεRI-mediated mast cell activation is associated with IgE autoantibodies in a subpopulation of patients with chronic spontaneous urticaria (CSU).
- BTK inhibition: FcεRI signalling associated with BTK activation in mast cells is linked to the development of symptoms of CSU.
- Silencing therapies: IgE-independent pathways of mast cell activation can be important in a subpopulation of patients with CSU refractory to omalizumab and responsive to anti-sialic acid-binding immunoglobulin-like lectin 8 (anti-Siglec-8) mAb treatment. Mast cells might be involved in eosinophilic gastrointestinal diseases. The beneficial effects of anti-Siglec-8 treatment may relate to its combined effects on eosinophils and mast cells.
- Mast cell depletion therapies: mast cells are the main players in mastocytosis and urticaria. These therapies may also help decipher the contribution of mast cells to other diseases.

for example SCF and/or blockage of its receptor KIT (CD117) (FIG. 3d). CDX-0159, a potent humanized anti-KIT mAb, selectively inhibited SCF-dependent KIT activation and KIT-dependent enhancement of mast cell degranulation in vitro. In a phase Ia RCT of healthy volunteers (NCT04146129), CDX-0159 showed a favourable safety profile and profound tryptase suppression for >2 months, indicative of systemic mast cell ablation. Dose-dependent increases in plasma SCF mirrored decreases in tryptase and are consistent with allosteric blockade of SCF binding to KIT. Since 2020, CDX-0159 is being investigated in phase Ib studies of CIndU and CSU (TABLE 1). In March 2021, an interim data update reported an 80% complete response rate in antihistamine-refractory cold urticaria and symptomatic dermographism.

Two tyrosine kinase inhibitors (TKIs) have been approved by the FDA for the treatment of adult patients with aggressive systemic mastocytosis (ASM) without the *KIT* D816V mutation or an unknown mutational status (imatinib) and with wild-type *KIT* and mutant *KIT* D816V (midostaurin) (TABLE 2). Midostaurin showed an overall response rate of 60–69%¹⁴¹ in patients with advanced systemic mastocytosis and improved the overall and relapse-free survival^{142,143}. The overall response rates for other TKIs ranged from 22% (nilotinib, advanced systemic mastocytosis including patients with *KIT* D816V (REF.¹⁴⁴)) to 33% (dasatinib, advanced systemic mastocytosis¹⁴⁵) and 19–56% (masitinib, ISM or cutaneous mastocytosis^{146,147}). The response rates to nilotinib and dasatinib reflected the decrease of mast cell numbers, tryptase or clinical improvement, whereas response rates for masitinib reflected specific symptoms only, as masitinib is weak in reducing mast cell numbers. Ripretinib is a novel ‘switch-control’ inhibitor of mutant *KIT* and *PDGFRA* kinases that showed inhibition of the growth of neoplastic mast cells and was effective in preclinical models of mastocytosis, gastrointestinal stromal tumours and lung cancer¹⁴⁸. Severe adverse events have been reported

during treatment with TKIs, for example diarrhoea, rash and asthenia for masitinib.

In addition, imatinib treatment reduced airway hyperresponsiveness, mast cell numbers and tryptase release in patients with severe asthma¹⁴⁹. In another recent phase III trial, masitinib therapy reduced asthma exacerbations by 35% compared with placebo in patients with severe uncontrolled asthma regardless of the baseline eosinophil level¹⁵⁰.

Avapritinib (BLU-285) is a potent and highly selective oral inhibitor of mutant *KIT* and *PDGFRA* with activation loop mutations. In the phase I EXPLORER study in adult patients with advanced systemic mastocytosis, avapritinib showed an overall response rate of 77% and complete and durable responses across all advanced systemic mastocytosis subtypes and in patients with poor prognosis¹⁵¹. Avapritinib reduced bone marrow mast cell infiltration, serum tryptase levels and the *KIT* D816V allele burden. It was well tolerated, and haematological adverse events were the most common reason for decreasing the dose. The drug is now being further evaluated in patients with ISM and advanced systemic mastocytosis (TABLE 1), and has been recently approved for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (TABLE 2).

Conclusions

The approval of omalizumab for asthma in 2003 and then for CSU in 2014 was a major breakthrough in the treatment of patients with mast cell-driven diseases and marked the beginning of defining the role of human mast cells by targeted treatment. Since then, many promising mast cell-targeted therapeutic agents, such as ligelizumab, fenebrutinib and remibrutinib, lirentelimab and CDX-0159, have entered clinical development. Their use continues to advance our understanding of the roles of mast cells in human diseases, not just in the diseases these treatments were primarily developed for but also beyond.

Responders and non-responders to treatments that target specific mast cell mediators or activators point to specific disease endotypes, where these mast cell targets do or do not play a role in the pathogenesis. This, in turn, will lead to endotype-specific therapies and, eventually, to personalized (precision) treatment (FIG. 1). As a consequence, the current ‘one-size-fits-all’ approach will be replaced by the use of treatments with the best benefit–risk ratio for every patient. The bigger picture is that these novel mast cell-targeted treatments, especially mast cell silencing and depletion treatments, will finally give us information on which diseases are mast cell-mediated and which are not.

Taken together, the use of mast cell-targeted treatments, primarily for bona fide mast cell-driven diseases such as mastocytosis and urticaria, has led to — and will continue to lead to — major advances in our understanding of human mast cell functions (BOX 2). The insights these studies provide into the pathogenesis of mast cell-driven and mast cell-associated diseases will increase our ability to help patients affected by these diseases.

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Author contributions

P.K. and M.Ma. conceived the idea for the Review. P.K. researched data for the article and wrote the first version of the manuscript under the supervision of M.Ma., with

constructive input from M.Me. and F.S. D.E.-A.-K. prepared figures under the supervision of P.K. and M.Ma., and contributed to the discussion of the content. All authors read and approved the final version of the manuscript.

Competing interests

P.K. was recently a speaker for Novartis and Roche. M.Me. was recently a speaker and/or adviser for Amgen, Aralez, ArgenX, Bayer, Beiersdorf, Celgene, Galderma, Menlo, Moxie, Novartis, Roche, Sanofi, Shire, Siennabio and Uriach. F.S. was recently a speaker and/or adviser for and/or has received research funding from Allakos, Blueprint, Celldex, Genentech, Novartis, Moxie and Uriach. M.Ma. was recently a speaker and/or adviser for and/or has received research funding from Allakos, Alnylam, Amgen, Aralez, ArgenX, AstraZeneca, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GInnovation, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third HarmonicBio, UCB and Uriach. D.E.-A.-K. declares no competing interests.

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Supplementary information

Understanding human mast cells: lesson from therapies for allergic and non-allergic diseases

In the format provided by the
authors and unedited

Supplementary Table 1. Mast cell-derived mediators

Mediators	Receptors	Proposed or potential function	Refs
Biogenic amines			
Histamine	H ₁ R	Bronchoconstriction, vasodilation and increased vascular permeability	1,2
	H ₂ R	Involved in Th1 lymphocyte cytokine production, vasodilation, bronchial smooth muscle relaxation, gastric acid secretion, increase in heart rate and airway mucus production	
	H ₃ R	Involved in blood–brain barrier function	
	H ₄ R	Chemotaxis of MC and eosinophils; potential role in itch, allergy and asthma	
Serotonin	5-HT receptors	Immunomodulation, cell growth and development, tumorigenesis, tissue regeneration	3,4
Dopamine	Dopamine 1-5 receptors	A neurotransmitter; controls locomotion, emotion, cognition, and neuroendocrine secretion; contributes to vasodilation	5
Polyamines	NMDA-R	Various metabolic functions	6
Proteases			
Tryptase	PAR	An important role in inflammation and a marker of MC activation	7
Chymase	PAR1,2	An important role in inflammatory response	7
Carboxypeptidase A3	Unknown	Involved in the degradation of endogenous proteins and the inactivation of venom-associated peptides	8
Cathepsin G	PAR	A role in inflammation and normal physiological processes	9
MMP1,2,9	CXCR-4, PAR1?	Involved in the cleavage of the extracellular matrix, potential pro-inflammatory activities	10-12
Active caspase 3	Unknown	Unknown, was shown to cleave IL-33	13
ADAMTS5	Unknown	Involved in aggrecan degradation	14
Granzyme B	CI-MPR	Contributes to cell death	15
Renin	Renin receptor	Triggers formation of angiotensin II; role in regulation of blood pressure	16
Other mediators			
Heparanase	Mannose-6-phosphate receptors	Implicated in control of degradation of heparin in MC secretory granules	17
Cathelicidin LL37	Proposed receptors: CXCR2, MRGPRX2, TLR, other	An antimicrobial peptide	18
Secretogranin III, chromogranin A	–	Involved in secretory granule biogenesis in MC	19
Proteoglycans			
Heparin	TMEM184A?	Implicated in regulation of the mediator content of MC cytoplasmic granules, increase of vascular permeability	20,21
Chondroitin sulfate, dermatan sulfate	Unknown	Potential anti-inflammatory properties; implicated in wound repair and fibrosis	2,22
Lysosomal enzymes			
β-Glucuronidase, β-D-galactosidase, N-acetyl-β-glucosaminidase	–	Implicated in lysosomal degradation processes	23
β-Hexosaminidase	–	A marker of MC degranulation; a probable role in defense against bacterial invasion	2,17,23,24
Arylsulfatase A	–	Implicated in lysosomal degradation processes	23
Cathepsin B, C, L, D, E, S	Proposed receptors: MRGPR, PAR	Implicated in lysosomal degradation processes and regulation of levels of stored proteases in MC secretory granules; possible role in cancer and inflammation	25
Lipid mediators			
PGD ₂	DP1, CRTh2/DP2, TP	MC are the largest source of PGD ₂ in the body; PGD ₂ contributes to smooth muscle contraction, vascular leak and vasodilation, modulates migration and activation of immune cells	26,27
PGE ₂	EP1-4	Smooth muscle relaxation (EP2) and contraction (EP1, EP3); pro-inflammatory and anti-inflammatory properties	28
LTC ₄ , LTD ₄	CysLT ₁ R, CysLT ₂ R, CysLT ₃ R	Inflammatory responses including bronchoconstriction, vasodilation, increased microvascular permeability, mucus secretion, and eosinophil survival	2,29,30
LTB ₄	BLT1, BLT2	A potent activator and chemoattractant for leukocytes, involved in airway hyperresponsiveness	31,32

PAF	PAF receptor	Bronchoconstriction; increases vascular permeability and edema; involved in chemoattraction of neutrophils and eosinophils	33,34
TXA ₂ , TXB ₂	TX receptor	Implicated in vasoconstriction and platelet aggregation	33,35
S1P	S1P1-S1P5	Implicated in initiation and maintenance of diverse aspects of immune cell activation and function	36,37
Cytokines, growth factors and mitogens			
IL-1 β	IL-1R	A pro-inflammatory cytokine. MC-derived IL-1 β contributed to the development of arthritis, and skin inflammation in mice	38
IL-2	IL-2R	Contributes to Treg cell development and homeostasis	39
IL-4	IL-4R	A critical role in the development of Th2 cells and subsequent allergic reactions	38,40
IL-5	IL-5R	A type-2 cytokine with important effects on growth, adhesion, transendothelial migration, chemotaxis, activation and prolonged survival of eosinophils	38,40,41
IL-6	IL-6R (CD126)	A pro-inflammatory cytokine produced during a variety of inflammatory responses	38
IL-9	IL-9R (CD129)	Involved in type 2 immunity, including allergic diseases and host defenses against parasitic infections	42
IL-10	IL-10R1/2	Anti-inflammatory and immunosuppressive effects; shifts Th1/Th2 balance in favor of Th1 cell	41,43
IL-11	IL-11R α	Might be involved in the pathogenesis of asthma, ie airway hyperresponsiveness, and lung inflammation	44
IL-12	IL-12R β 1 (CD212)	Induction of Th1 responses; stimulation of IFN- γ production from Th1 cells and NK cells	45
IL-13	IL-4R α , IL-13R α 1, IL-13R α 2	An important cytokine in type-2 immune responses with functions that partially overlap with those of IL-4	41,46
IL-15	IL-15R	Located intracellularly and controls MC survival in mice	47
IL-16	CD4, CD9	A pro-inflammatory cytokine; a chemoattractant for T cells, eosinophils, monocytes, dendritic cells, and MC	48
IL-17	IL-17	A pro-inflammatory cytokine	49
IL-25	IL-25R	A type-2 immunity cytokine	50
IL-31	IL-31R	Plays a key role in itch induction	51
IL-33	ST2	Induces the production of IgE and the Th2-associated interleukins by various cells; possible cardioprotective role	52
TSLP	TSLPR	A type-2 immunity cytokine, alarmin. MC produce TSLP following aggregation of Fc ϵ R1 in the presence of IL-4	53
IFN- γ	IFNGR	A Th1 cytokine that may be important in the promotion of atherogenesis, diet-induced obesity and glucose intolerance	38
TNF- α	TNFR1, TNFR2	Pro-inflammatory properties	54
EGF	HER	Stimulation of proliferation and differentiation of various cells including fibroblasts, endothelial cells, and epithelial cells	55
GM-CSF	CSF2RA, CSF2RB	Regulation of differentiation, proliferation, and survival of various cells; might participate in allergic diseases, for example by promoting eosinophil survival	38
FGF2/bFGF	FGFR	A potential pro-angiogenic factor	56
NGF	TrkA receptors	Regulation of the development, growth, survival, and function of central and peripheral neurons	57
PDGF	PDGFR α , PDGFR β	Contribution to angiogenesis by facilitating the growth of blood vessels; possible contribution to the pathogenesis of atrial fibrillation	58
SCF	KIT	Contribution to differentiation, growth, chemotaxis and survival of various cells including MC	59
TGF- β 1	TGF β R	Contributes to fibrosis, angiogenesis, and tissue repair; can increase type I collagen production in fibroblasts	54
VEGF/VPF	VEGFR1, VEGFR2	A pro-angiogenic factor that can enhance vascular permeability and angiogenesis processes by promoting endothelial cell proliferation and migration	55
Chemokines			
CCL1 (I-309)	CCR8	Cell migration and many other functions	38
CCL2 (MCP-1)	CCR2, DARC, D6		38
CCL3 (MIP1 α)	CCR1, D6		38
CCL4 (MIP1 β)	CCR5, D6		38
CCL5 (RANTES)	CCR1, CCR3, CCR5, DARC, D6		60

CCL7 (MCP3)	CCR2, CCR3, DARC, D6		61
CCL8 (MCP2)	CCR2, CCR3, DARC, D6		62
CCL9 (MIP1 γ)	CCR1		63
CCL11 (eotaxin)	CCR3, DARC, D6		60
CCL17 (TARC)	CCR4, D6		61
CCL20 (MIP3 α)	CCR6		61
CCL22 (MDC)	CCR4, D6		61
CXCL2 (GRO β)	CXCR2, DARC		45
CXCL10 (IP10)	CXCR3		64

ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; GM-CSF: granulocyte-macrophage colony-stimulating factor; EGF: epidermal growth factor; FGF2/bFGF: fibroblast growth factor / basic fibroblast growth factor; IFN: interferon; IL: interleukin; LT: leukotriene; MC: mast cell(s); MIP1: the macrophage inflammatory proteins; MMP: matrix metalloproteinases; MRGPR: Mas-related G protein–coupled receptor; NGF: nerve growth factor; PAF: platelet-activating factor; PAR: protease activated receptor; PDGF: platelet-derived growth factor; PG: prostaglandin; S1P: sphingosine-1-phosphate; SCF: stem cell factor; TGF- β : transforming growth factor beta; TP: thromboxane prostanoid receptor; TSLP: thymic stromal lymphopoietin; TX: thromboxane; VEGF/VPF: vascular endothelial growth factor/vascular permeability factor

Supplementary Table 2. Mast cell receptors and their ligands

Human [Murine counterpart if differs]	Important ligands	Receptor family or subfamily	Described effects (mast cells)	Refs	Expression of receptor on other cells
Activating receptors					
H ₁ R	Histamine	GPCR	MC activation	⁶⁵	Many cells
H ₂ R	Histamine	GPCR	Decreases chemotaxis	⁶⁵	Many cells
H ₃ R	Histamine	GPCR	Expressed in brain MC, auto-receptor	^{66,67}	Neurons, eosinophils, DC, monocytes
H ₄ R	Histamine	GPCR	Histamine and cytokine generation, enhances chemotaxis	⁶⁵	Various immune and other cells
5-HT _{1A}	Serotonin	GPCR	MC adhesion and migration	⁶⁸	Neurons, platelets, lymphocytes, and monocytes
D ₁ R, D ₃ R	Dopamine	GPCR	Inhibition or induction of MC degranulation	⁶⁹	Lymphocytes, macrophages, neutrophils, NK cells
Undefined receptor	Polyamines	GPCR	Activation of MC; maintenance of MC granule homeostasis	⁷⁰	Unknown
PAR1	Thrombin, chymase	GPCR	MC activation	⁷¹	Vascular, immune and epithelial cells, astrocytes, neurons
PAR2	Tryptase, chymase	GPCR	MC activation	⁷¹	Vascular, immune and epithelial cells, astrocytes, neurons
DP1	PGD ₂	GPCR	MC maturation	⁷²	Basophils, eosinophils, Th2 cells, DC, and other cells
CRTH ₂ /DP2	PGD ₂	GPCR	A potential role in pro-inflammatory activities	⁷³⁻⁷⁵	Th2 cells, eosinophils, basophils and other cells
CysLT ₁ R, CysLT ₂ R	LTC ₄ , LTD ₄ , LTE ₄	GPCR	Activation of MC and cytokine generation	²⁹	Structural and hematopoietic cells
BLT1, BLT2	LTB ₄	GPCR	Found in immature MC; related to LTB ₄ -dependent chemotaxis	^{31,76}	T cells, DC, osteoclasts, granulocytes, eosinophils, and other cells
Chemokine receptors: CXCR1–4, CX3CR1, CCR1, CCR3–5	Respective chemokines	GPCR	Chemotaxis of MC, potential to affect MC degranulation, e.g. in allergic settings	⁷⁷	Hematopoietic and lymphatic cells
MRGPRX1 [MrgprC11]	γ1-MSH, compound 48/80, BAM22, chloroquine	GPCR	Activation and degranulation of MC	⁷⁸	Neurons
MRGPRX2 [MrgprB2]	Basic secretagogues, e. g. neuropeptides	GPCR	Activation and degranulation of MC	^{79,80}	Neurons, keratinocytes, basophils, eosinophils, thymocytes, T-lymphocytes
EP3R	PGE ₂	GPCR	MC mediator release	⁸¹	Widely expressed
A3AR	Adenosine	GPCR	Degranulation of MC	⁸²	Widely expressed
PAFR	PAF	GPCR	Activation and degranulation of MC; regulates MC chemotaxis	^{83,84}	Majority of cells of the vascular and innate immune systems
NK1R, NK2R, NK3R	SP, Senktide	GPCR	Degranulation of MC	^{85,86}	Many cells
VPAC2	VIP	GPCR	Degranulation of MC	⁸⁶	Lymphocytes, DC, NK cells and macrophages
CGRPR	CGRP	GPCR	Controversial data regarding contribution to MC degranulation	⁸⁶	Predominantly in neurons
KIT receptor (CD117)	SCF	Type III receptor tyrosine kinase	MC differentiation, growth, survival and apoptosis; role in	^{87,88}	Hematopoietic cells, melanocytes and other cells

		family	MC migration, adhesion and IL-6 secretion		
C3aR	C3a	GPCR	MC activation and degranulation	⁸⁹	T cells, neutrophils, basophils, eosinophils, monocytes/macrophages and other cells
C5aR	C5a	GPCR	MC activation and degranulation	⁹⁰	T cells, neutrophils, basophils, eosinophils, monocytes/ macrophages and other cells
Death receptors: Fas and TRAIL-R1, TRAIL-R2	Fas, TRAIL	TNF-R superfamily	MC apoptosis	⁹¹	Keratinocytes, fibroblasts, melanocytes, eosinophils, T cells, macrophages, neutrophils, NK cells and other cells
IL-4R α	IL-4, IL-13	Type I cytokine receptor family	Influence MC function and differentiation/growth. IL-4 can promote degranulation and enhance cytokine production, induction of Fc ϵ R1 expression	^{92,93}	Th2 cells, B cells, macrophages
IL-5R	IL-5	Type I cytokine receptor	Mediates SCF-dependent comitogenesis of MC. IL-5 augments cytokine production by MC	⁹³	Eosinophils, basophils, B cells
IL-6R (CD126)	IL-6	Type I cytokine receptor	Supports MC growth	^{93,94}	Many cells
IL-9R	IL-9	Type I cytokine receptor	Enhances the growth of human MC progenitors	⁹⁵	A variety of hematopoietic cells
IL-25R (IL-17RA/RB)	IL-25 (IL-17E)	The IL-17 receptor family	Allergen-induced expression of IL-25R in atopic asthmatic airways and late-phase cutaneous responses	⁵⁰	Eosinophils, endothelial cells, and T lymphocytes.
CD4, CD9	IL-16	Immunoglobulin superfamily (CD4), tetraspanin family (CD9)	A possible role in antiviral defense	^{96,97}	Many cells
IL-18R	IL-18	Immunoglobulin superfamily, IL-1 receptor family	Production of cytokines by MCs	⁹⁸	T cells, NK cells, macrophages, epithelial cells, chondrocytes, DC and other cell types
IFNGR	IFN- γ	Class II family of cytokine receptors	Inhibition of growth and/or induction of MC apoptosis. Inhibition of MC-associated cytotoxicity and serotonin release. In other studies, promotion of MC survival and histamine release	⁹⁹	Various cells
TrkA	NGF	Tyrosine kinases family	Promotes certain aspects of MC development and/or maturation	⁵⁷	Neurons
VEGFR1, VEGFR2 [Flt-1, KDR/Flk-1]	VEGF/VPF	Tyrosine kinase receptors	MC chemotaxis	¹⁰⁰	Many cells
GM-CSFR (CSF2R, CD116)	GM-CSF	Type I cytokine receptors	Potentially controls MC differentiation	^{101,102}	Many cells
TSLPR and IL-7R α	TSLP	Type I cytokine receptor	Cytokine and chemokine release by MC	¹⁰³	Hematopoietic cell lineages, including B cells, T cells, eosinophils, and DC
CD48	2B4, <i>E. coli</i> FimH, <i>S. aureus</i> ,	The CD2	Degranulation, cytokine release	^{104,105}	Various hematopoietic cells

	and <i>M. tuberculosis</i> antigens	subfamily of Ig-superfamily			
S1P1R, S1P2R	S1P	GPCR	Migration of MC, MC degranulation and cytokine and chemokine release	36,106	Many cells
P1 receptors: A3R	Adenosine	GPCR	Degranulation?	107	Many cells
P2 receptors: P2X and P2Y	ATP, ADP, UTP, UDP, UDP-glucose	GPCR	Production of cytokines, chemokines and lipid mediators by MC, apoptosis	108,109	Many cells
CRHR	CRH	GPCR	Selective secretion of VEGF	110	Lymphocytes, cells of pituitary, brainstem, skin and testis
TLR	PAMPs, e.g. flagellin, LPS	PRR	Cytokine, chemokine, lipid mediators secretion	111	Many cells
ST2L (IL-33R), sST2	IL-33	IL-1 receptor family	ST2: Production of MC cytokines, promoting differentiation, survival, and chemotaxis of MC sST2: Inhibitory effects	112-114	Th2 cells
FcεRI	IgE-bound antigen	Ig-superfamily	Degranulation of MC, eicosanoid, cytokine and chemokine release	115	Basophils, eosinophils, DC
FcγRI (CD64)	IgG immune complexes, up-regulation by IFN-γ	Ig-superfamily	Degranulation of MC	116	Macrophages, monocytes
FcγRIIA (CD32)	IgG immune complexes	Ig-superfamily	Degranulation of MC	117	Various immune cells
FcγRIIIA (CD16)	IgG immune complexes	Ig-superfamily	Degranulation of MC	118	NK cells, neutrophils, monocytes, macrophages
CADM1	CADM1, CADM2 (Nect-3), CADM3 (Nect-1), Nectin-3, CRTAM	Ig-superfamily	Supports MC adhesion to other cells, e.g. airway smooth muscle cells and fibroblasts	119	Keratinocytes, DC, neuron cells, NK cells and other cells
Inhibitory receptors					
E-NPP3 (CD203c)	ATP	E-NPP family	Inhibition of MC ATP-dependent activation	120	Basophils
Cannabinoid receptors: CB1, CB2	Endocannabinoids	GPCR	Inhibition of MC degranulation	121,122	Many cells
CD200R	Glycoprotein OX-2 (CD200)	Ig-superfamily	Inhibition of MC activation	123,124	Basophils
EP2, EP4	PGE ₂	GPCR	Inhibition of MC activation, suppression of FcεRI-mediated mediator generation by MC	81,125	Many cells
P1R: A2a, A2b	Adenosine	GPCR	Inhibition of MC degranulation; however, some pro-inflammatory properties for A2b were described	126-128	Many cells
IL-10R1, IL-10R2	IL-10	Type II cytokine receptors	Inhibition of IgE-induced activation and cytokine generation	129-132	Many cells
Siglec 2, 3,5,6,7, 8, 10	Mucins, 6'-sulfo-sLe ^x glycan	Ig-superfamily	Inhibition of FcεRI-triggered activation of MC	133,134	Eosinophils (Siglec-7,8) and other cells
CD300a, CD300f [Lmir-1, 3]	Phosphatidylserine, phosphatidylethanolamine, ceramides	Ig-superfamily	Inhibition of IgE/FcεRI-mediated activation of MC (CD300a); inhibitory and activating roles (CD300f)	135,136	Eosinophils
FcγRIIB	IgG immune complexes	Ig-superfamily	Inhibition of MC degranulation, mediators release and SCF-mediated cell proliferation	137,138	B cells

SIRP α (CD172a)	CD47	Ig-superfamily	Inhibition of IgE-induced MC activation and degranulation	¹³⁹	Myeloid, hematopoietic neurons
ILT (CD85) [PIR-B]	MHC-I molecules	Ig-superfamily	Inhibition of IgE-induced MC activation and degranulation	¹⁴⁰	B cells, DC, monocytes, macrophages
PECAM-1 (CD31)	$\alpha v\beta 3$, CD38	Ig-superfamily	Inhibition of MC activation and degranulation	¹⁴¹	Endothelial cells, neutrophils, NK, monocytes, platelets
LAIR-1 (CD305)	Collagens	Ig-superfamily	Inhibition of Fc ϵ RI-mediated degranulation	¹⁴²	Most immune cells
CD72 (Lyb-2)	CD100 (Semaphorin-4D)	C-type lectin-like	Suppression of MC growth, SCF-induced chemotaxis, and IgE-dependent degranulation.	¹⁴³	B-cells, basophils
LILRB4 [Gp49B1]	$\alpha v\beta 3$	Ig-superfamily	Inhibition of IgE-dependent MC activation	¹⁴⁴	Neutrophils, macrophages, NK
Allergin-1L,S1,S2	Has not yet been identified	Ig-superfamily	Inhibition of IgE-dependent MC activation	¹⁴⁵	DC, macrophages, neutrophils
MAFA	E-cadherin	C-type lectin-like	Inhibition of MC activation	¹⁴⁶	NK cells, basophils
$\beta 2$ -adrenoceptors	$\beta 2$ -adrenoceptor agonists, e.g. salbutamol	GPCR	Inhibition of IgE-dependent release of histamine	¹⁴⁷	Many cells
GPR35	Kynurenic acid, lysophosphatidic Acid	GPCR	Inhibitory effects	¹⁴⁸	Basophils, eosinophils, other cells
Unknown	Glycosaminoglycans, e.g. heparin, chondroitin sulfate	Unknown	Inhibitory effect on MC	¹⁴⁹	Unknown
Unknown	Polyamines	Unknown	Stimulatory or inhibitory effect on MC	²²	Probably many cells

cAMP: cyclic adenosine monophosphate; CADM1: cell adhesion molecule 1; CRH: corticotropin-releasing hormone; CRTh2: chemoattractant receptor-homologous molecule expressed on Th2 cells; DC: dendritic cell(s); DP: D prostanoid receptor; GM-CSF: granulocyte-macrophage colony-stimulating factor; GPCR: G-protein coupled receptor; H₁₋₄R: histamine 1-4 receptors; IFNGR: IFN- γ receptor; IFN: interferon; IL: interleukin; LAIR-1: leukocyte-associated Ig-like receptors-1; LT: leukotriene; MRGPRX: Mas-related G protein-coupled receptor X; MAFA: the mast cell function-associated antigen; MC: mast cell(s); NGF: nerve growth factor; PAF: platelet-activating factor; PAR: protease activated receptor; PECAM-1: platelet endothelial cell adhesion molecule-1; PG: prostaglandin; PI3K: phosphatidylinositol 3 kinase; PIR: paired Ig-like receptors; PKA: protein kinase A; PRR: pattern recognition receptors; S1P: sphingosine-1-phosphate; SCF: stem cell factor; Siglec: sialic acid-binding Ig-like lectins; TGF: transforming growth factor; TSLP: thymic stromal lymphopoietin; VEGF/VPF: vascular endothelial growth factor/vascular permeability factor

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