Mast Cells as Key Players in Allergy and Inflammation

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Abstract

Mast cells (MCs) are a key structural and functional component of both the innate and the adaptive immune systems. They are involved in many different processes, but play a major role in the response to infections and in inflammatory reactions. In addition, MCs are the main effector cells in allergy.

MC biology is far more complex than initially believed. Thus, MCs may act directly or indirectly against pathogens and show a wide variety of membrane receptors with the ability to activate cells in response to various stimuli. Depending on where MCs complete the final stages of maturation, the composition of their cytoplasmic granules may vary considerably, and the clinical symptoms associated with tissue MC activation and degranulation may be also different. MCs are activated by complex signalling pathways characterized by multimolecular activating and inhibitory interactions.

This article provides a comprehensive overview of MC biology, focusing predominantly on mechanisms of MC activation and the role of MCs in the pathogenesis of allergic diseases.

Key words: Allergy. Inflammation. KIT. Mast cell. Signalling. Activation. IgE.

Resumen

Actualmente el mastocito (MC) es considerado como un componente estructural y funcional clave del sistema inmunitario, tanto innato como adquirido. El MC está involucrado en muchos procesos biológicos diferentes, pero juega un papel primordial en la respuesta inmune frente a infecciones y en las reacciones inflamatorias. Además, el MC es la principal célula efectora en los procesos alérgicos.

La biología mastocitaria es mucho más compleja de lo que se podía pensar en un principio. Así, los MCs pueden actuar frente a patógenos tanto de forma directa como indirecta, y presentan una amplia variedad de receptores de membrana capaces de inducir la activación de la célula en respuesta a diferentes estímulos. Dependiendo del lugar donde los MCs completan los estadíos finales de su maduración, la composición de sus gránulos citoplasmáticos puede variar considerablemente, y los síntomas clínicos asociados a la activación y desgranulación de los MCs tisulares pueden ser también diferentes. La activación mastocitaria se produce como consecuencia de complejas vías de señalización caracterizadas por interacciones multimoleculares activadoras e inhibidoras.

Este artículo muestra una revisión integral de la biología mastocitaria, predominantemente enfocado a los mecanismos de activación mastocitaria y en el papel que los MCs desempeñan en la patogenia de las enfermedades alérgicas.

Palabras clave: Alergia. Inflamación. KIT. Mastocito. Señalización. Activación. IgE.

Introduction

Recent major advances in the ontogeny, physiology, metabolism, proteomics, and genetics of mast cells (MCs) have improved our understanding of their impact on health and disease. MCs are a key structural and functional component of both the innate and the adaptive immune systems and are involved in many biological processes. They play a pivotal role in the immune response to infection by pathogenic parasites and in inflammatory reactions; at the same time, MCs are the main effector cells in allergic diseases.

The mechanisms that regulate MC function have been extensively investigated and include complex multimolecular pathways that control the activation and inhibition of cell signalling. Among the wide number of molecules involved in these pathways, 2 transmembrane receptors on the surface of MCs are particularly relevant: (*1*) the tyrosine-kinase (TK) receptor of the stem cell factor (SCF), known as KIT, which plays major roles in the proliferation, differentiation, and survival of MCs: and (*2*) the high-affinity IgE receptor (FcεRI), which is involved in the underlying mechanisms of IgE-mediated MC activation and typically occurs in immediate hypersensitivity reactions (type I).

In this review, we provide a comprehensive picture of MC biology, with emphasis on its role in the inflammatory response and allergic diseases.

Structure and Function of Mast Cells

MCs are effector cells of the immune system that were first identified in 1878 by Paul Ehrlich, who showed their unique tinctorial properties [1], for example, metachromasia, which consists in the ability to stain a different color from that of the stain used. In morphological terms, normal MCs are 7-12 µm in diameter and round to ovoid in shape with a central round nucleus and numerous granules filling the cytoplasm, often hiding the nucleus completely [2] (Figure 1).

Functionally, MCs are derived from pluripotent hematopoietic progenitors in the bone marrow [3-6], from where MCs migrate through the bloodstream as immature cells to reach the peripheral tissues [4,7]. Here, they finish their differentiation under the influence of the microenvironment [8,9]. Once complete functionality is achieved, MCs become one of the most important cells in the immune system, playing a key role in the mechanisms underlying the initiation and perpetuation of the inflammatory response [10-14].

Despite being a minority cell population compared with all the other cells in the immune system, MCs are present in practically all human tissues, particularly those that act as physical barriers against external microorganisms such as the skin and the gastrointestinal and respiratory tracts [15]. This strategic distribution of MCs, together with the existence of a large number of membrane receptors with the ability to induce cell activation in response to various stimuli, enables MCs to be the first line of defense against pathogens, allergens, and other potentially harmful environmental agents. Therefore, specific bacterial compounds can directly activate MCs through interactions with membrane receptors such as Toll-like receptors [13,16,17] and CD48 [18-20]. MCs also express IgG receptors (FcγR) and complement receptors, which can recognize previously opsonized microorganisms [21-23]. The microorganisms MCs act against mostly include parasites (helminths, nematodes, and protozoa), as well as some bacteria (particularly gram-negative bacteria), viruses, and fungi. Once the pathogen is recognized, MCs act directly either through their phagocytic ability under specific circumstances [20,24] or via the production of antimicrobial peptides such as cathelicidin (LL37) [25]. MCs also act indirectly against microorganisms through the release of potent inflammatory mediators, some of which are preformed and stored within the cytoplasmic granules, whereas others are synthesized de novo.

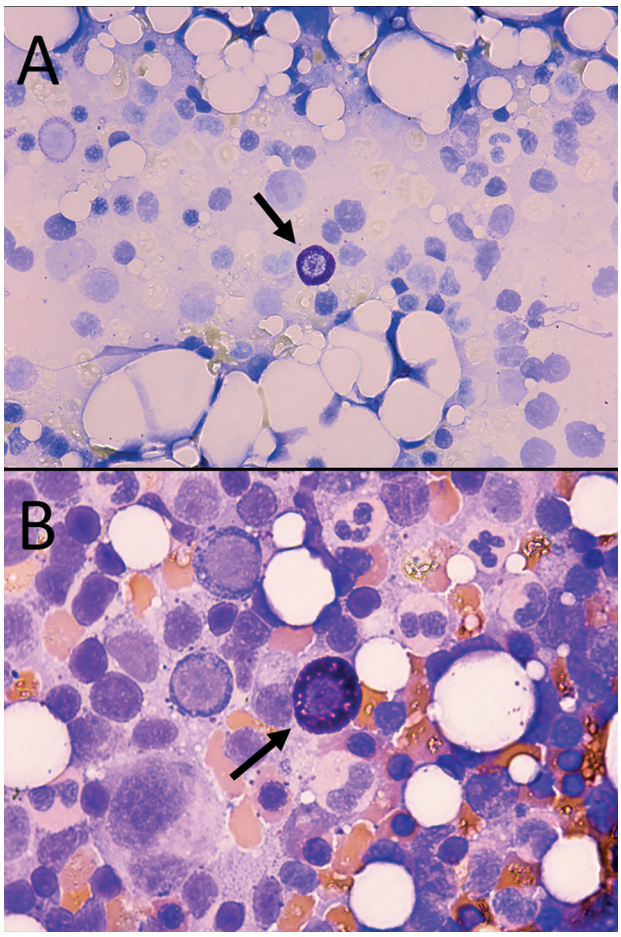

Figure 1. Cytomorphological appearance of normal mast cells (arrows) in bone marrow smears. A, Blue toluidine stain (×60); B, May-Grünwald-Giemsa stain (×100).

The process of MC mediator release has mainly been studied in anaphylactic reactions, in which the MC participates as the main effector cell. In such reactions, activation of MCs results from an interaction between FcεRI on the membrane surface and specific allergens to which patients have previously been sensitized [26,27]. Furthermore, MCs have been involved in the pathogenesis of several inflammatory diseases, such as rheumatoid arthritis [28,29], scleroderma [30,31], interstitial cystitis [32,33], multiple sclerosis [34,35], and irritable bowel disease [36-39], as well as in processes

such as wound healing [40-42], angiogenesis [43,44], and the development of tumors [45,46].

Ontogeny and Development of Mast Cells

MCs derive from progenitor cells in bone marrow [3-6], where they start their maturation under the influence of a variety of growth factors and cytokines such as SCF, interleukins (eg, IL-4, IL-6, IL-9, IL-10, IL-12, IL-15, and IL-18), nerve growth factor, transforming growth factor beta (TGF-β), and thrombopoietin [47]. In contrast to other hematopoietic cells that complete their differentiation within the bone marrow, MCs migrate as immature cells through the bloodstream to peripheral tissues where they complete their maturation. Mature MCs in peripheral tissues then exert their effects under the influence of SCF and other microenvironmental molecules including adhesion molecules (eg, integrins and cadherins) and diverse chemokines [47].

Once in peripheral tissues, the MC acquires a specific phenotype, which is shared by all MCs independently of the tissue where they reside. The phenotype is characterized by strong expression of 3 different molecules [48-50]: (*1*) the antigen CD117 (KIT), which is the receptor for SCF; (*2*) FcεRI, the high-affinity serum IgE receptor; and (*3*) intracytoplasmic tryptase, which is the most abundant protein stored in the granules of MCs. According to the pattern of expression of cytoplasmic tryptase and other MC proteases, 3 main phenotypically different subtypes of MCs can be distinguished [51,52], as follows: (*1*) MCs that only contain tryptase (MC_T), which are located in the alveoli of the lung and in the small intestinal mucosa; (*2*) MCs containing tryptase, chymase, carboxypeptidase A (CPA), and cathepsin G (MC_{TC}), which predominate in the skin and in the small intestinal submucosa; and (*3*) MCs that contain chymase, CPA, and cathepsin G in the absence of tryptase (MC_C), which mainly reside in the intestinal and nasal submucosa.

The pattern of cytokines expressed by the different subtypes of MCs described above is considerably heterogeneous. Thus, whereas IL-4 is found preferentially in MC_{TC}, production of IL-5 and IL-6 is limited to MC_T [53]. Other differential characteristics among the phenotypic MC subtypes include the dependence on helper T ($CD4^+$) lymphocytes of MC_T and the expression of the receptor for the C5a complement activation fragment (CD88) on MC_{TC} [54]. Altogether, these findings show that the pattern of synthesis and release of cytokines by MCs varies depending on the tissue where they reside, thus suggesting different biological functions for each subtype of MC. Furthermore, MCs are able to reversibly modify the expression of certain molecules in response to environmental or infectious factors [55]. In itself, this ability constitutes an adaptive mechanism of the immune response.

Immunophenotypic Features of Mast Cells

From an immunophenotypical perspective, normal MCs display different antigenic profiles depending on their maturation stage and the tissue where they reside. Several in vitro models of differentiation have shown that MCs arise from pluripotent hematopoietic progenitor cells, which typically express CD34, CD45, CD117, CD116, CD38, CD13, CD33 (Siglec-3), CD123, and, to a lesser extent, CD203c [3,4,56]. By contrast, expression of molecules associated with more mature MCs, such as CD327 (Siglec-6), CD329 (Siglec-8), and FcεRI, and expression of intracytoplasmic proteases and mediators such as tryptase, CPA, chymase, and histamine are typically absent in bone marrow MC precursors [4,57,58].

During maturation, MC precursors in bone marrow progressively lose expression of markers associated with early stages of differentiation such as CD34, CD38, CD123, and CD116; at the same time, the intensity of expression of other antigens such as CD117, CD45, CD33, and CD203c gradually increases, remaining high until the end of the differentiation process [59]. As they mature, MCs start to express proteins associated with the inflammatory response (eg, FcεRI), cytoplasmic mediators (eg, CPA, tryptase, chymase, and histamine), integrins (eg, CD49b and CD49c), and immunomodulatory molecules (eg, Siglec-6 and Siglec-8) [4,57,58]. Unlike these markers, antigens such as CD58, CD63, CD147, CD151, CD172a, CD182, and CD184 show relatively constant levels of expression during the different stages of MC maturation [59].

Finally, during the last stage of cell differentiation in peripheral tissues, the MC acquires the expression of a number of functional proteins involved in MC activation, such as CD69 [60] and HLA-DR [61]; at the same time, the MC increases the expression of other molecules that were already present at early stages of differentiation including CD63, CD84, and CD203c [49,59].

Although MCs represent only a small fraction of all hematopoietic cells in bone marrow under normal conditions, it is relatively easy to identify and count them using multiparametric flow cytometry [48-50,62,63]. According to their antigenic features, the vast majority of MCs found in bone marrow are mature resting cells, which strongly express CD117, CD203c, and FcεRI, although none of these markers are specific to the MC lineage. Thus, in bone marrow, CD117 is also expressed by hematopoietic precursors, dendritic cells, $CD56^+$ natural killer cells, some plasma cells, and nonhematopoietic tumor cells [49]; in turn, CD203c and FcεRI are also systematically expressed by basophils [9,64]. For this reason, the identification of MCs by flow cytometry is based on the use of a rational combination of monoclonal antibodies against different antigens; therefore, the expression of CD117, CD203c, FcεRI, CD45, and CD33, together with the absence of expression of CD34, CD38, and CD138, constitutes a unique antigenic profile associated with mature MCs, which enables them to be identified and differentiated from other cell populations in bone marrow.

Structure and Function of the KIT Receptor

The SCF receptor, which is known as KIT, is one of the most relevant receptors of MCs. Despite the fact that it is also present in hematopoietic precursor cells, melanocytes, interstitial cells of Cajal, and germline cells [65-69], in none

of these cells are the levels of expression of KIT as high as those found in MCs. The importance of KIT and the processes regulated by this receptor have been largely established based upon genetically modified animal models. Thus, c-kit–deficient and SCF-deficient mice lack mature MCs and suffer from hypoplastic anemia, hypopigmentation, and sterility [70,71]. In contrast to other protein receptors expressed by MCs whose function is usually restricted to advanced stages of differentiation, the KIT receptor exerts its function throughout the development of MCs, playing a crucial role in their proliferation, differentiation, migration, and survival [72-75].

The KIT receptor (CD117) is a transmembrane glycoprotein that belongs to the type III TK family of receptors, which is coded by c-kit, a gene located in the pericentromeric region of the long arm of chromosome 4 (4q11-q12) [76,77]. The KIT receptor is composed of 976 amino acids distributed over 21 exons, with a total molecular weight of 145 kDa [78]. From a structural perspective, KIT shows a unique topology shared by other receptors of the type III TK family, such as the platelet-derived growth factor receptor (PDGFR), the macrophage colony-stimulating factor receptor (CSF-1), and the Fl cytokine receptor (Flt3). The extracellular region of KIT contains 5 immunoglobulin-like domains and constitutes the binding site for the SCF [79,80]. The transmembrane portion of the receptor connects the extracellular domain to the intracellular part of the molecule, which comprises 1 juxtamembrane domain and 2 TK domains including an adenosine triphosphate (ATP)–binding site (TK1 domain) and a phosphotransferase region (TK2 domain) linked by a kinase insert domain. The catalytic activity of KIT resides in the TK domains and is related to phosphorylation of proteins through the transfer of phosphate groups obtained from ATP; in turn, the juxtamembrane domain has a regulatory role in the receptor through the inhibition of its activity in the absence of SCF [81,82] (Figure 2).

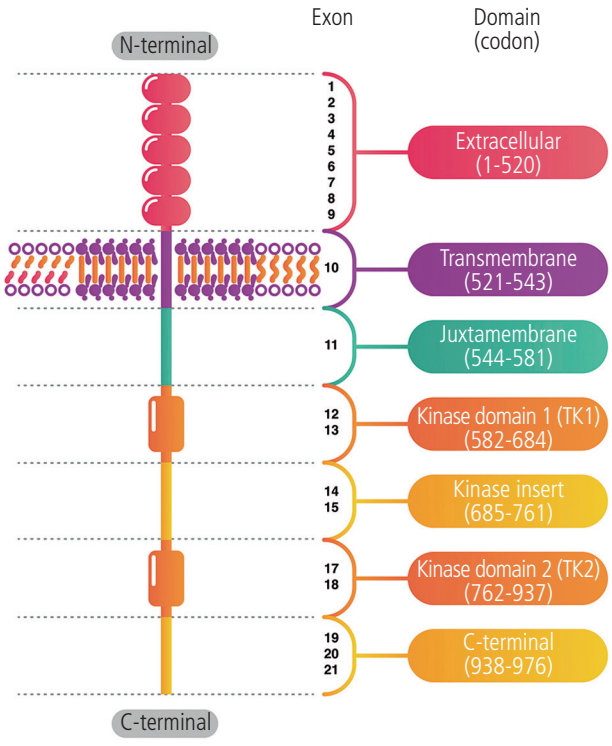

Figure 2. Structure of the KIT receptor.

SCF is a glycoprotein encoded in chromosome 12 (12q22-q24) [83], which is produced by stromal cells, fibroblasts, and endothelial cells [69]. The 2 currently recognized biologically active isoforms of SCF are a transmembrane form (mSCF) and a soluble form (sSCF). These isoforms are formed by alternative splicing of the same RNA transcript that either include exon 6 (sSCF) or exclude exon 6 (mSCF) in the mature mRNA; thus, SCF is initially synthesized as a membrane-bound polypeptide (mSCF) which would be proteolytically cleaved within the sequences encoded by exon 6 to release a soluble protein (sSCF) [83].

The interaction between SCF and KIT plays a key role in MC biology. This interaction results from non–covalent binding of SCF homodimers to the immunoglobulin-like domains in the extracellular region of KIT, which induces dimerization of the receptor [74,84,85]; as a consequence, the intrinsic TK activity in the intracellular region of KIT is stimulated, catalyzing phosphorylation of tyrosine residues by transferring phosphate groups obtained from ATP bound to the receptor [86]. Once phosphorylated, these tyrosine residues serve as binding sites for proteins containing Src-homology 2 (SH2) domains, and binding of these proteins generates activation signals through signaling pathways such as rat sarcoma/extracellular signal-regulated kinase (Ras/ERK) [87], Janus kinase/signal transducers and activators of transcription (JAK/STAT) [88-90], phosphatidylinositol triphosphate [91,92], and several kinases of the Src family [93]. These signaling pathways induce the activation of transcription factors and the synthesis of proteins involved in the modulation of proliferation, differentiation, migration, adhesion, secretion, and survival of MCs [94].

Given the importance of the processes mediated by the activation of KIT, strong regulatory mechanisms that exist under normal conditions prevent disproportionate hyperactivation states of the receptor and ensure the development of normal mastopoiesis. One such regulatory mechanism is the monoubiquitination of KIT by the action of ubiquitin ligases immediately after KIT-SCF binding, which results in the internalization of the receptor and its subsequent degradation in lysosomes [95-97]. In addition, several molecules that are activated during the intracellular transduction of signaling generated by the KIT/SCF interaction, such as SHP-1 ("Src-homology region 2 domain containing phosphatase-1"), protein kinase C (PKC) or suppressor of cytokine signaling-1 (SOCS-1), are also involved in the regulation of the process. Thus, SHP-1 catalyzes the dephosphorylation of KIT by interacting with a tyrosine residue in the juxtramembrane domain, negatively modulating the activity of the receptor [98]. By contrast, PKC promotes the phosphorylation of serine residues in the kinase insert region of KIT, thereby inhibiting its activity. The activation of PKC is mediated by diacylglycerol, which is generated from phosphatidic acid by the action of the enzyme phospholipase D, which is in turn activated by phosphatidylinositol 3-kinase (PI3K) [99]. Finally, SOCS-1 exerts its regulatory effect via selective suppression of KIT-induced mitogenesis [100].

Mutations in the KIT receptor–encoding proto-oncogene (c-kit) have been extensively reported in the literature. These mutations are associated with diseases characterized by neoplastic cell growth in cell lines expressing KIT, which include MCs, stromal cells, germline cells, melanocytes, hematopoietic progenitors in bone marrow, and a wide variety of neoplastic cells from various tumors. Thus, although KIT-driven disorders mostly include mastocytosis and gastrointestinal stromal tumors, where KIT mutations are detected in ~95% and ~75% of cases, respectively [101-103], KIT mutations have also been described in a subset of patients with seminoma [104], germinoma [65], melanoma [105], small cell lung cancer [106], colon cancer [107], neuroblastoma [108], and breast cancer [109], as well as in hematologic malignancies such as acute leukemia [110], myelodysplastic syndrome [111], and myeloproliferative neoplasm [112]. Most KIT mutations tend to cluster in small regions of the protein, especially at exons 11 and 17, although mutations involving other exons have been also reported. In mastocytosis, the most common KIT mutation is a somatic activating point mutation caused by the substitution of adenine with thymine at nucleotide sequence 2447 in the c-kit gene, which results in the replacement of aspartic acid by valine at codon 816 (exon 17) of the KIT receptor [112]. By contrast, the most common site of KIT mutations in gastrointestinal stromal tumors is exon 11, which encodes the juxtamembrane domain of the molecule; these mutations mostly consist of deletions or substitutions involving codons 550-560 [103]. Of note, the specific site where KIT mutations arise in KIT-driven diseases is of critical importance when deciding on therapy; thus, mutations involving exon 17 of KIT are resistant to imatinib mesylate [113,114], whereas most of those arising outside exon 17 are sensitive to this TK inhibitor [115,116].

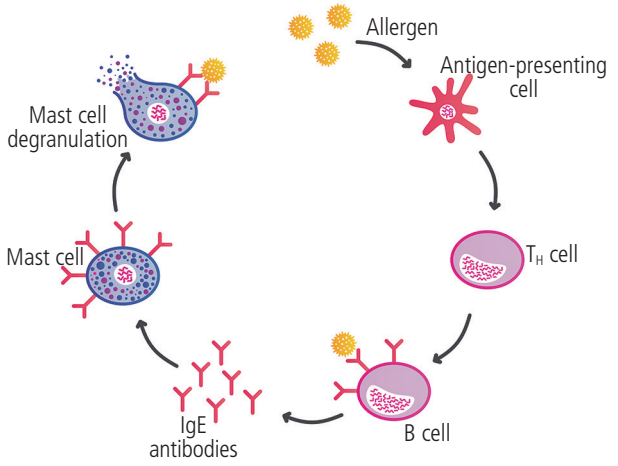

Figure 3. Mechanism of allergic inflammation in type I hypersensitivity reactions. After the initial exposure, an allergen is presented to T_H cells via antigen-presenting cells; this provides assistance in the regulation of cellular immunity and promotes isotype switching and production of specific IgE antibodies by B cells. Subsequent antigen exposure induces cross-linking of antigen-IgE complexes and FcεRI on the surface of the MC, which results in the activation and degranulation of MCs.

Mast Cell Activation Mechanisms

MCs express a wide variety of membrane receptors involved in both the innate and the acquired immune responses. Although FcεRI, Toll-like receptors, complement receptors (CR1-5), and the IgG receptors FcγRI (CD64) and FcγRII (CD32) are the main receptors involved in the activation of MCs, they can be also activated by neuropeptides, cytokines, chemokines, and other inflammatory substances [117], as well as by physical stimuli such as pressure or heat [118]. The most clinically relevant MC activation mechanism is that involved in type I hypersensitivity allergic reactions, which are mediated by cross-linking of antigen-specific IgE immune complexes and FcεRI receptors on the membrane surface of MCs (Figure 3). Although FcεRI is typically expressed by MCs, other cells such as basophils and, to a lesser extent, Langerhans cells, a subpopulation of monocytes and eosinophil granulocytes can also express this receptor. Structurally, FcεRI is a tetramer composed of the following: (*1*) an α chain, whose extracellular domain constitutes the IgE binding site; (*2*) a β chain, which enhances binding stability and amplifies signal transduction; and (*3*) a homodimer of γ chains, which is involved in the conduction of the signal to the interior of the cell [27,119]. The process of intracellular signalling is necessary for the activation and further effector response of MCs and depends mainly on the phosphorylation of immunoreceptors containing activation sequences based on tyrosine (ITAMs, immunoreceptor tyrosine-based activation motifs), which are present in both β and γ chains of the FcεRI [120]. Phosphorylation of ITAM domains in FcεRI occurs in a stepwise fashion through the action of different proteins with TK activity (Figure 4). Initially, an Src family TK called Lyn, which is located adjacent to FcεRI, phosphorylates the β chain, thus inducing the subsequent phosphorylation of the γ chain, which in turn promotes the activation of a ZAP-70 family TK protein called Syk. This protein is capable of phosphorylating different substrates, including the linker for activation of T cells (LAT), SLP-76, Vav, and phospholipase Cγ (PLCγ). Once activated, these molecules determine the development of intracellular stimuli, which are essential for the release of mediators stored inside MC cytoplasmic granules and for the synthesis of cytokine and the activation of phospholipase A2, with the subsequent generation of arachidonic acid (AA) from phospholipids in the cell membrane. The activation process is complemented by the phosphorylation of the adaptor protein Gab2 via the action of another Src family TK called Fyn. The phosphorylation of Gab2 promotes the generation of phosphatidylinositol triphosphate, which in turn leads to the recruitment of molecules such as Btk and PLCγ towards the cell membrane. The latter step is necessary for the increase in intracellular calcium and the degranulation process [121].

In parallel to this multimolecular signalling process leading to MC degranulation, several molecules with mostly inhibitory effects are activated in order to avoid an excessive or inappropriate response. These molecules include receptors containing tyrosine-rich inhibition sequences, known as (ITIMs, immunoreceptor tyrosine-based inhibition motifs) [122], that promote the action of dephosphorylating

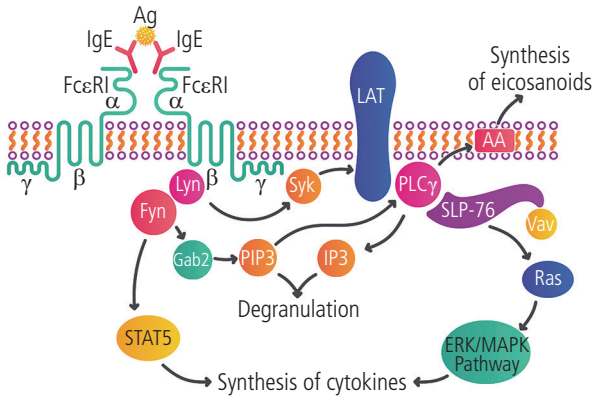

Figure 4. Schematic representation of main protein interactions and downstream signaling events following IgE-mediated FcεRI activation. Ag, antigen; FcεRI, high affinity IgE receptor; STAT5, signal transducers and activators of transcription-5; PIP3, phosphatidylinositol triphosphate; IP3, inositol triphosphate; LAT, linker for activation of T cells; PLCγ, phospholipase Cγ; Ras, rat sarcoma; AA, arachidonic acid; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.

molecules such as SHP-1, SHP-2 (Src-homology region 2 domain containing phosphatase-2), and SHIP (Src-homology 2 containing inositol phosphatase) and also of the adaptor protein NTAL (non–T cell activation linker), which is activated, together with LAT, after the stimulation of FcεRI. NTAL is believed to exert mostly inhibitory effects, as shown by the increase in the secretory activity of MCs in NTAL-deficient mouse mutants [123]. Besides the intracellular activation and inhibition pathways described above, the participation of other molecules with mixed (activating and inhibitory) properties highlights the considerable complexity of the mechanisms involved in the regulation of the signalling process resulting from stimulation of FcεRI during IgE-mediated allergic reactions.

Mast Cell Mediators

The final consequence of MC activation is the release of a wide variety of proinflammatory and vasoactive substances into the extracellular environment, including mediators constitutively stored inside the cytoplasmic granules of MCs (primary MC mediators), mediators synthesized de novo upon MC activation (secondary MC mediators), and diverse cytokines [124,125], which results in a broad spectrum of clinical manifestations (Table). The release of preformed mediators from MCs occurs in the early phase of the immune response, a few seconds or minutes after the contact with the antigen. These preformed mediators include biogenic amines (eg, histamine and serotonin), proteases (eg, tryptase, CPA, and chymase), proteoglycans (eg, heparin and chondroitin sulphate), and inflammatory cytokines (eg, TNFα). This phase is followed by the release of diverse mediators newly synthesised from membrane phospholipids, which include prostaglandins (PGs), leukotrienes (LTs), and platelet-activating factor (PAF), as well as a variety of cytokines and chemokines that facilitate the activation and recruitment of other cells of the immune system, leading to the late phase of the immune response that typically occurs between 2 and 6 hours after exposure to an allergen.

Table. Main Symptoms and Signs Associated With the Release of Mast Cell Mediators

Type of Mediator	Mediator	Symptom(s)/sign(s)
Preformed mediators	Histamine	Headache, hypotension, urticaria with or without angioedema, pruritus, diarrhea
	Tryptase	Endothelial activation with associated inflammatory reaction
	Chymase/CPA	Hypertension, arrythmia
	Proteoglycan (heparin)	Bleeding diathesis
Lipid mediators	PAF	Abdominal cramping, pulmonary edema, urticaria, bronchoconstriction, hypotension, arrythmia
	PGD2	Mucus secretion, bronchoconstriction, vascular instability
	LTC4, LTD4 and LTE4	Mucus secretion, edema formation, vascular instability
Cytokines	TNF, IL1-α, IL-1β, IL-6, IL-18, GM-CSF, LIF, INF-α, IFN-β	Induction of inflammation
	IL-3, IL-4, IL-5, IL-9, IL-13, IL-15, IL-16	Type 2 helper T cytokines
	IL-12, IFN-γ	Type 1 helper T cytokines
	IL-10, TGF-β, VEGF	Regulation of inflammation and angiogenesis
Chemokines	CCL2, CCL3, CCL4, CCL5, CCL11, CCL20	Recruitment of effector cells (including dendritic cells), regulation of the immune response
	CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, CXCL11	Recruitment of effector cells, regulation of the immune response

Abbreviations: CCL, CC-chemokine ligand; CPA, carboxypeptidase; CXCL, CXC-chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; INF, interferon; IL, interleukin, LIF, leukemia inhibitory factor; LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; TGF-β, transforming growth factor-β; TNF, tumor-necrosis factor; VEGF, vascular endothelial growth factor.

Histamine

Histamine is the most important vasoactive mediator released from human MCs. Given its low molecular mass, histamine has high diffusion capacity once it is secreted and fulfils different biological functions after binding to specific receptors (H1, H2, H3, and H4). The most relevant effects of histamine include contraction of smooth muscle tissue, vasodilation, increased vascular permeability, nerve stimulation, and increased glandular secretion [126,127]. Histamine is rapidly metabolized via methylation or oxidation, both of which result in the generation of the metabolites N-methyl histamine and imidazole acetic acid, which are excreted in urine.

Neutral Proteases

The protein content of MC granules mainly comprises neutral proteases with hydrolytic activity on tissue surface–bound proteins, extracellular matrix proteins, inactive forms of proenzymes, and other proinflammatory peptide mediators; thus, neutral proteases help to generate and amplify tissue damage occurring after MC degranulation. Furthermore, these proteases participate in the regulation of processes associated with inflammation by activating various proteins that inhibit inflammation and also by inhibiting proinflammatory proteins.

The most abundant MC protease is tryptase, which is stored in the intracytoplasmic granules of MCs (and, albeit to a lesser extent, of basophils) as tetramers that form complexes with heparin [128,129]. The isoforms of tryptase recognized in serum are α-tryptase, which is constitutively secreted by MCs as inactive enzyme, and β-tryptase, which is released in large amounts during MC degranulation. A commercially available assay can be used to measure total serum tryptase levels, which are the sum of α- and β-tryptase isoforms. Therefore, the high levels of total serum tryptase frequently found in patients with mastocytosis are the result of increased chronic release of α-tryptase as a consequence of an increased total MC burden [130-132]. In contrast, increased total serum tryptase levels detected in patients with anaphylaxis more likely reflect the acute release of β-tryptase that typically occurs after MC degranulation in this setting [128,133]. Of note, the measurement of total serum tryptase has proved to be more useful than other MC mediators such as plasma histamine or urine histamine metabolites in the diagnostic work-up of both anaphylaxis and mastocytosis [134]. The greater diagnostic efficiency of serum tryptase over other MC mediators relies on its high specificity, the simplicity and speed of the assay, and slower metabolic degradation, which enables the measurement of serum tryptase for up to 6 hours after release without interference in the results by factors such as ingestion of food with a high content of histamine. The main biological effects of tryptase on the human body include contraction of smooth muscle [135], degradation of neuropeptides [136,137], activation of collagenase [138], proliferation of fibroblasts [139], generation of C3a [140] and bradykinin [141], and inactivation of fibrinogen [142]. Tryptase is also capable of promoting the recruitment of other immune cells (143), actively participates in remodelling processes (144) and angiogenesis (145), and exerts a protective function against the potential damaging effect of substances generated during the inflammation process, such as neurotensin and endothelin (146).

Other MC proteins with enzymatic activity are chymase and CPA, which are stored in MC granules as macromolecular complexes with proteoglycans. The main effect of chymase is the generation of angiotensin II through hydrolysis of angiotensin I [147,148]; interestingly, this mechanism might be involved in the development of the vasoconstrictive signs and symptoms observed in some patients with MC disorders. In addition, chymase induces mucous hypersecretion, degradation of the extracellular matrix through cleavage of proteins such as fibronectin and collagen, activation of metalloproteases in situ in atherosclerotic plaques and of TGF-β growth factor, and induction of apoptosis in smooth muscle cells of blood vessels [149-151]. In turn, although the effects of CPA in humans remain less well understood, an important role in innate immunity has been ascribed to this protease because of its ability to hydrolyse certain toxins and potentially harmful substances generated during the inflammatory response such as neurotensin and endothelin-1 [152].

Proteoglycans

The main function of proteoglycans stored in the secretory granules of MCs such as heparin and chondroitin sulfate is to form stable complexes with other MC mediators, thus facilitating their storage and their transportation through the lymphatic vessels [153]. Proteoglycans have also been implicated in the regulation of the enzymatic activity of MC proteases and in proapoptotic pathways [154].

Lipid Mediators

MC activation also induces the synthesis and further release of proinflammatory lipid mediators such as eicosanoids and PAF. The process of synthesis of these mediators begins with the activation of phospholipase A2, which promotes the generation of AA and lysophosphatidylcholine from phospholipids present on the MC membrane [155,156]. Once generated, AA can be metabolized by the action of 2 enzymes, cyclooxygenase (COX) and lipoxygenase (LO), resulting in the production of PGs and LTs, respectively [157]. In turn, PAF is formed by acetylation of lysophosphatidylcholine through the action of an acetyltransferase [158].

The main PG generated upon activation of MCs is PGD2, which has a potent vasodilatory effect, increases vascular permeability [159], and promotes chemotaxis of eosinophils [160,161]. In addition, in the respiratory tract, PGD2 has bronchoconstrictive properties [162]. The action of LO on AA produces LTA4, which can be metabolized to LTB4 through a hydroxylation process or to cysteinyl-LTs (ie, LTC4, LTD4, LTE4) through various enzymes acting in a stepwise fashion [163]. The main biological effect of LTB4 is chemotaxis of neutrophils, while cysteinyl-LTs, particularly LTC4 and LTD4, induce contraction of smooth muscle tissue, bronchoconstriction, increased vascular permeability, and mucous secretion [164]. In turn, PAF is a potent mediator capable of acting at low concentrations that has a very short half-life, as it is inactivated by an acetyl hydrolase present in

plasma and numerous tissues just a few minutes after being released from MCs. Nevertheless, upon binding to specific receptors, PAF produces a wide variety of symptoms such as bronchoconstriction, mucous secretion, vasodilation, increased vascular permeability, and platelet aggregation [165]. Besides these direct effects, PAF indirectly participates in the inflammatory response through the activation and chemotaxis of leukocytes and through the induction of release of other mediators by MCs and platelets such as histamine and both thromboxanes and serotonin, respectively [166].

Cytokines and Chemokines

Similar to other cells of the immune system, MCs produce a wide variety of cytokines and chemokines, which are synthesized de novo after activation of MCs and further released into the extracellular medium. Importantly, these molecules contribute to the maintenance of the inflammatory process via recruitment of other immune cells such as lymphocytes, neutrophils, and eosinophils and via the induction of expression of adhesion molecules on leukocytes and endothelial cells. The most relevant cytokines produced by MCs include TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-12, IL-13, IL-15, IL-16, IL-18, granulocyte-macrophage colony-stimulating factor, interferon (IFN) α, IFN-β, and IFN-γ, and the chemokines CCL2, CCL3, CCL4, CCL5, and CXCL8 [14,124,167]. Other molecules synthesized and released by MCs, such as TGF-β and IL-10, are involved in the regulation of the process through anti-inflammatory action [168,169]. Of these molecules, TNF-α constitutes the most abundant cytokine secreted by MCs; it is noteworthy that TNF-α is not only synthesized de novo after activation of MCs but is also stored in small amounts inside MC granules and then immediately released together with other preformed MC mediators during the process of exocytosis. Furthermore, TNF-α induces expression of adhesion molecules in endothelial cells and of integrins in leukocytes, thus facilitating binding between both cell types. TNF-α also stimulates the release of chemokines, thus facilitating recruitment of leukocytes to tissues where the inflammatory response is occurring [170].

Conclusions

MCs are one of the key effectors of early innate immunity and play a central role not only in host defense against invading pathogens and other environmental threats, but also in the underlying mechanisms of implementation, perpetuation, and regulation of the inflammatory response. Thus, normal mature MCs are involved in many physiological and pathological processes such as inflammation, angiogenesis, wound healing, allergic diseases, and carcinogenesis.

The large number of molecules involved in the regulation of MC downstream signalling pathways, along with the broad spectrum of biological effects produced by activated MCs, make these cells one of the most paradigmatic examples of the fascinating complexity of the human immune system. Moreover, increasing knowledge accumulated over the years on the biology of MCs has led to the development of drugs that target specific molecules involved in activation of MCs such as omalizumab. This humanized murine monoclonal antibody is directed against the FcεRI-binding site of free serum IgE, which prevents its binding to MCs; thus, omalizumab has proven to be effective in several well-known IgE-driven diseases such as chronic urticaria [171] and allergic asthma [172], and, more recently, in allergic rhinitis [173], atopic dermatitis [174], and clonal MC disorders [175-177]. Omalizumab has also been administered as coadjuvant treatment in allergen immunotherapy regimens [178,179]. The clinical benefits of omalizumab in these IgE-related disorders has led to the exploration of the potential utility of novel anti-IgE therapies, which have shown promising preliminary results.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Ehrlich P. Beiträge zur Theorie und Praxis der histologischen Färbung [dissertation]. Leipzig: Leipzig University; 1878. 65 p.
2. Sperr WR, Escribano L, Jordan JH, Schernthaner GH, Kundi M, Horny HP, et al. Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. Leuk Res. 2001;25(7):529-36.
3. Kirshenbaum AS, Kessler SW, Goff JP, Metcalfe DD. Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells. J Immunol. 1991;146:1410-5.
4. Rottem M, Okada T, Goff JP, Metcalfe DD. Mast cells cultured from the peripheral blood of normal donors and patients with mastocytosis originate from a CD34+/Fc epsilon RI- cell population. Blood. 1994;84(8):2489-96.
5. Agis H, Willheim M, Sperr WR, Wilfing A, Krömer E, Kabrna E, et al. Monocytes do not make mast cells when cultured in the presence of SCF: Characterization of the circulating mast cell progenitor as a c-kit+, CD34+, Ly-, CD14-, CD17-, colony-forming cell. J Immunol. 1993;151:4221-7.
6. Kitamura Y, Yokoyama M, Matsuda H, Ohno T. Spleen colony forming cell as a common precursor for tissue mast cells and granulocytes. Nature. 1981;291:159-60.
7. Kitamura Y, Ito A. Mast cell-committed progenitors. Proc Natl Acad Sci U S A. 2005;102(32):11129-30.
8. Kitamura Y. Heterogeneity of mast cells and phenotypic change between subpopulations. Annu Rev Immunol. 1989;7:59-76.

9. Valent P, Spanblöchl E, Sperr WR, Sillaber C, Zsebo KM, Agis H, 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;80:2237-45.
10. Gurish MF, Austen KF. The diverse roles of mast cells. J Exp Med. 2001;194(0022-1007):F1-5.
11. Mekori YA. The mastocyte: the "other" inflammatory cell in immunopathogenesis. J Allergy Clin Immunol. 2004;114(1):52-7.
12. Crivellato E, Ribatti D. Involvement of mast cells in angiogenesis and chronic inflammation. Curr Drug Targets Inflamm Allergy. 2005;4(1):9-11.
13. Tkaczyk C, Jensen BM, Iwaki S, Gilfillan AM. Adaptive and innate immune reactions regulating mast cell activation: from receptor-mediated signaling to responses. ImmunolAllergy ClinNorth Am. 2006;26(3):427-50.
14. Rao KN, Brown MA. Mast cells: multifaceted immune cells with diverse roles in health and disease. Ann N Y Acad Sci. 2008 Nov;1143:83-104.
15. Church MK, Levi-Schaffer F. The human mast cell. J Allergy Clin Immunol. 1997;99(2):155-60.
16. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001;2(8):675-80.
17. Takeuchi O, Sato S, Horiuchi T, Hoshino K, Takeda K, Dong Z, et al. Cutting edge: role of Toll-like receptor 1 in mediating immune response to microbial lipoproteins. J Immunol. 2002;169(1):10-4.
18. Malaviya R, Gao Z, Thankavel K, van der Merwe PA, Abraham SN. The mast cell tumor necrosis factor alpha response to FimH-expressing Escherichia coli is mediated by the glycosylphosphatidylinositol-anchored molecule CD48. Proc Natl Acad Sci U S A. 1999;96(14):8110-5.
19. Muñoz S, Hernández-Pando R, Abraham SN, Enciso JA. Mast cell activation by Mycobacterium tuberculosis: mediator release and role of CD48. J Immunol. 2003;170(11):5590-6.
20. Féger F, Ribadeau Dumas A, Leriche L, Valent P, Arock M. Kit and c-kit mutations in mastocytosis: a short overview with special reference to novel molecular and diagnostic concepts. Int Arch Allergy Immunol. 2002;127(2):110-4.
21. Zwirner J, Götze O, Sieber A, Kapp A, Begemann G, Zuberbier T, et al. The human mast cell line HMC-1 binds and responds to C3a but not C3a(desArg). Scand J Immunol. 1998;47(1):19-24.
22. Okayama Y, Kirshenbaum AS, Metcalfe DD. Expression of a functional high-affinity IgG receptor, Fc gamma RI, on human mast cells: Up-regulation by IFN-gamma. J Immunol. 2000;164(8):4332-9.
23. Woolhiser MR, Brockow K, Metcalfe DD. Activation of human mast cells by aggregated IgG through FcgammaRI: additive effects of C3a. Clin Immunol 2004;110(2):172-80.
24. Malaviya R, Ross EA, MacGregor JI, Ikeda T, Little JR, Jakschik BA, et al. Mast cell phagocytosis of FimH-expressing enterobacteria. J Immunol 1994;152(4):1907-14.
25. Di Nardo A, Vitiello A, Gallo RL. Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. J Immunol. 2003;170(5):2274-8.
26. Pecht I, Corcia A. Stimulus-secretion coupling mechanisms in mast cells. Biophys Chem. 1987;26(2-3):291-301.
27. Kinet JP. The high-affinity IgE receptor (Fc epsilon RI): from physiology to pathology. Annu Rev Immunol. 1999;17:931-72.
28. Woolley DE, Tetlow LC. Mast cell activation and its relation to proinflammatory cytokine production in the rheumatoid lesion. Arthritis Res. 2000;2(1):65-74.
29. Lee DM, Friend DS, Gurish MF, Benoist C, Mathis D, Brenner MB. Mast cells: a cellular link between autoantibodies and inflammatory arthritis. Science. 2002;297(5587):1689-92.
30. Gruber BL. Mast cells in scleroderma. Clin Dermatol. 1994;12(3):397-406.
31. Ozbilgin MK, Inan S. The roles of transforming growth factor type beta3 (TGF-beta3) and mast cells in the pathogenesis of scleroderma. Clin Rheumatol. 2003;22(3):189-95.
32. Lynes WL, Flynn SD, Shortliffe LD, Lemmers M, Zipser R, Roberts LJ 2nd, et al. Mast cell involvement in interstitial cystitis. J Urol. 1987;138(4):746-52.
33. Theoharides TC, Sant GR, el-Mansoury M, Letourneau R, Ucci AA, Meares EM. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. J Urol. 1995;153(3 Pt 1):629-36.
34. Krüger PG, Bø L, Myhr KM, Karlsen AE, Taule A, Nyland HI, et al. Mast cells and multiple sclerosis: a light and electron microscopic study of mast cells in multiple sclerosis emphasizing staining procedures. Acta Neurol Scand. 1990;81(1):31-6.
35. Walker ME, Hatfield JK, Brown MA. New insights into the role of mast cells in autoimmunity: evidence for a common mechanism of action? Biochim Biophys Acta. 2012;1822(1):57-65.
36. Weston AP, Biddle WL, Bhatia PS, Miner PB. Terminal ileal mucosal mast cells in irritable bowel syndrome. Dig Dis Sci. 1993;38(9):1590-5.
37. O'Sullivan M, Clayton N, Breslin NP, Harman I, Bountra C, McLaren A, et al. Increased mast cells in the irritable bowel syndrome. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2000;12(5):449-57.
38. Vivinus-Nébot M, Dainese R, Anty R, Saint-Paul MC, Nano JL, Gonthier N, et al. Combination of allergic factors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. Am J Gastroenterol. 2012;107(1):75-81.
39. Theoharides TC. Mast cells in irritable bowel syndrome and ulcerative colitis: function not numbers is what makes all the difference. Dig Dis Sci. 2014;59(5):897-8.
40. Trabucchi E, Radaelli E, Marazzi M, Foschi D, Musazzi M, Veronesi AM, et al. The role of mast cells in wound healing. Int J Tissue React. 1988;10(6):367-72.
41. Levi-Schaffer F, Kupietzky A. Mast cells enhance migration and proliferation of fibroblasts into an in vitro wound. Exp Cell Res. 1990;188(1):42-9.
42. Noli C, Miolo A. The mast cell in wound healing. Vet Dermatol. 2001;12(6):303-13.
43. Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, et al. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev. 1999;13(11):1382-97.
44. de Souza DA, Borges AC, Santana AC, Oliver C, Jamur MC. Mast Cell Proteases 6 and 7 Stimulate Angiogenesis by Inducing Endothelial Cells to Release Angiogenic Factors. PloS One. 2015;10(12):e0144081.

45. Galinsky DST, Nechushtan H. Mast cells and cancer-no longer just basic science. Crit Rev Oncol Hematol. 2008;68(2):115-30.
46. Maltby S, Khazaie K, McNagny KM. Mast cells in tumor growth: angiogenesis, tissue remodelling and immune-modulation. Biochim Biophys Acta. 2009;1796(1):19-26.
47. Okayama Y, Kawakami T. Development, migration, and survival of mast cells. Immunol Res. 2006;34(2):97-115.
48. Orfao A, Escribano L, Villarrubia J, Velasco JL, Cerveró C, Ciudad J, et al. Flow cytometric analysis of mast cells from normal and pathological human bone marrow samples: identification and enumeration. Am J Pathol. 1996;149(5):1493-9.
49. Escribano L, Orfao A, Villarrubia J, Díaz-Agustín B, Cerveró C, Rios A, et al. Immunophenotypic characterization of human bone marrow mast cells. A flow cytometric study of normal and pathological bone marrow samples. Anal Cell Pathol. 1998;16(3):151-9.
50. Escribano L, Garcia Montero AC, Núñez R, Orfao A, Red Española de Mastocitosis. Flow cytometric analysis of normal and neoplastic mast cells: role in diagnosis and follow-up of mast cell disease. Immunol Allergy Clin North Am. 2006;26(3):535-47.
51. 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 U S A. 1986;83(12):4464-8.
52. Weidner N, Austen KF. Heterogeneity of mast cells at multiple body sites. Fluorescent determination of avidin binding and immunofluorescent determination of chymase, tryptase, and carboxypeptidase content. Pathol Res Pract. 1993;189(2):156-62.
53. Bradding P, Okayama Y, Howarth PH, Church MK, Holgate ST. Heterogeneity of human mast cells based on cytokine content. J Immunol. 1995;155(1):297-307.
54. Oskeritzian CA, Zhao W, Min H-K, Xia H-Z, Pozez A, Kiev J, et al. Surface CD88 functionally distinguishes the MCTC from the MCT type of human lung mast cell. J Allergy Clin Immunol. 2005;115(6):1162-8.
55. Friend DS, Ghildyal N, Austen KF, Gurish MF, Matsumoto R, Stevens RL. Mast cells that reside at different locations in the jejunum of mice infected with Trichinella spiralis exhibit sequential changes in their granule ultrastructure and chymase phenotype. J Cell Biol. 1996;135(1):279-90.
56. 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):2333-42.
57. Shimizu Y, Sakai K, Miura T, Narita T, Tsukagoshi H, Satoh Y, et al. Characterization of "adult-type" mast cells derived from human bone marrow CD34(+) cells cultured in the presence of stem cell factor and interleukin-6. Interleukin-4 is not required for constitutive expression of CD54, Fc epsilon RI alpha and chymase, and CD13 expression is reduced during differentiation. Clin Exp Allergy. 2002;32(6):872-80.
58. Yokoi H, Myers A, Matsumoto K, Crocker PR, Saito H, Bochner BS. Alteration and acquisition of Siglecs during in vitro maturation of CD34+ progenitors into human mast cells. Allergy. 2006;61(6):769-76.
59. Schernthaner G-H, Hauswirth AW, Baghestanian M, Agis H, Ghannadan M, Worda C, et al. Detection of differentiation- and activation-linked cell surface antigens on cultured mast cell progenitors. Allergy. 2005;60(10):1248-55.
60. Díaz-Agustín B, Escribano L, Bravo P, Herrero S, Nuñez R, Navalón R, et al. The CD69 early activation molecule is overexpressed in human bone marrow mast cells from adults with indolent systemic mast cell disease. Br J Haematol. 1999;106(2):400-5.
61. Frandji P, Oskéritzian C, Cacaraci F, Lapeyre J, Peronet R, David B, et al. Antigen-dependent stimulation by bone marrow-derived mast cells of MHC class II-restricted T cell hybridoma. J Immunol. 1993;151(11):6318-28.
62. Morgado JM, Sánchez-Muñoz L, Teodósio C, Escribano L. Identification and immunophenotypic characterization of normal and pathological mast cells. Methods Mol Biol. 2014;1192:205-26.
63. Teodosio C, Mayado A, Sánchez-Muñoz L, Morgado JM, Jara-Acevedo M, Álvarez-Twose I, et al. The immunophenotype of mast cells and its utility in the diagnostic work-up of systemic mastocytosis. J Leukoc Biol. 2015;97(1):49-59.
64. Gane P, Pecquet C, Crespeau H, Lambin P, Leynadier F, Rouger P. Flow cytometric monitoring of allergen induced basophil activation. Cytometry. 1995;19(4):361-5.
65. Strohmeyer T, Peter S, Hartmann M, Munemitsu S, Ackermann R, Ullrich A, et al. Expression of the hst-1 and c-kit protooncogenes in human testicular germ cell tumors. Cancer Res. 1991;51(7):1811-6.
66. Halaban R, Tyrrell L, Longley J, Yarden Y, Rubin J. Pigmentation and proliferation of human melanocytes and the effects of melanocyte-stimulating hormone and ultraviolet B light. Ann N Y Acad Sci. 1993;680:290-301.
67. Simmons PJ, Aylett GW, Niutta S, To LB, Juttner CA, Ashman LK. c-kit is expressed by primitive human hematopoietic cells that give rise to colony-forming cells in stroma-dependent or cytokine-supplemented culture. Exp Hematol. 1994;22(2):157-65.
68. Huizinga JD, Thuneberg L, Klüppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. Nature. 1995;373(6512):347-9.
69. Ashman LK. The biology of stem cell factor and its receptor C-kit. Int J Biochem Cell Biol. 1999;31(10):1037-51.
70. Kitamura Y, Go S, Hatanaka K. Decrease of mast cells in W/Wv mice and their increase by bone marrow transplantation. Blood. 1978;52(2):447-52.
71. Kitamura Y, Go S. Decreased production of mast cells in S1/S1d anemic mice. Blood. 1979;53(3):492-7.
72. Irani AM, Nilsson G, Miettinen U, Craig SS, Ashman LK, Ishizaka T, et al. Recombinant human stem cell factor stimulates differentiation of mast cells from dispersed human fetal liver cells. Blood. 1992;80(12):3009-21.
73. Galli SJ, Tsai M, Wershil BK, Tam SY, Costa JJ. Regulation of mouse and human mast cell development, survival and function by stem cell factor, the ligand for the c-kit receptor. Int Arch Allergy Immunol. 1995;107(1-3):51-3.
74. Lennartsson J, Jelacic T, Linnekin D, Shivakrupa R. Normal and oncogenic forms of the receptor tyrosine kinase kit. Stem Cells. 2005;23(1):16-43.
75. Kitamura Y, Oboki K, Ito A. Molecular mechanisms of mast cell development. Immunol Allergy Clin North Am. 2006;26(3):387-405; v.

76. Yarden Y, Kuang WJ, Yang-Feng T, Coussens L, Munemitsu S, Dull TJ, et al. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J. 1987;6(11):3341-51.
77. Qiu FH, Ray P, Brown K, Barker PE, Jhanwar S, Ruddle FH, et al. Primary structure of c-kit: relationship with the CSF-1/PDGF receptor kinase family--oncogenic activation of v-kit involves deletion of extracellular domain and C terminus. EMBO J. 1988;7(4):1003-11.
78. Giebel LB, Strunk KM, Holmes SA, Spritz RA. Organization and nucleotide sequence of the human KIT (mast/stem cell growth factor receptor) proto-oncogene. Oncogene. 1992;7(11):2207-17.
79. Lev S, Blechman J, Nishikawa S, Givol D, Yarden Y. Interspecies molecular chimeras of kit help define the binding site of the stem cell factor. Mol Cell Biol. 1993;13(4):2224-34.
80. Lemmon MA, Pinchasi D, Zhou M, Lax I, Schlessinger J. Kit receptor dimerization is driven by bivalent binding of stem cell factor. J Biol Chem. 1997;272(10):6311-7.
81. Hubbard SR. Juxtamembrane autoinhibition in receptor tyrosine kinases. Nat Rev Mol Cell Biol. 2004;5(6):464-71.
82. Mol CD, Dougan DR, Schneider TR, Skene RJ, Kraus ML, Scheibe DN, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem. 2004;279(30):31655-63.
83. Anderson DM, Williams DE, Tushinski R, Gimpel S, Eisenman J, Cannizzaro LA, et al. Alternate splicing of mRNAs encoding human mast cell growth factor and localization of the gene to chromosome 12q22-q24. Cell Growth Differ. 1991;2(8):373-8.
84. Blume-Jensen P, Claesson-Welsh L, Siegbahn A, Zsebo KM, Westermark B, Heldin CH. Activation of the human c-kit product by ligand-induced dimerization mediates circular actin reorganization and chemotaxis. EMBO J. 1991;10(13):4121-8.
85. Zhang Z, Zhang R, Joachimiak A, Schlessinger J, Kong XP. Crystal structure of human stem cell factor: implication for stem cell factor receptor dimerization and activation. Proc Natl Acad Sci U S A. 2000;97(14):7732-7.
86. Liu H, Chen X, Focia PJ, He X. Structural basis for stem cell factor-KIT signaling and activation of class III receptor tyrosine kinases. EMBO J. 2007;26(3):891-901.
87. Mor A, Shefler I, Salamon P, Kloog Y, Mekori YA. Characterization of ERK activation in human mast cells stimulated by contact with T cells. Inflammation. 2010;33(2):119-25.
88. Weiler SR, Mou S, DeBerry CS, Keller JR, Ruscetti FW, Ferris DK, et al. JAK2 is associated with the c-kit proto-oncogene product and is phosphorylated in response to stem cell factor. Blood. 1996;87(9):3688-93.
89. Deberry C, Mou S, Linnekin D. Stat1 associates with c-kit and is activated in response to stem cell factor. Biochem J. 1997;327(Pt 1):73-80.
90. Morales JK, Falanga YT, Depcrynski A, Fernando J, Ryan JJ. Mast cell homeostasis and the JAK-STAT pathway. Genes Immun. 2010;11(8):599-608.
91. Serve H, Yee NS, Stella G, Sepp-Lorenzino L, Tan JC, Besmer P. Differential roles of PI3-kinase and Kit tyrosine 821 in Kit receptor-mediated proliferation, survival and cell adhesion in mast cells. EMBO J. 1995;14(3):473-83.
92. Vosseller K, Stella G, Yee NS, Besmer P. c-kit receptor signaling through its phosphatidylinositide-3′-kinase-binding site and protein kinase C: role in mast cell enhancement of degranulation, adhesion, and membrane ruffling. Mol Biol Cell. 1997;8(5):909-22.
93. Ueda S, Mizuki M, Ikeda H, Tsujimura T, Matsumura I, Nakano K, et al. Critical roles of c-Kit tyrosine residues 567 and 719 in stem cell factor-induced chemotaxis: contribution of src family kinase and PI3-kinase on calcium mobilization and cell migration. Blood. 2002;99(9):3342-9.
94. Rönnstrand L. Signal transduction via the stem cell factor receptor/c-Kit. Cell Mol Life Sci. 2004;61(19-20):2535-48.
95. Miyazawa K, Toyama K, Gotoh A, Hendrie PC, Mantel C, Broxmeyer HE. Ligand-dependent polyubiquitination of c-kit gene product: a possible mechanism of receptor down modulation in M07e cells. Blood. 1994;83(1):137-45.
96. Yee NS, Hsiau CW, Serve H, Vosseller K, Besmer P. Mechanism of down-regulation of c-kit receptor. Roles of receptor tyrosine kinase, phosphatidylinositol 3′-kinase, and protein kinase C. J Biol Chem. 1994;269(50):31991-8.
97. Zadjali F, Pike ACW, Vesterlund M, Sun J, Wu C, Li SSC, et al. Structural basis for c-KIT inhibition by the suppressor of cytokine signaling 6 (SOCS6) ubiquitin ligase. J Biol Chem. 2011;286(1):480-90.
98. Kozlowski M, Larose L, Lee F, Le DM, Rottapel R, Siminovitch KA. SHP-1 binds and negatively modulates the c-Kit receptor by interaction with tyrosine 569 in the c-Kit juxtamembrane domain. Mol Cell Biol. 1998;18(4):2089-99.
99. Edling CE, Pedersen M, Carlsson L, Rönnstrand L, Palmer RH, Hallberg B. Haematopoietic progenitor cells utilise conventional PKC to suppress PKB/Akt activity in response to c-Kit stimulation. Br J Haematol. 2007;136(2):260-8.
100. Rottapel R, Ilangumaran S, Neale C, La Rose J, Ho JM-Y, Nguyen MH-H, et al. The tumor suppressor activity of SOCS-1. Oncogene. 2002;21(28):4351-62.
101. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn. 2011;13(2):180-8.
102. Jara-Acevedo M, Teodosio C, Sanchez-Muñoz L, Álvarez-Twose I, Mayado A, Caldas C, et al. Detection of the KIT D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications. Mod Pathol. 2015;28(8):1138-49.
103. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577-80.
104. Strohmeyer T, Reese D, Press M, Ackermann R, Hartmann M, Slamon D. Expression of the c-kit proto-oncogene and its ligand stem cell factor (SCF) in normal and malignant human testicular tissue. J Urol. 1995;153(2):511-5.
105. Willmore-Payne C, Holden JA, Tripp S, Layfield LJ. Human malignant melanoma: detection of BRAF- and c-kit-activating mutations by high-resolution amplicon melting analysis. Hum Pathol. 2005;36(5):486-93.
106. Sekido Y, Obata Y, Ueda R, Hida T, Suyama M, Shimokata K, et al. Preferential expression of c-kit protooncogene transcripts in small cell lung cancer. Cancer Res. 1991;51(9):2416-9.
107. Toyota M, Hinoda Y, Takaoka A, Makiguchi Y, Takahashi T, Itoh F, et al. Expression of c-kit and kit ligand in human colon carcinoma cells. Tumour Biol. 1993;14(5):295-302.

108. Beck D, Gross N, Brognara CB, Perruisseau G. Expression of stem cell factor and its receptor by human neuroblastoma cells and tumors. Blood. 1995;86(8):3132-8.
109. Hines SJ, Organ C, Kornstein MJ, Krystal GW. Coexpression of the c-kit and stem cell factor genes in breast carcinomas. Cell Growth Differ. 1995;6(6):769-79.
110. Bene MC, Bernier M, Casasnovas RO, Castoldi G, Knapp W, Lanza F, et al. The reliability and specificity of c-kit for the diagnosis of acute myeloid leukemias and undifferentiated leukemias. The European Group for the Immunological Classification of Leukemias (EGIL). Blood. 1998;92(2):596-9.
111. Fritsche-Polanz R, Jordan JH, Feix A, Sperr WR, Sunder-Plassmann G, Valent P, et al. Mutation analysis of C-KIT in patients with myelodysplastic syndromes without mastocytosis and cases of systemic mastocytosis. Br J Haematol. 2001;113(2):357-64.
112. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, 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 U S A. 1995;92(23):10560-4.
113. Laine E, Chauvot de Beauchêne I, Perahia D, Auclair C, Tchertanov L. Mutation D816V alters the internal structure and dynamics of c-KIT receptor cytoplasmic region: implications for dimerization and activation mechanisms. PLoS Comput Biol. 2011;7(6):e1002068.
114. Ma Y, Zeng S, Metcalfe DD, Akin C, Dimitrijevic S, Butterfield JH, et al. The c-KIT mutation causing human mastocytosis is resistant to STI571 and other KIT kinase inhibitors; kinases with enzymatic site mutations show different inhibitor sensitivity profiles than wild-type kinases and those with regulatory-type mutations. Blood. 2002;99(5):1741-4.
115. Frost MJ, Ferrao PT, Hughes TP, Ashman LK. Juxtamembrane mutant V560GKit is more sensitive to Imatinib (STI571) compared with wild-type c-kit whereas the kinase domain mutant D816VKit is resistant. Mol Cancer Ther. 2002;1(12):1115-24.
116. Akin C, Brockow K, D'Ambrosio C, Kirshenbaum AS, Ma Y, Longley BJ, et al. Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit. Exp Hematol. 2003;31(8):686-92.
117. Yu Y, Blokhuis BR, Garssen J, Redegeld FA. Non-IgE mediated mast cell activation. Eur J Pharmacol. 2016;778:33-43.
118. Zhang D, Spielmann A, Wang L, Ding G, Huang F, Gu Q, et al. Mast-cell degranulation induced by physical stimuli involves the activation of transient-receptor-potential channel TRPV2. Physiol Res. 2012;61(1):113-24.
119. 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):187-9.
120. Rivera J, Gilfillan AM. Molecular regulation of mast cell activation. J Allergy Clin Immunol. 2006;117(6):1214-25; quiz 1226.
121. Kalesnikoff J, Galli SJ. New developments in mast cell biology. Nat Immunol. 2008 Nov;9(11):1215-23.
122. Katz HR. Inhibitory receptors and allergy. Curr Opin Immunol. 2002;14(6):698-704.
123. Volná P, Lebduska P, Dráberová L, Símová S, Heneberg P, Boubelík M, et al. Negative regulation of mast cell signaling and function by the adaptor LAB/NTAL. J Exp Med. 2004;200(8):1001-13.
124. Castells M. Mast cell mediators in allergic inflammation and mastocytosis. Immunol Allergy Clin North Am. 2006;26(3):465-85.
125. Ogawa Y, Grant JA. Mediators of anaphylaxis. Immunol Allergy Clin North Am. 2007;27(2):249-60, vii.
126. Repka-Ramirez MS. New concepts of histamine receptors and actions. Curr Allergy Asthma Rep. 2003;3(3):227-31.
127. O'Mahony L, Akdis M, Akdis CA. Regulation of the immune response and inflammation by histamine and histamine receptors. J Allergy Clin Immunol. 2011;128(6):1153-62.
128. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med. 1987;316(26):1622-6.
129. Pejler G, Abrink M, Ringvall M, Wernersson S. Mast cell proteases. Adv Immunol. 2007;95:167-255.
130. Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, et al. The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest. 1995;96(6):2702-10.
131. Sperr WR, Jordan J-H, Fiegl M, Escribano L, Bellas C, Dirnhofer S, et al. Serum tryptase levels in patients with mastocytosis: correlation with mast cell burden and implication for defining the category of disease. Int Arch Allergy Immunol. 2002;128(2):136-41.
132. Savini P, Rondoni M, Poletti G, Lanzi A, Quercia O, Soverini S, et al. Serum total tryptase level confirms itself as a more reliable marker of mast cells burden in mast cell leukaemia (aleukaemic variant). Case Rep Hematol. 2015;2015:737302.
133. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am. 2006;26(3):451-63.
134. Schwartz LB, Bradford TR, Rouse C, Irani AM, Rasp G, Van der Zwan JK, et al. Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. J Clin Immunol. 1994;14(3):190-204.
135. Johnson PR, Ammit AJ, Carlin SM, Armour CL, Caughey GH, Black JL. Mast cell tryptase potentiates histamine-induced contraction in human sensitized bronchus. Eur Respir J. 1997;10(1):38-43.
136. Caughey GH, Leidig F, Viro NF, Nadel JA. Substance P and vasoactive intestinal peptide degradation by mast cell tryptase and chymase. J Pharmacol Exp Ther. 1988;244(1):133-7.
137. Tam EK, Caughey GH. Degradation of airway neuropeptides by human lung tryptase. Am J Respir Cell Mol Biol. 1990;3(1):27-32.
138. Birkedal-Hansen H, Cobb CM, Taylor RE, Fullmer HM. Activation of fibroblast procollagenase by mast cell proteases. Biochim Biophys Acta. 1976;438(1):273-86.
139. Abe M, Kurosawa M, Ishikawa O, Miyachi Y, Kido H. Mast cell tryptase stimulates both human dermal fibroblast proliferation and type I collagen production. Clin Exp Allergy. 1998;28(12):1509-17.
140. Fukuoka Y, Xia H-Z, Sanchez-Muñoz LB, Dellinger AL, Escribano L, Schwartz LB. Generation of anaphylatoxins by human beta-tryptase from C3, C4, and C5. J Immunol. 2008;180(9):6307-16.

141. Imamura T, Dubin A, Moore W, Tanaka R, Travis J. Induction of vascular permeability enhancement by human tryptase: dependence on activation of prekallikrein and direct release of bradykinin from kininogens. Lab Invest. 1996;74(5):861-70.
142. Prieto-García A, Castells MC, Hansbro PM, Stevens RL. Mast cell-restricted tetramer-forming tryptases and their beneficial roles in hemostasis and blood coagulation. Immunol Allergy Clin North Am. 2014;34(2):263-81.
143. Walls AF, He S, Teran LM, Buckley MG, Jung KS, Holgate ST, et al. Granulocyte recruitment by human mast cell tryptase. Int Arch Allergy Immunol. 1995;107(1-3):372-3.
144. Douaiher J, Succar J, Lancerotto L, Gurish MF, Orgill DP, Hamilton MJ, et al. Development of mast cells and importance of their tryptase and chymase serine proteases in inflammation and wound healing. Adv Immunol. 2014;122:211-52.
145. Blair RJ, Meng H, Marchese MJ, Ren S, Schwartz LB, Tonnesen MG, et al. Human mast cells stimulate vascular tube formation. Tryptase is a novel, potent angiogenic factor. J Clin Invest. 1997;99(11):2691-700.
146. Piliponsky AM, Chen C-C, Nishimura T, Metz M, Rios EJ, Dobner PR, et al. Neurotensin increases mortality and mast cells reduce neurotensin levels in a mouse model of sepsis. Nat Med. 2008;14(4):392-8.
147. Reilly CF, Tewksbury DA, Schechter NM, Travis J. Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. J Biol Chem. 1982;257(15):8619-22.
148. Jenne DE, Tschopp J. Angiotensin II-forming heart chymase is a mast-cell-specific enzyme. Biochem J. 1991;276 (Pt 2):567-8.
149. Sommerhoff CP, Caughey GH, Finkbeiner WE, Lazarus SC, Basbaum CB, Nadel JA. Mast cell chymase. A potent secretagogue for airway gland serous cells. J Immunol Baltim Md 1950. 1989;142(7):2450-6.
150. Kofford MW, Schwartz LB, Schechter NM, Yager DR, Diegelmann RF, Graham MF. Cleavage of type I procollagen by human mast cell chymase initiates collagen fibril formation and generates a unique carboxyl-terminal propeptide. J Biol Chem. 1997;272(11):7127-31.
151. Tchougounova E, Lundequist A, Fajardo I, Winberg J-O, Abrink M, Pejler G. A key role for mast cell chymase in the activation of pro-matrix metalloprotease-9 and pro-matrix metalloprotease-2. J Biol Chem. 2005;280(10):9291-6.
152. Caughey GH. Mast cell proteases as protective and inflammatory mediators. Adv Exp Med Biol. 2011;716:212-34.
153. Serafin WE, Katz HR, Austen KF, Stevens RL. Complexes of heparin proteoglycans, chondroitin sulfate E proteoglycans, and [3H]diisopropyl fluorophosphate-binding proteins are exocytosed from activated mouse bone marrow-derived mast cells. J Biol Chem. 1986;261(32):15017-21.
154. Rönnberg E, Melo FR, Pejler G. Mast cell proteoglycans. J Histochem Cytochem. 2012;60(12):950-62.
155. Fujishima H, Sanchez Mejia RO, Bingham CO, Lam BK, Sapirstein A, Bonventre JV, et al. Cytosolic phospholipase A2 is essential for both the immediate and the delayed phases of eicosanoid generation in mouse bone marrow-derived mast cells. Proc Natl Acad Sci U S A. 1999;96(9):4803-7.
156. Nakatani N, Uozumi N, Kume K, Murakami M, Kudo I, Shimizu T. Role of cytosolic phospholipase A2 in the production of lipid mediators and histamine release in mouse bone-marrow-derived mast cells. Biochem J. 2000;352 Pt 2:311-7.
157. Schleimer RP, Fox CC, Naclerio RM, Plaut M, Creticos PS, Togias AG, et al. Role of human basophils and mast cells in the pathogenesis of allergic diseases. J Allergy Clin Immunol. 1985;76(2 Pt 2):369-74.
158. Snyder F, Fitzgerald V, Blank ML. Biosynthesis of platelet-activating factor and enzyme inhibitors. Adv Exp Med Biol. 1996;416:5-10.
159. Morrow JD, Minton TA, Awad JA, Roberts LJ. Release of markedly increased quantities of prostaglandin D2 from the skin in vivo in humans following the application of sorbic acid. Arch Dermatol. 1994;130(11):1408-12.
160. Hirai H, Tanaka K, Yoshie O, Ogawa K, Kenmotsu K, Takamori Y, et al. Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. J Exp Med. 2001;193(2):255-61.
161. Fujitani Y, Kanaoka Y, Aritake K, Uodome N, Okazaki-Hatake K, Urade Y. Pronounced eosinophilic lung inflammation and Th2 cytokine release in human lipocalin-type prostaglandin D synthase transgenic mice. J Immunol. 2002;168(1):443-9.
162. Liu MC, Bleecker ER, Lichtenstein LM, Kagey-Sobotka A, Niv Y, McLemore TL, et al. Evidence for elevated levels of histamine, prostaglandin D2, and other bronchoconstricting prostaglandins in the airways of subjects with mild asthma. Am Rev Respir Dis. 1990;142(1):126-32.
163. Samuelsson B, Dahlén SE, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science. 1987;237(4819):1171-6.
164. Singh RK, Gupta S, Dastidar S, Ray A. Cysteinyl leukotrienes and their receptors: molecular and functional characteristics. Pharmacology. 2010;85(6):336-49.
165. Spina D, Coyle AJ, Page CP. The role of platelet activating factor in allergic inflammation. Pulm Pharmacol. 1989;2(1):13-9.
166. Korth R, Riess H, Brehm G, Hiller E. Unsaturated platelet-activating factor: influence on aggregation, serotonin release and thromboxane synthesis of human thrombocytes. Thromb Res. 1986;41(5):699-706.
167. Marshall JS. Mast-cell responses to pathogens. Nat Rev Immunol. 2004;4(10):787-99.
168. Williams LM, Ricchetti G, Sarma U, Smallie T, Foxwell BMJ. Interleukin-10 suppression of myeloid cell activation--a continuing puzzle. Immunology. 2004;113(3):281-92.
169. Li MO, Flavell RA. Contextual regulation of inflammation: a duet by transforming growth factor-beta and interleukin-10. Immunity. 2008;28(4):468-76.
170. Bradley JR. TNF-mediated inflammatory disease. J Pathol. 2008;214(2):149-60.
171. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol. 2008;122(3):569-73.
172. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001;108(2):184-90.
173. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Omalizumab Seasonal Allergic Rhinitis

Trail Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA. 2001;286(23):2956-67.
174. Wang H-H, Li Y-C, Huang Y-C. Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis. J Allergy Clin Immunol. 2016;138(6):1719-22.e1.
175. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. J Allergy Clin Immunol. 2007;119(6):1550-1.
176. Matito A, Blázquez-Goñi C, Morgado JM, Alvarez-Twose I, Mollejo M, Sánchez-Muñoz L, et al. Short-term omalizumab treatment in an adolescent with cutaneous mastocytosis. Ann Allergy Asthma Immunol. 2013;111(5):425-6.
177. Jagdis A, Vadas P. Omalizumab effectively prevents recurrent refractory anaphylaxis in a patient with monoclonal mast cell activation syndrome. Ann Allergy Asthma Immunol. 2014;113(1):115-6.
178. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol. 2002;109(2):274-80.
179. Kontou-Fili K. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis. Allergy. 2008;63(3):376-8.

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