REVIEWS

Mast Cells as Key Players in Allergy and Inflammation

González-de-Olano D1*, Álvarez-Twose I2,3*

1Department of Allergy, Hospital Universitario Ramón y Cajal, Madrid, Spain
2Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast), Hospital Virgen del Valle, Toledo, Spain
3Spanish Network on Mastocytosis (REMA)

*Both authors contributed equally to the manuscript and should be considered first authors.

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 inhibitorias.

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 patogénesis 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 (FceRI), 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 (FcyR) 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.

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 FceRI 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) FceRI, 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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{TC}, production of IL-5 and IL-6 is limited to MC\textsubscript{T} [53]. Other differential characteristics among the phenotypic MC subtypes include the dependence on helper T (CD4\textsuperscript{+}) lymphocytes of MC\textsubscript{T} and the expression of the receptor for the C5a complement activation fragment (CD88) on MC\textsubscript{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\textsuperscript{+} 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).

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 mastopoesis. 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 juxtamembrane 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 sezinoma [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 also been reported. In mastocytosis, the most common KIT mutation is a somatic activating point mutation caused by the substitution 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].

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 trisphosphate, 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...
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, INF-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 fulfills 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 trypsin, 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 trypsin recognized in serum are α-trypsin, which is constitutively secreted by MCs as inactive enzyme, and β-trypsin, which is released in large amounts during MC degranulation. A commercially available assay can be used to measure total serum trypsin levels, which are the sum of α- and β-trypsin isoforms. Therefore, the high levels of total serum trypsin frequently found in patients with mastocytosis are the result of increased chronic release of α-trypsin as a consequence of an increased total MC burden [130-132]. In contrast, increased total serum trypsin levels detected in patients with anaphylaxis more likely reflect the acute release of β-trypsin that typically occurs after MC degranulation in this setting [128,133]. Of note, the measurement of total serum trypsin 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 trypsin 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 trypsin 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 trypsin 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]. Trypsin 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 hydrolyze 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 lipooxygenase (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, mucus secretions, 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 on endothelial cells 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-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.

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Iván Álvarez-Twose

Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast)
Hospital Virgen del Valle
Toledo, Spain
E-mail: ivana@sescam.jccm.es