



Cells in focus

Mast cells in allergy and beyond

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Abstract

Mast cells (MC) are highly granulated tissue dwelling cells, widely distributed throughout the body in connective tissues and on mucosal surfaces. They are derived from bone marrow progenitors that migrate into the blood and subsequently into the tissues, where they undergo final maturation. Mast cell proliferation, differentiation, survival and activation are regulated by stem cell factor, the ligand for the c-kit tyrosine kinase receptor, expressed on the mast cell surface. They release a large number of pro-inflammatory and immunoregulatory mediators after activation induced by either immunoglobulin E-dependent or immunoglobulin E-independent mechanisms. Mast cells have been most widely studied in the context of allergic reactions and parasite infections, but there is now compelling evidences that they are important players in innate and acquired immunity, wound healing, fibrosis, tumors and autoimmune diseases. This review will discuss current advances in these fields.

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Keywords: Mast cells; c-kit; Stem cell factor; Allergy

Cell facts

- Mast cells are high affinity IgE receptor bearing tissue dwelling cells containing prominent cytoplasmic granules and key cells in allergy.
- Mast cell proliferation, differentiation, survival and activation are regulated by stem cell factor.
- Mast cells and their mediators participate in innate and acquired immunity, wound healing, tissue remodeling, angiogenesis and autoimmune diseases.

1. Introduction

Mast cells (MC) are tissue dwelling cells containing prominent cytoplasmic granules. They have a pivotal role in allergic reactions and take part in other pathophysiological conditions such as innate and acquired immunity (Mekori & Metcalfe, 2000), wound healing, fibrosis, tumors and autoimmune diseases (Benoist &

Mathis, 2002) (Fig. 1). MC are widely distributed throughout the body, in connective tissues and on mucosal surfaces where they are frequently located in close proximity to blood vessels and peripheral nerves. Due to this strategic location, they are exposed to environmental stimuli such as microorganisms and allergens (Galli, Maurer, & Lantz, 1999) with which they can react, both within minutes and/or over a period of hours, and undergo regulated secretion of preformed and newly synthesized mediators. Until very recently, studies on human MC have been hampered because of the difficulty to obtain large amounts of highly

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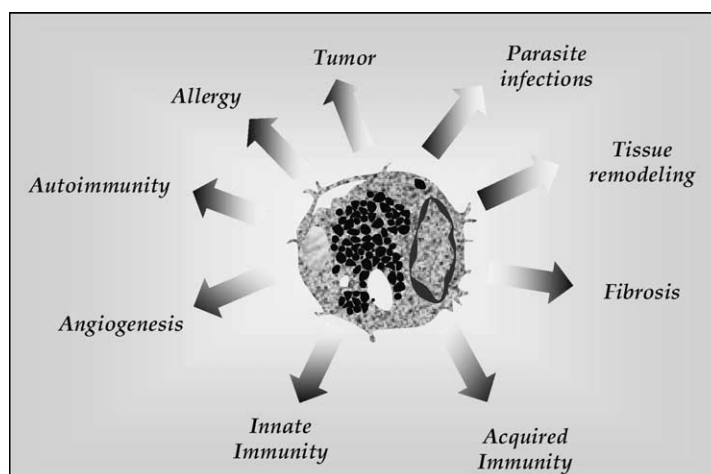


Fig. 1. Roles of mast cells in different physiopathological processes. Mast cell versatility is demonstrated by its participation in many different pathophysiological processes.

purified MC. Recently, however, with new methodologies for human MC obtention, many advances have been made in the understanding of MC biology.

This article provides new evidences on the well-established properties of MC in type I hypersensitivity reactions and on other less “classical” pathophysiological roles.

2. Cell origin and plasticity

2.1. Mast cell origin and development

MC are derived from progenitors expressing CD34, CD117 (c-kit) and CD13 in humans, and from Thy-1^{lo} c-kit^{hi} cells in the mouse, circulating in the peripheral blood and lymphatics and migrating into vascularized tissues, where they undergo final maturation under the influence of local factors. Several studies indicate that MC proliferation, differentiation and survival are stringently regulated by stem cell factor (SCF), the ligand for the c-kit tyrosine kinase growth factor receptor, which is expressed on the MC surface. In addition, other mediators such as interleukin (IL)-3, IL-4, IL-9, IL-10, nerve growth factor (NGF), some chemokines and retinoids can regulate MC differentiation (Marone, Galli, & Kitamura, 2002). Before full granule maturation, circulating progenitors of MC also display the low affinity IgG receptor FcγRIIb, and contain mRNA

for MC proteases. MC express the high affinity IgE receptor, FcεRI, early in their development, but apparently only after they undergo lineage-commitment.

2.2. Mast cell survival and death

MC numbers in tissues are relatively constant, even though MC hyperplasia is observed in both the inflammatory and in the repair/remodeling stage of various inflammatory/fibrotic disorders (Bischoff & Sellge, 2002).

The survival of human mature MC in tissues appears to depend largely on the local production of SCF since its withdrawal results in apoptosis (Iemura, Tsai, Ando, Wershil, & Galli, 1994). Moreover, other cytokines are involved in MC survival and growth. For example, IL-3 induces mouse MC growth and enhances their development in response to SCF in vitro while in humans its role is still controversial. MC progenitors and human intestinal MC (Bischoff & Sellge, 2002) but not tissue-derived mature MC from lung, uterus, kidney, tonsils and skin express IL-3 receptor. NGF has also been reported to be a survival factor for rat peritoneal MC (RPMC) (Kawamoto et al., 1995) and for human cord blood-derived mast cells (CBMC) in the presence of SCF (Kanbe et al., 2000).

Mouse bone marrow derived-MC (BMMC), RPMC and the murine C57 and MCP-5 lines express the death receptor Fas (Apo-1/CD95), but only the C57

are susceptible to Fas dependent apoptosis. We have recently found that human lung and CBMC express functional tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL) receptors and that SCF prevents their apoptosis induced by TRAIL receptor ligation. This would suggest a novel mechanism for the pro-survival effects of SCF on MC.

2.3. Mast cell heterogeneity

MC can be heterogeneous in phenotype and functions (Metcalf, Baram, & Mekori, 1997). Historically, in rodents two main MC subtypes have been described according to their phenotype and tissue localization: (i) T cell-dependent mucosal MC (MMC), mainly found in the mucosa of the gastrointestinal system and in the lamina propria of the respiratory tract; (ii) T cell-independent connective tissue MC (CTMC) localized in the sub-mucosa of the gastrointestinal tract, in the skin and in the peritoneum. However, the MMC and CTMC differ in many other aspects. In humans, by analogy to rodents, two main MC subtypes have been described, according to their distinct protease patterns: one residing preferentially in mucosal tissues and containing only tryptase (MC_T); the other one found in connective tissues containing tryptase, chymase, cathepsin G and carboxypeptidase (MC_{TC}) (Table 1). In addition MC that express only chymase (MC_C) have been shown in several human tissues (Weidner & Austen, 1993) and in bone marrow during myelodysplasia or mastocytosis (Horny, Greschniok,

Jordan, Menke, & Valent, 2003), although their role has not yet fully been elucidated. Human MC phenotypes are also heterogenic in their cytokine content. For example, IL-4 is distributed preferentially in the MC_{TC} subset. In contrast, IL-5 and IL-6 is restricted almost exclusively to the MC_T subset. In addition to these differences, both MC_T and MC_{TC} express FcεRI and participate in IgE-dependent allergic or anti-parasite reactions. It is important to note that CBMC and the human mast cell line HMC-1, derived from a patient with leukemia, frequently used as a source of MC for in vitro studies, are mainly MC_T.

2.4. Mast cell activation

MC undergo regulated exocytosis when a multi-valent antigen causes the aggregation of occupied FcεRI on their surface. This event is followed by the immediate release of preformed granular mediators such as histamine, tryptase and chymase (much more slowly). Activated MC can also very rapidly synthesize and release prostaglandin (PG)-D₂, thromboxanes, leukotrienes (LTs) and platelet-activating factor (PAF). MC are important sources of an array of cytokines, growth factors, and chemokines (Mekori & Metcalfe, 2000).

CBMC are activated by IgG-dependent stimuli only after incubation with interferon (IFN)-γ that upregulates the expression of FcγRI. Under these conditions the expression of FcγRII is also increased, but it does not induce MC activation. In contrast, the expression

Table 1
Characteristics of the two major human mast cell phenotypes

Classification	MC _T (immune system associated)	MC _{TC} (non-immune system associated)
Location	GI tract mucosa, respiratory tract, lamina propria	Sub-mucosa of GI tract and skin
IgE dependency	IgE-dependent activation IgE-independent activation ^a	IgE-dependent and independent activation
Major enzymes	Tryptase	Tryptase, chymase, cathepsin G, carboxypeptidase
Major arachidonic acid metabolites	LTC ₄ , PG-D ₂ (↓)	LTC ₄ (↓), PG-D ₂
Major cytokines	IL-4 (↓), IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-16, TNF-α, GM-CSF, SCF, TGF-β	IL-5 (↓), IL-6 (↓), IL-3, IL-4, IL-7, IL-8, IL-10, IL-13, IL-16, TNF-α, SCF
Pathological phenotype	Increased around sites of T _H -activation Increased in allergic and parasitic diseases Decreased in AIDS and chronic immunodeficiency diseases	Increased in fibrotic diseases Unchanged in allergic and parasitic diseases Unchanged in AIDS and chronic immunodeficiency diseases

MC_T: mast cells containing only tryptase; MC_{TC}: mast cells containing both tryptase and chymase; (↓): decrease.

^a Recently shown by our group (Piliponsky et al., 2003).

of Fc γ RIII is not increased (Woolhiser, Okayama, Gilfillan, & Metcalfe, 2001). RPMC and MC_{TC} isolated from the skin degranulate in response to several non-immunological agents, such as compound 48/80, basic polypeptides (polylysine, polyarginine), morphine sulphate, substance P, and the anaphylatoxin C5a (Lowman, Rees, Benyon, & Church, 1988). In addition compound 48/80 tested in the skin of patients with scleroderma increased local MC releasability compared with healthy subjects, suggesting that MC in disease can differ in their functional properties than MC in health (Pearson et al., 1988). In contrast to RPMC and MC_{TC}, murine BMMC and MC_T have been described as unresponsive to IgE-independent activation. However, MC activation can be profoundly affected by the microenvironment. For example, mouse BMMC were shown to acquire responsiveness to IgE-independent stimuli when in co-culture with mouse 3T3 fibroblasts. In accordance with this, we have recently observed that human lung mast cells (HLMC), that are mostly MC_T, become responsive to eosinophil major basic protein (MBP) when in co-culture with human lung fibroblasts and that the fibroblast-derived membrane form of SCF is responsible for this process (Piliponsky, Gleich, Nagler, Bar, & Levi-Schaffer, 2003). MC also express a large number of surface receptors (Ott & Cambier, 2000), that inhibit the release of pro-inflammatory mediators. For example Katz et al. have recently demonstrated in gp49B^{-/-} mice that activation of the Ig superfamily member gp49B1 on MC inhibits their activation upon IgE-dependent and independent stimuli, suggesting new approaches to modulate the allergic reactions.

3. Cell function and associated pathology

3.1. Mast cells in allergic inflammation

In allergy, apart from their classical role in eliciting the early phase, MC also have an important function in its late and chronic stages. In these stages they may interact with and be activated by infiltrated inflammatory cells such as eosinophils and lymphocytes and by resident structural cells such as epithelial, smooth muscle cells and fibroblasts (Fig. 2). Most of the evidences for these interactions come from *in vitro* studies. For example, we have found that IgE-challenged RPMC

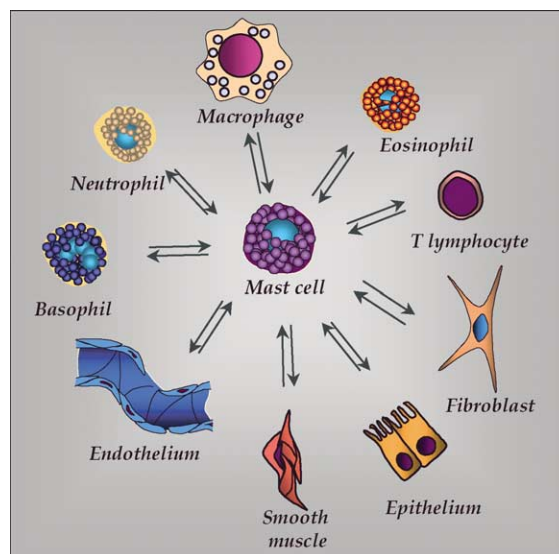


Fig. 2. Mast cell interactions with other cells during allergic inflammation. The interactions between the mast cell and several types of cells are explained in further detail in the text.

are sensitive to reactivation induced by eosinophil sonicate and eosinophil-derived MBP (Piliponsky, Pickholtz, Gleich, & Levi-Schaffer, 2001). In addition, HLMC are activated by MBP to release histamine and PG-D₂ when in co-culture with human lung fibroblasts (Piliponsky et al., 2003). Activated MC release mediators that contribute to eosinophil recruitment, activation and survival. For example, MC-derived TNF- α enhances eosinophil survival through autocrine production of granulocyte-macrophage colony stimulating factor (GM-CSF), a process regulated by nuclear factor kappa B (NF κ B) and sensitive to steroids (Levi-Schaffer, Temkin, Malamud, Feld, & Zilberman, 1998). In addition, MC-derived tryptase induces IL-6 and IL-8 release in eosinophils by the mitogen-activated protein kinase (MAPK)/activator protein (AP)-1 pathway (Temkin, Kantor, Weg, Hartman, & Levi-Schaffer, 2002). MC also stimulate macrophages and epithelial cells to generate lymphocyte and eosinophil chemoattractants, and through the release of IL-4, they promote the development of Th2. In asthma it has been recently observed that the number of infiltrated MC into airway smooth muscle correlates with the degree of airway hyperresponsiveness, a phenomena attributed in the past exclusively to the eosinophils (Brightling et al., 2002).

3.2. Mast cells in innate immunity

Since MC are mainly found in the host–environment interface from which microorganisms can penetrate, they can constitute one of the first inflammatory cells establishing a direct contact with the invading pathogens. Using MC c-kit deficient W/W^v mice and the c-kit knock-in mice it was demonstrated that during a bacterial infection induced by lipopolysaccharide (LPS), MC specifically secrete TNF- α to recruit into the site of infection circulating leukocytes with bactericidal properties such as neutrophils (Malaviya, Ikeda, Ross, & Abraham, 1996). In addition, Maurer et al. found that repetitive administration of SCF and consequent MC hyperplasia, can improve the survival of normal mice with acute bacterial peritonitis induced by cecal ligation and puncture (CLP) (Maurer et al., 1998). In these cases MC can be triggered by the interaction of CD48, a glycosylphosphatidylinositol-anchored molecule expressed in MC, or by Toll-like receptor (TLR)-2. For example, bacterial peptidoglycan and yeast zymosan were potent inducers of GM-CSF, IL-1 β , and LTs generation in TLR-2 activated CBMC while a synthetic triacylated lipopeptide induced short-term degranulation, but failed to induce LTs production (McCurdy, Olynch, Maher, & Marshall, 2003). During bacterial infection MC can also be activated by the host's complement system, since in vivo inflammatory response to CLP is significantly reduced in C4- or C3-deficient mice compared to wild-type mice.

New evidences indicate that MC are also involved in HIV-1 infection. The HIV-1 glycoprotein gp120 stimulates IL-4 and IL-13 release from MC via gp120 interaction with the V_H3 region of IgE. In addition, the Tat protein, secreted by HIV-1 infected cells, is a potent chemoattractant for Fc ϵ RI⁺ cells and upregulates the expression of CCR3 on their surface.

3.3. Mast cells in acquired immunity

The role of MC in acquired immunity has been demonstrated to be regulated by IL-3 which is probably derived from T cells that recognize the infecting agents. IL-3 enhances immunity in mice infected with the intestinal nematode *Strongyloides venezuelensis* and increases the number of tissue MC. In addition,

IL-4 and IL-13 are required for the MC response that induces the expulsion of *Trichinella spiralis* and *Trichuris muris*.

The role of MC in acquired immunity as antigen presenting cells (APC) has also been suggested. In fact human MC constitutively express MHC class I molecules and express MHC class II molecules after treatment with IFN- γ and TNF- α . Furthermore MHC class II molecules are found in HMC-1 and bind the staphylococcal enterotoxin A (SEA) leading to ultrastructural changes that suggest MC degranulation.

3.4. Mast cells in tissue remodeling, fibrosis and angiogenesis

MC have been implicated in physiological wound healing as well as in fibrosis. In several fibrotic diseases such idiopathic lung fibrosis, bleomycin or radiation-induced fibrosis, asthma, scleroderma, chronic graft-versus-host-disease (cGvHD), liver fibrosis, Crohn's disease and inflammatory bowel disease (Levi-Schaffer & Piliponsky, 2003), MC hyperplasia and signs of degranulation are present. In a rodent model of peritoneal adhesions and of Crohn's disease nedocromil sodium, a MC stabilizer, decreased the severity of the disease (Xu et al., 2002), indicating the important pathogenic role of the MC in chronic inflammation and fibrosis.

MC have the potential to directly influence the fibroblasts, the main players of fibrosis, and/or indirectly other cells leading to a pro-fibrotic response. For example, HMC-1, that produces matrix metalloproteinase (MMP)-9 and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2, induces human lung, skin and intestinal fibroblasts proliferation by mediators such as histamine and tryptase and enables retraction of the collagen matrix. It is interesting to note that while HMC-1 increases collagen production in the skin (Garbuzenko et al., 2002), it decreases collagen production in the lung and intestine (Xu, Rivkind, Pappo, Pikarsky, & Levi-Schaffer, 2002). Some of the MC associated cytokines such as transforming growth factor (TGF)- β , IL-4, IL-6, IL-13, and NGF display pro-fibrogenic activities. For example, NGF enhances human lung, skin and conjunctival fibroblasts migration, differentiation into myofibroblasts, and contraction of collagen gels, but not proliferation and collagen synthesis, indicating

an important role of this factor at the beginning and end stages of wound repair (Micera et al., 2001).

MC have also been linked for almost two decades to neovascularization, during haemangioma, rheumatoid arthritis (RA), nasal polyps, wound healing and ovulation (Levi-Schaffer & Pe'er, 2001). Human inflamed tissue and murine MC from tissue with anaphylaxis were shown to contain in their cytoplasmic granules fibroblast growth factor (FGF)-2 and vascular endothelial growth factor (VEGF). In addition heparin, histamine, tryptase, TGF- β , TNF- α , IL-8 have been shown to have pro-angiogenic properties, while others such as endostatin have anti-angiogenic effects.

3.5. Mast cells in autoimmune diseases

MC have been implicated in several autoimmune diseases, including Sjogren's syndrome, chronic idiopathic urticaria, autoimmune thyroiditis and experimental vasculitis. A correlation between the number and/or distribution of mast cells and the development of experimental allergic encephalomyelitis (EAE), the animal model of multiple sclerosis, has been reported (Benoist & Mathis, 2002). The direct contribution of MC in EAE comes from studies in mast cell deficient *W/W^v* mice, where the onset of myelin oligodendrocyte glycoproteins (MOG)-induced EAE is delayed and less severe than in control mice. MC might also have an early and coordinating role in the pathogenesis of RA. An increased number of MC and tryptase are found in the swollen paws of mice with collagen-induced arthritis and in the synovial fluid of patients with RA (Benoist & Mathis, 2002). In this context, the MC-derived TNF- α may stimulate the synovial fibroblasts to produce SCF, suggesting a potential mechanism for the perpetuation and amplification of the local inflammation in this pathological condition.

4. Conclusions

As reported in this review, during the last few years novel aspects of MC biology have been discovered. Based on these findings new frontiers have opened to explore and understand the complex role of these

cells in health and disease. This may ultimately lead to novel approaches for the treatment and/or prophylaxis of mast cell-associated diseases.

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