

## The Human Mast Cell

### *An Overview*

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#### **Summary**

Mast cells are fascinating, multifunctional, tissue-dwelling cells that have been traditionally associated with the allergic response. However, recent studies suggest these cells may be capable of regulating inflammation, host defense, and innate immunity. The purpose of this review is to present salient aspects of mast cell biology in the context of mast cell function in physiology and disease. After their development from bone marrow-derived progenitor cells that are primed with stem cell factor, mast cells continue their maturation and differentiation in peripheral tissue, developing into two well-described subsets of cells, MC<sub>T</sub> and MC<sub>TC</sub> cells. These cells can be distinguished on the basis of their tissue location, dependence on T lymphocytes, and their granule contents. Mast cells can undergo activation by antigens/allergens (acting via the high-affinity receptor for immunoglobulin E, also referred to as FcεRI), superoxides, complement proteins, neuropeptides, and lipoproteins. After activation, mast cells express histamine, leukotrienes, and prostanoids, as well as proteases, and many cytokines and chemokines. These mediators may be pivotal to the genesis of an inflammatory response. By virtue of their location and mediator expression, mast cells may play an active role in many diseases, such as allergy, parasitic diseases, atherosclerosis, malignancy, asthma, pulmonary fibrosis, and arthritis. Recent data also suggest that mast cells play a vital role in host defense against pathogens by elaboration of tumor necrosis factor alpha. Mast cells also express the Toll-like receptor, which may further accentuate their role in the immune-inflammatory response. This chapter summarizes the many well-known and novel functional aspects of human mast cell biology and emphasizes their unique role in the inflammatory response.

**Key Words:** Mast cells; immunoglobulin E; cytokine; gene expression; host defense; inflammation.

## 1. Introduction

Paul Ehrlich was the first researcher to describe cells in connective tissue that stained reddish–purple (referred to as metachromasia) with aniline dyes, calling them “mästzellen,” a term that may have referred to feeding or could be interpreted as “well-fed” based on their granule contents (*1*). The metachromasia exhibited by mast cells is caused by the interaction of dyes with acidic heparin, a well-known constituent of mast cell granules. The discovery of these cells by Paul Ehrlich and the historical development of mast cell research are described in greater detail in Chapter 1. Mast cells tend to be located perivascularly and in sentinel locations to respond to noxious stimuli as well as to allergens. The mast cell expresses the high-affinity receptor for immunoglobulin E (FcεRI) and the crosslinking of IgE occupying this receptor leads to mast cell activation and the manifestations of immediate-type hypersensitivity (*2–4*). In some cases, other ligand–receptor interactions can lead to mast cell degranulation, which are summarized in **Fig. 1**.

## 2. Mast Cell Development and Differentiation

Mast cells develop from progenitor cells that in turn arise from uncommitted hematopoietic stem cells in the bone marrow (*5,6*). These cells express the receptor for stem cell factor (SCF receptor or c-kit) that binds to SCF, the latter being a major growth factor for mast cells (*5–7*). Researchers have described a CD34<sup>+</sup>, c-kit<sup>+</sup>, and CD13<sup>−</sup> precursor that develops into mast cells in the presence of specific growth factors (*8,9*). Mast cell progenitors also have been described in peripheral blood by others, which may suggest the presence of a distinct pool of cells separate from leukocytes or mononuclear cells (*10*). The interactions between SCF and c-kit and the subsequent signaling that follows are crucial for the growth and development of mast cells (*11*). In humans, studies have demonstrated that mutations of c-kit and elevated levels of the c-kit proto-oncogene are associated with the development of the syndrome of mastocytosis, a condition characterized by mast cell infiltration of skin and other tissues (*12,13*). SCF has multiple biological effects on mast cells, including modulating differentiation and homing, prolonging viability, inducing mast cell hyperplasia, and enhancing mediator production (*7*). However, mast cells that have been deprived of SCF undergo programmed cell death (PCD) or apoptosis (*14*). It is likely that PCD in mast cells is mediated by the modulation of Bcl-2 and Bcl-XL (*15*). Interleukin 6 (IL-6), eotaxin, and nerve growth factor (NGF) also enhance mast cell development from hematopoietic stem cells, and the development of mast cells from stem cells derived from umbilical cord blood often requires SCF in conjunction with IL-6 (*5,16*). Adventitial cells, including fibroblasts, contribute to further differentiation and maturation of mast cells in tissue by elaboration of SCF, NGF, or other mechanisms (*17,18*). After tissue

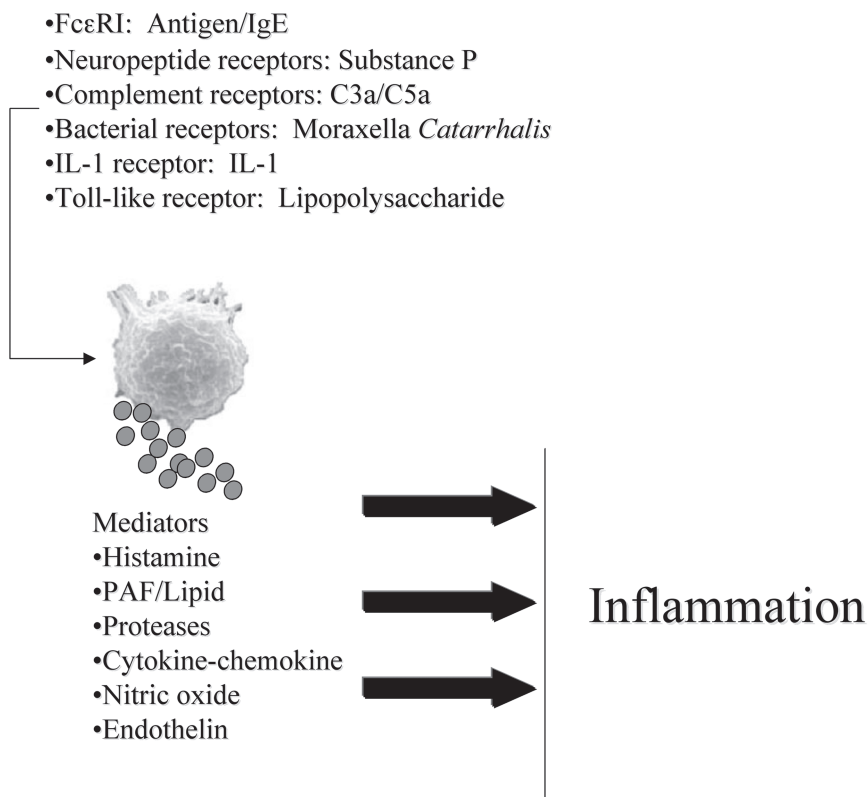


Fig. 1. Mast cells undergo activation by IgE-dependent and IgE-independent stimuli, leading to release of a cascade of mediators culminating in the inflammatory response. Histamine, platelet-activating factor (PAF), lipid mediators (leukotrienes, prostanoids), proteases, cytokines, chemokines, nitric oxide, and endothelin may be released in the tissue, which can lead to inflammatory cell recruitment, endothelial activation, and cellular adhesion.

localization, mast cells can undergo further differentiation into distinct subsets. Two mast cell subtypes have been described in tissue—the mucosal ( $MC_T$ ) or connective tissue ( $MC_{TC}$ ) mast cell (**Table 1**). These subtypes are based on structural, biochemical, and functional differences and have been well characterized by several researchers (**3,19–21**). Please *see* Chapter 4 for more information.

Distinctive features help differentiate the two subsets. For example, the  $MC_T$  mast cell predominantly expresses the protease tryptase (**Fig. 2A** demonstrates tryptase staining of mast cells derived from umbilical cord blood mononuclear cells). This subset usually is localized to mucosal surfaces, often in close prox-

**Table 1**  
**Mast Cell Subtypes**

Feature	MC <sub>TC</sub> cell	MC <sub>T</sub> cell
Structural features		
Grating/lattice granule	++	–
Scroll granules	Poor	Rich
Tissue distribution		
Skin	++	–
Intestinal submucosa	++	+
Intestinal mucosa	+	++
Alveolar wall	–	++
Bronchi	+	++
Nasal mucosa	++	++
Conjunctiva	++	+
Mediator synthesized		
Histamine	+++	+++
Chymase	++	–
Tryptase	++	++
Carboxypeptidase	++	–
Cathepsin G	++	–
LTC <sub>4</sub>	++	++
PGD <sub>2</sub>	++	++
TNF- $\alpha$	++	++
IL-4, IL-5, IL-6, IL-13	++	++

imity to T cells. These T lymphocytes are especially of the T-helper 2-type (Th2 secreting IL-4 and IL-5). This subset usually is seen in increased numbers infiltrating the mucosa in patients suffering from allergic and parasitic disease. Because of their unique T cell-dependence, the numbers of MC<sub>T</sub> cells are diminished in individuals infected with human immunodeficiency virus (HIV) (3). Structurally, granules from MC<sub>T</sub> are scroll-rich (**Fig. 2B** demonstrates a typical scroll-like granule in mast cells developed from umbilical cord blood mononuclear cells).

The MC<sub>TC</sub> mast cell, however, expresses tryptase, chymase, carboxypeptidase, and cathepsin G. It tends to predominate in the gastrointestinal tract as well as in skin, synovium, and subcutaneous tissue (**Table 1**). Increased numbers of MC<sub>TC</sub> mast cells are seen in fibrotic diseases whereas its numbers are relatively unchanged in allergic or parasitic diseases and in HIV infection. The presence of these MC<sub>TC</sub> cells could help explain why patients with HIV infection continue to have allergic reactions (e.g., to medications). MC<sub>TC</sub> mast cells have lattice and grating structures and are scroll-poor.

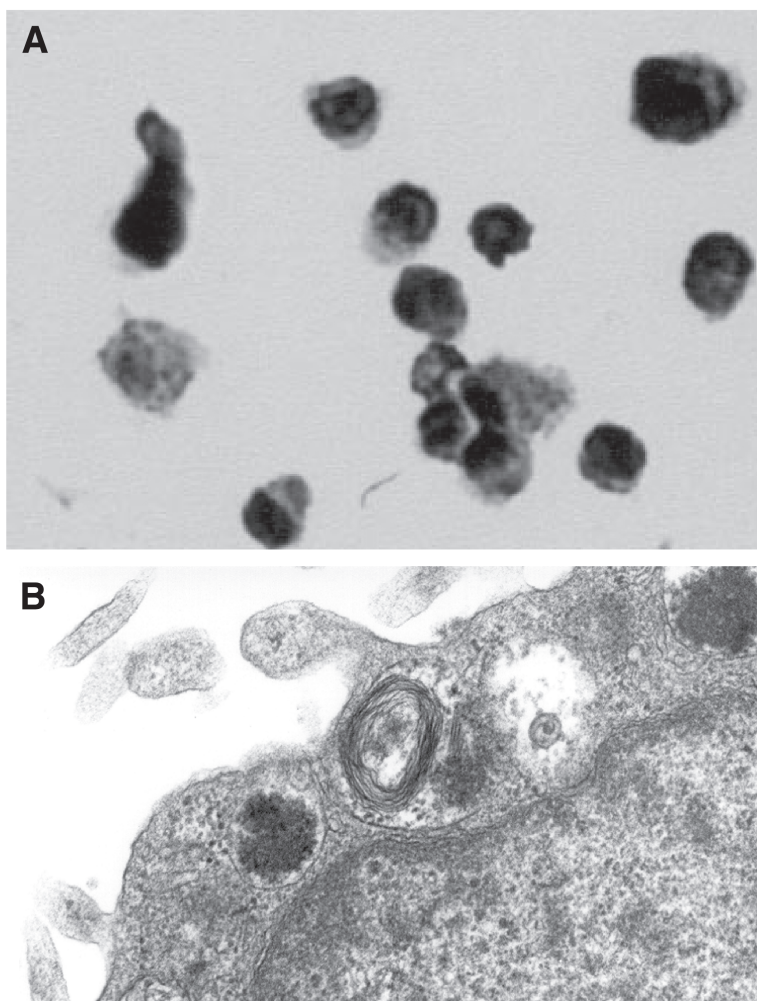


Fig. 2. (A) Tryptase immunostaining of human cord blood-derived mast cells ( $\times 400$ ). In this specimen, more than 95% of human cord blood-derived mast cells expressed tryptase, with only 20% expressing chymase. (B) Ultrastructurally, mast cells demonstrate microvilli-like projections on the surface and typical granules. This picture demonstrates the presence of scroll-like granules within the mast cell derived from umbilical cord blood mononuclear cells.

### 3. Mast Cell Activation and Mediator Production

Human mast cells and basophils express the receptor for IgE, Fc $\epsilon$ RI (2). Fc $\epsilon$ RI (in contrast to the other receptor for IgE, Fc $\epsilon$ RII) binds IgE with high affinity (22). The other receptor for IgE, Fc $\epsilon$ RII, has been detected on eosino-

phils, mononuclear cells, lymphocytes, and platelets. Fc $\epsilon$ RI is a multimeric complex composed of four chains, designated as  $\alpha$  (which has the IgE-binding domain),  $\beta$ , and the two disulfide-linked  $\gamma$  chains (23,24). Typically, multivalent antigen binds to IgE, which in turn binds by the Fc portion to the  $\alpha$ -chain of Fc $\epsilon$ RI, leading subsequently to receptor aggregation and internalization and culminating in receptor-mediated signaling. The  $\beta$  and  $\gamma$  chains of Fc $\epsilon$ RI possess the immune receptor tyrosine-based activation motifs, which are considered pivotal to signal transduction (25). The bridging of two IgE molecules by multivalent antigen or by univalent antigen in presence of a carrier molecule results in activation of Lyn kinase, which then phosphorylates the  $\beta$  and  $\gamma$  chains (22). The absence of Lyn has been associated with defective mast cell signaling in mice (26). Syk kinase then becomes activated sequentially, followed by involvement of phospholipase C  $\gamma$ , mitogen-activated protein kinases (MAPK), and phosphoinositol-3 kinase (27). The generation of inositol triphosphate and of diacylglycerol and other second messengers leads to release of calcium intracellularly as well as protein kinase C activation, events culminating in Fc $\epsilon$ RI-mediated secretion. Degranulation appears to be associated with activation of G proteins that cause actin polymerization and relocalization. These events also are accompanied by the transcription of several cytokine genes, leading to further evolution of the inflammatory cascade.

In a typical allergic reaction, antigen/allergen (for example, latex or peanut allergen) crosslinks two IgE molecules occupying Fc $\epsilon$ RI, resulting in a cascade of rapid sequence signaling events and leading to degranulation and elaboration of mediators (28). Mast cells also can be activated to degranulate by a variety of stimuli including; opiates, components of the complement cascade (29–31), neuropeptides (vasoactive intestinal peptide, calcitonin gene-related peptide, and substance P), superoxide anion, radio-contrast media, oxidized low-density lipoproteins, histamine releasing factors, chemokines (monocyte chemotactic proteins-1, -2, and -3 [MCP-1, -2, -3], and monocyte inflammatory peptide 1  $\alpha$  [MIP-1  $\alpha$ ]), regulated upon activation normal T-cell-expressed and secreted (RANTES), connective tissue-activating peptide, pathogenic bacteria (32,33), parasites (34,35), enterotoxin B (36), cholera toxin (37), or changes in osmolality (38,39). We have recently demonstrated that IL-1, catecholamines, and cell–cell interactions (e.g., mast cell–fibroblast contact) can enhance mast cell activation and cytokine expression (40–43), which indicates the occurrence of multiple pathways of mast cell activation.

Mediators secreted by mast cells can be subdivided into preformed (secretory granule-associated) and others newly synthesized after cellular activation (3,44). Preformed mediators (summarized in **Fig. 3**) include histamine, proteoglycans (heparin, chondroitin sulfate E), serotonin, proteases (such as tryptase, chymase,  $\beta$ -hexosaminidase,  $\beta$ -glucuronidase,  $\beta$ -D-galactosidase, cathepsin G,

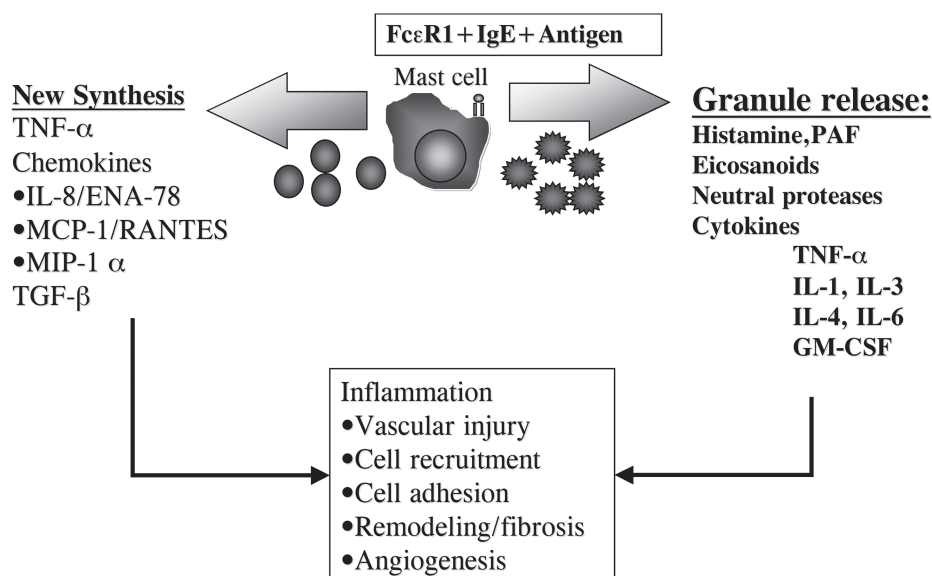


Fig. 3. After activation of mast cells by IgE and antigen, the release of preformed and newly synthesized mediators occurs, leading to acute and chronic inflammatory effects, mediated by vascular injury, cellular recruitment, and culminating in tissue remodeling and angiogenesis.

and carboxypeptidase), some cytokines (tumor necrosis factor [TNF]-α), and basic fibroblast growth factor (bFGF). The newly generated products include the lipid mediators (prostaglandin D<sub>2</sub> and leukotrienes, generated from arachidonic acid), thromboxanes, 5,12-hydroxy-eicosatetraenoic acid, nitrogen radicals, oxygen radicals, inflammatory cytokines, and several chemokines.

#### 4. The Mediators Expressed by Mast Cells and Their Role in the Inflammatory Response

Plaut et al. (45) first demonstrated that murine mast cells were capable of expressing many cytokines. Since then, we and others have shown that human mast cells express a spectrum of cytokines and chemokines (3,46,47). Both in vivo and in vitro studies have shown that human mast cells are capable of expressing pleiotropic cytokines and growth factors, such as TNF-α (3,48–51), granulocyte macrophage colony-stimulating factor (52), IL-3 and IL-4 (36,53–59), IL-5 (54–56,60), IL-6 (55,56,61–64), IL-8 (54,65,66), IL-10 (67), IL-13 (68–70), IL-16 (71), MIP-1 α (72), MIP-1 β (73), regulated upon activation normal T-cell-expressed and -secreted (3,73), and MCP-1 (74,75). Human mast cells also are capable of expressing growth factors. Vascular endothelial



growth factor (VEGF), a cytokine crucial to angiogenesis and the growth of blood vessels, and NGF (76,77), are recognized products of mast cells. Auto-crane production of SCF has been shown from mast cells (78,79).

It is likely that heterogeneity of human mast cells exists in regards to cytokine expression in vivo and studies by Bradding et al. (63), demonstrated this phenomenon in mast cells obtained from bronchial biopsies of patients suffering from asthma. By immunocytochemistry, these investigators noted that although MC<sub>TC</sub> cells predominantly expressed IL-4, the MC<sub>TC</sub> cells expressed both IL-5 and IL-6 (63). In our studies, cord blood-derived mast cells expressed the eosinophil-active growth factors IL-5 and GM-CSF and the eosinophil chemotactic C-X-C chemokine, IL-8, after activation (42). The production of these cytokines in cord blood-derived mast cells was further enhanced by the addition of the monokines IL-1 $\beta$  and TNF- $\alpha$  in a dose-dependent manner while dexamethasone inhibited production of these cytokines. How these various cytokines and chemokines interact with the inflammatory response is summarized below.

Mast cells have been incriminated in such diverse diseases as allergy, asthma, rheumatoid arthritis, atherosclerosis, interstitial cystitis, inflammatory bowel disease, progressive systemic sclerosis, chronic graft-vs-host disease, fibrotic diseases, sarcoidosis, asbestosis, ischemic heart disease, keloid scars, and malignancy (3). The mediators released by mast cells can independently and, in synergy with macrophage- and T-cell-derived cytokines, induce much of the inflammatory pathology observed in inflammation and serve to orchestrate a complex immune response. Histamine, LTB<sub>4</sub>, LTC<sub>4</sub>, PAF, and PGD<sub>2</sub> may have multiple effects on inflammatory cell recruitment (eosinophils), smooth muscle hyperplasia, and vascular dilatation (80,81). Trypsin, chymase, and TNF- $\alpha$  from mast cells activate fibroblasts, leading to collagen deposition and fibrosis. Mast cell-derived TNF- $\alpha$  regulates NF- $\kappa$ B-dependent induction of endothelial adhesion molecule expression on endothelial cells in vivo (49). Mast cell granules and trypsin also can potentiate endotoxin-induced IL-6 production by endothelial cells. Mast cell-derived cytokines and chemokines further regulate IgE synthesis and cell migration, basophil histamine release, smooth muscle proliferation, and endothelial chemotaxis and proliferation. IL-4 and IL-13 can regulate adhesion molecule expression on endothelial cells but also can class switch B cells to synthesize IgE (82,83). Data suggest that mast cells also can directly activate B cells to switch to IgE. IL-5, another product of mast cells, also can serve to activate eosinophils while accentuating IgA production from B cells. Chemokines (such as IL-8) and leukotrienes (specifically LTC<sub>4</sub>) released by mast cells can recruit neutrophils and eosinophils to inflamed airways, which can further potentiate damage (3). Mast cells also have been postulated to provide the IL-4 pulse that allows the development of Th2 cells that



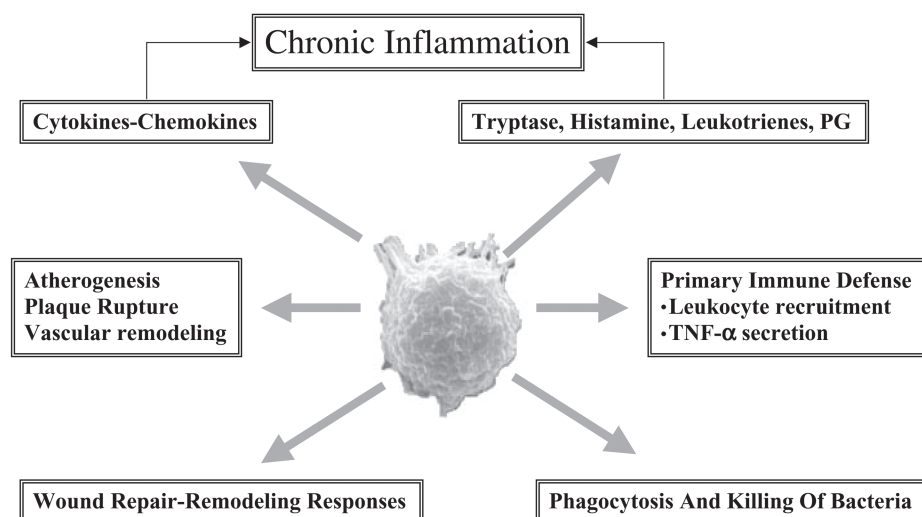


Fig. 4. Multiple roles of human mast cells in chronic disease states and immunophysiology or pathology.

selectively secrete IL-4 and IL-5 on activation (84). Exciting recent data also suggest that certain mast cell-derived chemokines, especially MIP-1 $\alpha$ , can potentiate a shift of T cells towards a Th1-phenotype, whereas others, such as MCP-1, can shift these cells functionally to a Th2-phenotype (85). Thus, T cells and mast cells can complement the functions of each other and contribute to the “cytokine pool” that leads subsequently to chronic inflammation.

## 5. Functions of Mast Cells in Physiological and Pathological States

Mast cells may play crucial roles in various disease states, including vascular disease, fibrotic states, rheumatological disease, certain malignancies, and in host defense against infectious pathogens. The probable roles of the mast cell in human diseases are summarized in Fig. 4.

### 5.1. Vascular Disease

Mast cells are uniquely positioned around capillary vessels and may thus play crucial roles in vascular injury and atherosclerosis (4). Mast cell granule components, released upon activation, could have both anticoagulant and thrombogenic functions (86–88). On the other hand, mast cells may play several pathological roles in atherosclerosis. Increased numbers of mast cells have been found in the shoulders of atherosclerotic plaques, and here they appear to be associated with plaque rupture culminating in luminal thrombosis (89). Kovanen et al. (90) found increased numbers of mast cells at the site of athero-

matous rupture in patients who had died of acute myocardial infarction. Mast cell chymase and cathepsin G have been shown to convert angiotensin I to angiotensin II, which is a potent vasoconstrictor and can mediate several vascular, biological responses (91,92). Mast cell chymase cleaves apolipoprotein B-100 of low-density lipoprotein, which facilitated lipid aggregation and foam cell development (93), while at the same time also degrading apolipoprotein A of high-density lipoprotein, thereby reducing cholesterol efflux and increasing lipid deposition and thereby atherosclerosis (94). On the other hand, mast cells have been reported to produce tissue plasminogen activator (95), as well as plasminogen activator inhibitor-1 (96). Mast cell tryptase also can cleave fibrinogen, thereby retarding coagulation (97). One can therefore surmise multiple effects of mast cells on atherothrombotic disease, and the ultimate role of mast cells in any given situation may depend on the balance of these various effects.

### **5.2. Host Defense**

Mast cells may play crucial roles in host defense by modulating both innate and adaptive immune responses (38,44,98). Various functions of mast cells make them crucial players in host defense. First, these cells can directly phagocytose foreign particles (and bacteria) and also express receptors, such as intercellular adhesion molecule (ICAM)-1 and ICAM-3, CD 43, CD 80, CD 86, and CD 40L, allowing interaction with T and B lymphocytes. Second, they enhance the development of Th2 cells and allow B cells to class switch to IgE. A role as antigen presenting cells has also been proposed for mast cells (99). By influencing both humoral and cell-mediated immune mechanisms, mast cells regulate host defense. Third, activated complement products (and neuropeptides), often generated during an innate immune response to an infectious event, induce mast cell degranulation, thereby integrating innate immunity and neuroimmune mechanisms. Fourth, mast cells are themselves capable of secreting a plethora of cytokines, chemokines, and other mediators that can activate lymphocytes and macrophages. These include the cytokines (TNF- $\alpha$ , IL-1  $\beta$ , IL-4, IL-5, IL-8, and IL-13 [32,100]), lipid mediators, and histamine, which can have profound effects on vascular endothelium, including the alteration of vascular permeability and adhesiveness. This can allow other circulating inflammatory cells to adhere and emigrate into tissue. Thus, mast cells are key players in host defense, with a role in immune surveillance, phagocytosis, and immune activation.

### **5.3. Tissue Remodeling/Fibrosis**

Mast cells are increased in numbers in many fibrotic diseases and may play a crucial role in the development of fibrosis (101). The percentages of mast cells in bronchoalveolar lavage fluid from patients with sarcoidosis or intersti-

tial fibrosis are greater than from control individuals (102), and patients with idiopathic interstitial pulmonary fibrosis show evidence of mast cell degranulation and elevated mast cell numbers (103). In the kidney tissue of patients with IgA nephropathy, mast cell numbers correlate with the degree of interstitial fibrosis and creatinine clearance. In these kidney tissues, mast cells express tryptase and bFGF (104), which may be partially responsible for the fibrosis observed. The mast cell appears to be the dominant source of bFGF in some patients with pulmonary fibrosis (105). Similarly, patients with pulmonary fibrosis associated with scleroderma show higher numbers of mast cells and quantities of histamine and tryptase in bronchoalveolar lavage fluid than patients with normal chest roentgenograms (106). Mast cells also are found in intimate contact with myofibroblasts in keloid scars, suggesting they may play a role in fibroblast activation and scar formation (107). Thus, it appears that mast cells play a pivotal role in fibrotic disorders (108,109).

The mechanisms behind this relationship between mast cells and fibrosis/tissue remodeling are unclear. Mast cell products, such as tryptase, TNF- $\alpha$ , and bFGF, induce fibroblast proliferation (105,110,111). However, fibroblasts appear to enhance mast cell survival, suggesting the presence of a bidirectional relationship between these cell types (3,112). Fibroblast expression of SCF and its interactions with c-kit on mast cells may provide one explanation for these observations. Fibroblasts, however, also are closely opposed to mast cells in fibrotic diseases, suggesting the additional possibility of cognate, cell-cell interaction such as that mediated by CD40-CD40L ligation (113,114). To further complicate the picture, mast cells are themselves capable of laying down some forms of collagen and mast cell tryptase can activate collagenases capable of matrix degradation. These data suggest multiple mechanisms by which and multiple levels where mast cells can regulate tissue fibrosis and repair (115).

#### **5.4. Systemic Mastocytosis and Malignancy**

A disorder characterized by excessive numbers of mast cells and tissue infiltration by these cells is systemic mastocytosis. In this condition, mutations of c-kit (Asp 816 Val mutation) occur (11,116-118), and a subsequent pathological infiltration of affected tissue by mast cells may be seen, resulting in many of the manifestations (119). The patients may present with skin lesions (pigmented macules that urticate with contact [Darrier's sign]) or systemic symptoms arising from mast cell infiltration of solid organs, such as the liver, spleen, lymph nodes, and bone marrow (119,120). Cutaneous manifestations include urticaria pigmentosa, diffuse and erythematous mastocytosis, mastocytoma (mast cell deposits or tumors), and telangiectasia macularis eruptiva perstans (121). Some patients have skin limited and indolent, slowly progressive disease, whereas others develop rapidly progressive and fatal mast cell leukemia,

a feature especially found in some patients with the c-kit mutation (*13,122,123*). Osteoporosis is often a feature of mastocytosis, and mast cells may contribute to bone resorption (*124*). Patients with mastocytosis may develop myeloproliferative syndromes, myelodysplasia, and/or lymphoreticular malignancy, the mechanisms of which are unknown (*125*). Interestingly, the marker,  $\alpha$ -tryptase is elevated in the serum of patients and provides us with an excellent diagnostic clinical tool (*126*). By inducing angiogenesis, the secretion of VEGF and bFGF, and the elaboration of collagenases, mast cells can contribute to tumor pathology and invasiveness (*127–129*).

### **5.5. HIV and Rheumatological Disease**

A probable role for mast cells and IgE-mediated pathology has been reported in HIV infection (*130*). The chemokine receptor, CCR3 is expressed on mast cells and may provide one explanation for the chemotactic effects of tat protein on mast cells (*130*). In one study, increased adventitial mast cell numbers were noted in the arteries of patients dying of cocaine toxicity (*131,132*), but the role of mast cells in HIV and cocaine-induced vascular pathology is unclear (*132*).

Mast cells may play a role in various arthritides. For example, the release of mast cell mediators ( $\alpha$ - and  $\beta$ -tryptase and histamine) has been demonstrated in the joint of various forms of inflammatory arthritis (*133,134*). In osteoarthritis, a degenerative but potentially inflammatory disorder, mast cell counts and tryptase and histamine levels are elevated in synovial fluid (*135,136*). Activated mast cells also are seen in the lesions present in patients with rheumatoid arthritis (*137–139*), whereas mast cell chemotactic activity and their expression of VEGF have been demonstrated in rheumatoid synovium (*140,141*). Mast cell infiltration of the minor salivary glands is observed in patients with Sjögren's syndrome, and this infiltration often is associated with fibrosis and c-kit expression (*142*). Patients with fibromyalgia demonstrate higher dermal deposits of IgG and increased dermal mast cell numbers, but the role these play in pathogenesis of the disease is unknown (*143*).

## **6. Conclusions**

Mast cells are fascinating, multifunctional, bone marrow-derived, tissue-dwelling cells. They can be activated to degranulate in minutes, not only by IgE and antigen signaling via the high affinity receptor for IgE, but also by a diverse group of stimuli. These cells can release a wide variety of immune mediators, including an expanding list of cytokines, chemokines, and growth factors. Mast cells have been shown to play roles in allergic inflammation and, more recently, they have been shown to modulate coagulation cascades, host defense, and tissue remodeling. The role of mast cells in asthma, atherosclero-

sis, HIV, cocaine abuse, fibrotic disorders, and rheumatological disease is being actively studied. The availability of novel molecular tools, such as the chip array technology, should shed more light on these true biological roles of these ubiquitous cells.

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## References

1. Bloom, G. D. (1984) A short history of the mast cell. *Acta Otolaryngol. Suppl.* **414**, 87–92.
2. Metcalfe, D. D., Baram, D., and Mekori, Y. A. (1997) Mast cells. *Physiol. Rev.* **77**, 1033–1079.
3. Church, M. K. and Levi-Schaffer, F. (1997) The human mast cell. *J. Allergy Clin. Immunol.* **99**, 155–160.
4. Kelley, J. L., Chi, D. S., Abou-Auda, W., Smith, J. K., and Krishnaswamy, G. (2000) The molecular role of mast cells in atherosclerotic cardiovascular disease. *Mol. Med. Today* **6**, 304–308.
5. Valent, P. (1995) Cytokines involved in growth and differentiation of human basophils and mast cells. *Exp. Dermatol.* **4**, 255–259.
6. Valent, P., Sillaber, C., and Bettelheim, P. (1991) The growth and differentiation of mast cells. *Prog. Growth Factor Res.* **3**, 27–41.
7. Galli, S. J., Tsai, M., Wershil, B. K., Tam, S. Y., and Costa, J. J. (1995) 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.* **107**, 51–53.
8. Kirshenbaum, A. S., Goff, J. P., Semere, T., Foster, B., Scott, L. M., and Metcalfe, D. D. (1999) Demonstration that human mast cells arise from a progenitor cell population that is CD34(+), c-kit(+), and expresses aminopeptidase N (CD13). *Blood* **94**, 2333–2342.
9. Kirshenbaum, A. S., Kessler, S. W., Goff, J. P., and Metcalfe, D. D. (1991) Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells. *J. Immunol.* **146**, 1410–1415.
10. Nilsson, G., Butterfield, J. H., Nilsson, K., and Siegbahn, A. (1994) Stem cell factor is a chemotactic factor for human mast cells. *J. Immunol.* **153**, 3717–3723.
11. Vliagoftis, H., Worobec, A. S., and Metcalfe, D. D. (1997) The protooncogene c-kit and c-kit ligand in human disease. *J. Allergy Clin. Immunol.* **100**, 435–440.
12. Nagata, H., Worobec, A. S., Semere, T., and Metcalfe, D. D. (1998) Elevated expression of the proto-oncogene c-kit in patients with mastocytosis. *Leukemia* **12**, 175–181.

13. Worobec, A. S., Semere, T., Nagata, H., and Metcalfe, D. D. (1998) Clinical correlates of the presence of the Asp816Val c-kit mutation in the peripheral blood mononuclear cells of patients with mastocytosis. *Cancer* **83**, 2120–2129.
14. Mekori, Y. A., Oh, C. K., and Metcalfe, D. D. (1995) The role of c-Kit and its ligand, stem cell factor, in mast cell apoptosis. *Int. Arch. Allergy Immunol.* **107**, 136–138.
15. Mekori, Y. A., Gilfillan, A. M., Akin, C., Hartmann, K., and Metcalfe, D. D. (2001) Human mast cell apoptosis is regulated through Bcl-2 and Bcl-XL. *J. Clin. Immunol.* **21**, 171–174.
16. Quackenbush, E. J., Wershil, B. K., Aguirre, V., and Gutierrez-Ramos, J. C. (1998) Eotaxin modulates myelopoiesis and mast cell development from embryonic hematopoietic progenitors. *Blood* **92**, 1887–1897.
17. Kirshenbaum, A. S., Goff, J. P., Albert, J. P., Kessler, S. W., and Metcalfe, D. D. (1994) Fibroblasts determine the fate of Fc epsilon RI+ cell populations in vitro by selectively supporting the viability of mast cells while internalizing and degrading basophils. *Int. Arch. Allergy Immunol.* **105**, 374–380.
18. Atkins, F. M., Friedman, M. M., Subba Rao, P. V., and Metcalfe, D. D. (1985) Interactions between mast cells, fibroblasts and connective tissue components. *Int. Arch. Allergy Appl. Immunol.* **77**, 96–102.
19. Schwartz, L. B. (1998) The mast cell, in *Textbook of Rheumatology* (Kelley, W. N., Harris, E. D., Ruddy, S., and Sledge, C. B., eds.), W.B. Saunders Company, Philadelphia, pp. 161–175.
20. Schwartz, L. B., Irani, A. M., Roller, K., Castells, M. C., and Schechter, N. M. (1987) Quantitation of histamine, tryptase, and chymase in dispersed human T and TC mast cells. *J. Immunol.* **138**, 2611–2615.
21. Kraemer, R. (1987) [Mechanisms of allergic reactions and potential therapeutic approach in childhood bronchial asthma] Mechanismen der allergischen Reaktion und mögliche therapeutische Ansätze beim kindlichen Asthma bronchiale. *Schweiz. Rundsch. Med. Prax.* **76**, 581–585.
22. Fung-Leung, W. P., Sousa-Hitzler, J., Ishaque, A., et al. (1996) Transgenic mice expressing the human high-affinity immunoglobulin (Ig) E receptor alpha chain respond to human IgE in mast cell degranulation and in allergic reactions. *J. Exp. Med.* **183**, 49–56.
23. Nadler, M. J., Matthews, S. A., Turner, H., and Kinet, J. P. (2000) Signal transduction by the high-affinity immunoglobulin E receptor Fc epsilon RI: coupling form to function. *Adv. Immunol.* **76**, 325–355.
24. Turner, H. and Kinet, J. P. (1999) Signalling through the high-affinity IgE receptor Fc epsilon RI. *Nature* **402**, B24–B30.
25. Daeron, M., Malbec, O., Latour, S., Espinosa, E., Pina, P., and Fridman, W. H. (1995) Regulation of tyrosine-containing activation motif-dependent cell signalling by Fc gamma RII. *Immunol. Lett.* **44**, 119–123.
26. Hibbs, M. L. and Dunn, A. R. (1997) Lyn, a src-like tyrosine kinase. *Int. J. Biochem. Cell Biol.* **29**, 397–400.

27. Suzuki, H., Takei, M., Yanagida, M., Nakahata, T., Kawakami, T., and Fukamachi, H. (1997) Early and late events in Fc epsilon RI signal transduction in human cultured mast cells. *J. Immunol.* **159**, 5881–5888.
28. Marone, G., Casolaro, V., Patella, V., Florio, G., and Triggiani, M. (1997) Molecular and cellular biology of mast cells and basophils. *Int. Arch. Allergy Immunol.* **114**, 207–217.
29. Schulman, E. S. (1993) The role of mast cells in inflammatory responses in the lung. *Crit. Rev. Immunol.* **13**, 35–70.
30. Schulman, E. S., Post, T. J., Henson, P. M., and Giclas, P. C. (1988) Differential effects of the complement peptides, C5a and C5a des Arg on human basophil and lung mast cell histamine release. *J. Clin. Invest.* **81**, 918–923.
31. Prodeus, A. P., Zhou, X., Maurer, M., Galli, S. J., and Carroll, M. C. (1997) Impaired mast cell-dependent natural immunity in complement C3-deficient mice. *Nature* **390**, 172–175.
32. Abraham, S. N. and Malaviya, R. (1997) Mast cells in infection and immunity. *Infect. Immun.* **65**, 3501–3508.
33. Malaviya, R. and Abraham, S. N. (1998) Clinical implications of mast cell-bacteria interaction. *J. Mol. Med.* **76**, 617–623.
34. Galli, S. J. and Wershil, B. K. (1996) The two faces of the mast cell. *Nature* **381**, 21–22.
35. Galli, S. J. (1993) New concepts about the mast cell. *N. Engl. J. Med.* **328**, 257–265.
36. Ackermann, L., Pelkonen, J., and Harvima, I. T. (1998) Staphylococcal enterotoxin B inhibits the production of interleukin-4 in a human mast-cell line HMC-1. *Immunology* **94**, 247–252.
37. McCloskey, M. A. (1988) Cholera toxin potentiates IgE-coupled inositol phospholipid hydrolysis and mediator secretion by RBL-2H3 cells. *Proc. Natl. Acad. Sci. USA* **85**, 7260–7264.
38. Galli, S. J., Maurer, M., and Lantz, C. S. (1999) Mast cells as sentinels of innate immunity. *Curr. Opin. Immunol.* **11**, 53–59.
39. Silber, G., Proud, D., Warner, J., et al. (1988) In vivo release of inflammatory mediators by hyperosmolar solutions. *Am. Rev. Respir. Dis.* **137**, 606–612.
40. Fitzgerald, S. M., Lee, S. A., Hall, H. K., Chi, D. S., and Krishnaswamy, G. (2004) Human lung fibroblasts express interleukin-6 in response to signaling after mast cell contact. *Am. J. Respir. Cell Mol. Biol.* **30**, 585–593.
41. Chi, D. S., Fitzgerald, S. M., Pitts, S., et al. (2004) MAPK-dependent regulation of IL-1- and beta-adrenoreceptor-induced inflammatory cytokine production from mast cells: implications for the stress response. *BMC Immunol.* **5**, 22.
42. Krishnaswamy, G., Hall, K., Youngberg, G., et al. (2002) Regulation of eosinophil-active cytokine production from human cord blood-derived mast cells. *J. Interferon Cytokine Res.* **22**, 379–388.
43. Lee, S. A., Fitzgerald, S. M., Huang, S. K., et al. (2004) Molecular regulation of interleukin-13 and monocyte chemoattractant protein-1 expression in human mast cells by interleukin-1beta. *Am. J. Respir. Cell Mol. Biol.* **31**, 283–291.



44. Abraham, S. N., Thankavel, K., and Malaviya, R. (1997) Mast cells as modulators of host defense in the lung. *Front. Biosci.* **2**, d78–d87.
45. Plaut, M., Pierce, J. H., Watson, C. J., Hanley-Hyde, J., Nordan, R. P., and Paul, W. E. (1989) Mast cell lines produce lymphokines in response to cross-linkage of Fc epsilon RI or to calcium ionophores. *Nature* **339**, 64–67.
46. Bradding, P. and Holgate, S. T. (1996) The mast cell as a source of cytokines in asthma. *Ann. N.Y. Acad. Sci.* **796**, 272–281.
47. Bradding, P. (1996) Human mast cell cytokines. *Clin. Exp. Allergy*. **26**, 13–19.
48. Malaviya, R., Ikeda, T., Ross, E., and Abraham, S. N. (1996) Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. *Nature* **381**, 77–80.
49. Walsh, L. J., Trinchieri, G., Waldorf, H. A., Whitaker, D., and Murphy, G. F. (1991) Human dermal mast cells contain and release tumor necrosis factor alpha, which induces endothelial leukocyte adhesion molecule 1. *Proc. Natl. Acad. Sci. USA* **88**, 4220–4224.
50. Bradding, P., Mediwake, R., Feather, I. H., et al. (1995) TNF alpha is localized to nasal mucosal mast cells and is released in acute allergic rhinitis. *Clin. Exp. Allergy* **25**, 406–415.
51. Anderson, W. H., Davidson, T. M., and Broide, D. H. (1996) Mast cell TNF mRNA expression in nasal mucosa demonstrated by *in situ* hybridization: a comparison of mast cell detection methods. *J. Immunol. Methods* **189**, 145–155.
52. Ackerman, V., Marini, M., Vittori, E., Bellini, A., Vassali, G., and Mattoli, S. (1994) Detection of cytokines and their cell sources in bronchial biopsy specimens from asthmatic patients. Relationship to atopic status, symptoms, and level of airway hyperresponsiveness. *Chest* **105**, 687–696.
53. Buckley, M. G., Williams, C. M., Thompson, J., et al. (1995) IL-4 enhances IL-3 and IL-8 gene expression in a human leukemic mast cell line. *Immunology* **84**, 410–415.
54. Krishnaswamy, G., Lakshman, T., Miller, A. R., et al. (1997) Multifunctional cytokine expression by human mast cells: regulation by T cell membrane contact and glucocorticoids. *J. Interferon. Cytokine. Res.* **17**, 167–176.
55. Bradding, P., Roberts, J. A., Britten, K. M., et al. (1994) Interleukin-4, -5, and -6 and tumor necrosis factor-alpha in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am. J. Respir. Cell Mol. Biol.* **10**, 471–480.
56. Bradding, P., Feather, I. H., Wilson, S., et al. (1993) Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. The mast cell as a source of IL- 4, IL-5, and IL-6 in human allergic mucosal inflammation. *J. Immunol.* **151**, 3853–3865.
57. Ying, S., Humbert, M., Barkans, J., et al. (1997) Expression of IL-4 and IL-5 mRNA and protein product by CD4+ and CD8+ T cells, eosinophils, and mast cells in bronchial biopsies obtained from atopic and nonatopic (intrinsic) asthmatics. *J. Immunol.* **158**, 3539–3544.

58. Ando, M., Miyazaki, E., Fukami, T., Kumamoto, T., and Tsuda, T. (1999) Interleukin-4-producing cells in idiopathic pulmonary fibrosis: an immunohistochemical study. *Respirology* **4**, 383–391.
59. Barata, L. T., Ying, S., Meng, Q., et al. (1998) IL-4- and IL-5-positive T lymphocytes, eosinophils, and mast cells in allergen-induced late-phase cutaneous reactions in atopic subjects. *J. Allergy Clin. Immunol.* **101**, 222–230.
60. Okayama, Y., Petit-Frere, C., Kassel, O., et al. (1995) IgE-dependent expression of mRNA for IL-4 and IL-5 in human lung mast cells. *J. Immunol.* **155**, 1796–1808.
61. Lippert, U., Kruger-Krasagakes, S., Moller, A., Kiessling, U., and Czarnetzki, B. M. (1995) Pharmacological modulation of IL-6 and IL-8 secretion by the H1-antagonist decarboethoxy-loratadine and dexamethasone by human mast and basophilic cell lines. *Exp. Dermatol.* **4**, 272–276.
62. Bradding, P., Feather, I. H., Wilson, S., Holgate, S. T., and Howarth, P. H. (1995) Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. *Am. J. Respir. Crit. Care Med.* **151**, 1900–1906.
63. Bradding, P., Okayama, Y., Howarth, P. H., Church, M. K., and Holgate, S. T. (1995) Heterogeneity of human mast cells based on cytokine content. *J. Immunol.* **155**, 297–307.
64. Kruger-Krasagakes, S., Grutzkau, A., Krasagakis, K., Hoffmann, S., and Henz, B. M. (1999) Adhesion of human mast cells to extracellular matrix provides a co-stimulatory signal for cytokine production. *Immunology* **98**, 253–257.
65. Grutzkau, A., Kruger-Krasagakes, S., Kogel, H., Moller, A., Lippert, U., and Henz, B. M. (1997) Detection of intracellular interleukin-8 in human mast cells: flow cytometry as a guide for immunoelectron microscopy. *J. Histochem. Cytochem.* **45**, 935–945.
66. Hultner, L., Kolsch, S., Stassen, M., et al. (2000) In activated mast cells, IL-1 up-regulates the production of several Th2-related cytokines including IL-9. *J. Immunol.* **164**, 5556–5563.
67. Ishizuka, T., Okayama, Y., Kobayashi, H., and Mori, M. (1999) Interleukin-10 is localized to and released by human lung mast cells. *Clin. Exp. Allergy* **29**, 1424–1432.
68. Burd, P. R., Thompson, W. C., Max, E. E., and Mills, F. C. (1995) Activated mast cells produce interleukin 13. *J. Exp. Med.* **181**, 1373–1380.
69. Toru, H., Pawankar, R., Ra, C., Yata, J., and Nakahata, T. (1998) Human mast cells produce IL-13 by high-affinity IgE receptor cross-linking: enhanced IL-13 production by IL-4-primed human mast cells. *J. Allergy Clin. Immunol.* **102**, 491–502.
70. Kanbe, N., Kurosawa, M., Yamashita, T., Kurimoto, F., Yanagihara, Y., and Miyachi, Y. (1999) Cord-blood-derived human cultured mast cells produce interleukin 13 in the presence of stem cell factor. *Int. Arch. Allergy Immunol.* **119**, 138–142.
71. Rumsaeng, V., Cruikshank, W. W., Foster, B., et al. (1997) Human mast cells produce the CD4+ T lymphocyte chemoattractant factor, IL-16. *J. Immunol.* **159**, 2904–2910.

72. Yano, K., Yamaguchi, M., de Mora, F., et al. (1997) Production of macrophage inflammatory protein-1 $\alpha$  by human mast cells: increased anti-IgE-dependent secretion after IgE-dependent enhancement of mast cell IgE-binding ability. *Lab. Invest.* **77**, 185–193.
73. Selvan, R. S., Butterfield, J. H., and Krangel, M. S. (1994) Expression of multiple chemokine genes by a human mast cell leukemia. *J. Biol. Chem.* **269**, 13,893–13,898.
74. Trautmann, A., Toksoy, A., Engelhardt, E., Brocker, E. B., and Gillitzer, R. (2000) Mast cell involvement in normal human skin wound healing: expression of monocyte chemoattractant protein-1 is correlated with recruitment of mast cells which synthesize interleukin-4 in vivo. *J. Pathol.* **190**, 100–106.
75. Baghestanian, M., Hofbauer, R., Kiener, H. P., et al. (1997) The c-kit ligand stem cell factor and anti-IgE promote expression of monocyte chemoattractant protein-1 in human lung mast cells. *Blood* **90**, 4438–4449.
76. Yamada, T., Sawatsubashi, M., Yakushiji, H., et al. (1998) Localization of vascular endothelial growth factor in synovial membrane mast cells: examination with “multi-labelling subtraction immunostainin.” *Virchows Arch.* **433**, 567–570.
77. Nilsson, G., Forsberg-Nilsson, K., Xiang, Z., Hallbook, F., Nilsson, K., and Metcalfe, D. D. (1997) Human mast cells express functional TrkA and are a source of nerve growth factor. *Eur. J. Immunol.* **27**, 2295–2301.
78. De Paulis, A., Minopoli, G., Arbustini, E., et al. (1999) Stem cell factor is localized in, released from, and cleaved by human mast cells. *J. Immunol.* **163**, 2799–2808.
79. Zhang, S., Anderson, D. F., Bradding, P., et al. (1998) Human mast cells express stem cell factor. *J. Pathol.* **186**, 59–66.
80. Krishnaswamy, G., Mukkamala, R., Yerra, L., and Smith, J. K. (1999) Molecular therapies for asthma. *Fed. Pract.* **2**, 16–26.
81. Byrd, R. P., Krishnaswamy, G., and Roy, T. M. (2000) Difficult-to-manage asthma. How to pinpoint the exacerbating factors. *Postgrad. Med.* **108**, 37–51.
82. Gauchat, J. F., Henchoz, S., Mazzei, G., et al. (1993) Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* **365**, 340–343.
83. Stadler, B. M. and Gauchat, D. (1987) [Current concepts in immunoregulation and its significance for allergies] Concepts nouveaux de l’immuno-regulation et leur signification pour l’allergie. *Rev. Med. Suisse Romande* **107**, 289–293.
84. Paul, W. E. and Seder, R. A. (1994) Lymphocyte responses and cytokines. *Cell* **76**, 241–251.
85. Karpus, W. J., Lukacs, N. W., Kennedy, K. J., Smith, W. S., Hurst, S. D., and Barrett, T. A. (1997) Differential CC chemokine-induced enhancement of T helper cell cytokine production. *J. Immunol.* **158**, 4129–4136.
86. Szczeklik, A. (2000) Atopy and sudden cardiac death. *Lancet* **355**, 2254.
87. Szczeklik, A., Sladek, K., Szczerba, A., and Dropinski, J. (1988) Serum immunoglobulin E response to myocardial infarction. *Circulation* **77**, 1245–1249.
88. Kauhanen, P., Kovanen, P. T., Reunala, T., and Lassila, R. (1998) Effects of skin mast cells on bleeding time and coagulation activation at the site of platelet plug formation. *Thromb. Haemost.* **79**, 843–847.

89. Jeziorska, M., McCollum, C., and Woolley, D. E. (1997) Mast cell distribution, activation, and phenotype in atherosclerotic lesions of human carotid arteries. *J. Pathol.* **182**, 115–122.
90. Kovanen, P. T., Kaartinen, M., and Paavonen, T. (1995) Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* **92**, 1084–1088.
91. Reilly, C. F., Schechter, N. B., and Travis, J. (1985) Inactivation of bradykinin and kallidin by cathepsin G and mast cell chymase. *Biochem. Biophys. Res. Commun.* **127**, 443–449.
92. Uehara, Y., Urata, H., Sasaguri, M., et al. (2000) Increased chymase activity in internal thoracic artery of patients with hypercholesterolemia. *Hypertension* **35**, 55–60.
93. Paananen, K. and Kovanen, P. T. (1994) Proteolysis and fusion of low density lipoprotein particles independently strengthen their binding to exocytosed mast cell granules. *J. Biol. Chem.* **269**, 2023–2031.
94. Lindstedt, L., Lee, M., Castro, G. R., Fruchart, J. C., and Kovanen, P. T. (1996) Chymase in exocytosed rat mast cell granules effectively proteolyzes apolipoprotein AI-containing lipoproteins, so reducing the cholesterol efflux-inducing ability of serum and aortic intimal fluid. *J. Clin. Invest.* **97**, 2174–2182.
95. Sillaber, C., Baghestanian, M., Bevec, D., et al. (1999) The mast cell as site of tissue-type plasminogen activator expression and fibrinolysis. *J. Immunol.* **162**, 1032–1041.
96. Cho, S. H., Tam, S. W., Demissie-Sanders, S., Filler, S. A., and Oh, C. K. (2000) Production of plasminogen activator inhibitor-1 by human mast cells and its possible role in asthma. *J. Immunol.* **165**, 3154–3161.
97. Schwartz, L. B., Bradford, T. R., Littman, B. H., and Wintroub, B. U. (1985) The fibrinogenolytic activity of purified tryptase from human lung mast cells. *J. Immunol.* **135**, 2762–2767.
98. Henz, B. M., Maurer, M., Lippert, U., Worm, M., and Babina, M. (2001) Mast cells as initiators of immunity and host defense. *Exp. Dermatol.* **10**, 1–10.
99. Mekori, Y. A. and Metcalfe, D. D. (1999) Mast cell-T cell interactions. *J. Allergy Clin. Immunol.* **104**, 517–523.
100. Arock, M., Ross, E., Lai-Kuen, R., Averlant, G., Gao, Z., and Abraham, S. N. (1998) Phagocytic and tumor necrosis factor alpha response of human mast cells following exposure to gram-negative and gram-positive bacteria. *Infect. Immun.* **66**, 6030–6034.
101. Levi-Schaffer, F. and Rubinchik, E. (1995) Mast cell role in fibrotic diseases. *Isr. J. Med. Sci.* **31**, 450–453.
102. Chlap, Z., Jedynak, U., and Sladek, K. (1998) [Mast cell: its significance in bronchoalveolar lavage fluid cytologic diagnosis of bronchial asthma and interstitial lung disease] Komorka tuczna: znaczenie w diagnostyce cytologicznej płynu oskrzelowo-pecherzykowego w astmie oskrzelowej i chorobach srodmiaszowych płuc. *Pneumonol. Alergol. Pol.* **66**, 321–329.

103. Hunt, L. W., Colby, T. V., Weiler, D. A., Sur, S., and Butterfield, J. H. (1992) Immunofluorescent staining for mast cells in idiopathic pulmonary fibrosis: quantification and evidence for extracellular release of mast cell tryptase. *Mayo Clin. Proc.* **67**, 941–948.
104. Ehara, T. and Shigematsu, H. (1998) Contribution of mast cells to the tubulointerstitial lesions in IgA nephritis. *Kidney Int.* **54**, 1675–1683.
105. Inoue, Y., King, T. E., Jr., Tinkle, S. S., Dockstader, K., and Newman, L. S. (1996) Human mast cell basic fibroblast growth factor in pulmonary fibrotic disorders. *Am. J. Pathol.* **149**, 2037–2054.
106. Chanez, P., Lacoste, J. Y., Guillot, B., et al. (1993) Mast cells' contribution to the fibrosing alveolitis of the scleroderma lung. *Am. Rev. Respir. Dis.* **147**, 1497–1502.
107. Lee, Y. S. and Vijayasingam, S. (1995) Mast cells and myofibroblasts in keloid: a light microscopic, immunohistochemical and ultrastructural study. *Ann. Acad. Med. Singapore* **24**, 902–905.
108. Pesci, A., Bertorelli, G., Gabrielli, M., and Olivieri, D. (1993) Mast cells in fibrotic lung disorders. *Chest* **103**, 989–996.
109. Jordana, M. (1993) Mast cells and fibrosis—who's on first? *Am. J. Respir. Cell Mol. Biol.* **8**, 7–8.
110. Yamashita, Y., Nakagomi, K., Takeda, T., Hasegawa, S., and Mitsui, Y. (1992) Effect of heparin on pulmonary fibroblasts and vascular cells. *Thorax* **47**, 634–639.
111. Jordana, M., Befus, A. D., Newhouse, M. T., Bienenstock, J., and Gauldie, J. (1988) Effect of histamine on proliferation of normal human adult lung fibroblasts. *Thorax* **43**, 552–558.
112. Levi-Schaffer, F., Kelav-Appelbaum, R., and Rubinchik, E. (1995) Human fore-skin mast cell viability and functional activity is maintained ex vivo by coculture with fibroblasts. *Cell Immunol.* **162**, 211–216.
113. Heard, B. E., Dewar, A., and Corrin, B. (1992) Apposition of fibroblasts to mast cells and lymphocytes in normal human lung and in cryptogenic fibrosing alveolitis. Ultrastructure and cell perimeter measurements. *J. Pathol.* **166**, 303–310.
114. Adawi, A., Zhang, Y., Baggs, R., et al. (1998) Blockade of CD40-CD40 ligand interactions protects against radiation-induced pulmonary inflammation and fibrosis. *Clin. Immunol. Immunopathol.* **89**, 222–230.
115. Williams, C. M. and Galli, S. J. (2000) The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. *J. Allergy Clin. Immunol.* **105**, 847–859.
116. Worobec, A. S., Akin, C., Scott, L. M., and Metcalfe, D. D. (1998) Cytogenetic abnormalities and their lack of relationship to the Asp816Val c-kit mutation in the pathogenesis of mastocytosis. *J. Allergy Clin. Immunol.* **102**, 523–524.
117. Nagata, H., Okada, T., Worobec, A. S., Semere, T., and Metcalfe, D. D. (1997) c-kit mutation in a population of patients with mastocytosis. *Int. Arch. Allergy Immunol.* **113**, 184–186.

118. Akin, C., Kirshenbaum, A. S., Semere, T., Worobec, A. S., Scott, L. M., and Metcalfe, D. D. (2000) Analysis of the surface expression of c-kit and occurrence of the c-kit Asp816Val activating mutation in T cells, B cells, and myelomonocytic cells in patients with mastocytosis. *Exp. Hematol.* **28**, 140–147.
119. Metcalfe, D. D. and Akin, C. (2001) Mastocytosis: molecular mechanisms and clinical disease heterogeneity. *Leuk. Res.* **25**, 577–582.
120. Hartmann, K. and Henz, B. M. (2001) Mastocytosis: recent advances in defining the disease. *Br. J. Dermatol.* **144**, 682–695.
121. Soter, N. A. (2000) Mastocytosis and the skin. *Hematol. Oncol. Clin. North Am.* **14**, 537–55, vi.
122. Horny, H. P., Ruck, P., Krober, S., and Kaiserling, E. (1997) Systemic mast cell disease (mastocytosis). General aspects and histopathological diagnosis. *Histol. Histopathol.* **12**, 1081–1089.
123. Pullarkat, V. A., Pullarkat, S. T., Calverley, D. C., and Brynes, R. K. (2000) Mast cell disease associated with acute myeloid leukemia: detection of a new c-kit mutation Asp816His. *Am. J. Hematol.* **65**, 307–309.
124. Lehmann, T., Beyeler, C., Lammle, B., et al. (1996) Severe osteoporosis due to systemic mast cell disease: successful treatment with interferon alpha-2B. *Br. J. Rheumatol.* **35**, 898–900.
125. Parker, R. I. (2000) Hematologic aspects of systemic mastocytosis. *Hematol. Oncol. Clin. North Am.* **14**, 557–568.
126. Schwartz, L. B., Sakai, K., Bradford, T. R., et al. (1995) 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.* **96**, 2702–2710.
127. Dabbous, M. K., Woolley, D. E., Haney, L., Carter, L. M., and Nicolson, G. L. (1986) Host-mediated effectors of tumor invasion: role of mast cells in matrix degradation. *Clin. Exp. Metastasis* **4**, 141–152.
128. Duncan, L. M., Richards, L. A., and Mihm, M. C., Jr. (1998) Increased mast cell density in invasive melanoma. *J. Cutan. Pathol.* **25**, 11–15.
129. Le Querrec, A., Duval, D., and Tobelem, G. (1993) Tumour angiogenesis. *Baillieres Clin. Haematol.* **6**, 711–730.
130. Marone, G., Florio, G., Triggiani, M., Petraroli, A., and De Paulis, A. (2000) Mechanisms of IgE elevation in HIV-1 infection. *Crit. Rev. Immunol.* **20**, 477–496.
131. Kolodgie, F. D., Virmani, R., Cornhill, J. F., Herderick, E. E., and Smialek, J. (1991) Increase in atherosclerosis and adventitial mast cells in cocaine abusers: an alternative mechanism of cocaine-associated coronary vasospasm and thrombosis. *J. Am. Coll. Cardiol.* **17**, 1553–1560.
132. Kelley, J., Chi, D. S., Henry, J., Stone, W. L., Smith, J. K., and Krishnaswamy, G. (2000) HIV- and cocaine-induced cardiovascular disease: pathogenesis and clinical implications. *Cardiovasc. Rev. Rep.* **XXI**, 365–370.

133. Buckley, M. G., Walters, C., Wong, W. M., et al. (1997) Mast cell activation in arthritis: detection of alpha- and beta-tryptase, histamine and eosinophil cationic protein in synovial fluid. *Clin. Sci. (Colch.)* **93**, 363–370.
134. Mican, J. M. and Metcalfe, D. D. (1990) Arthritis and mast cell activation. *J. Allergy Clin. Immunol.* **86**, 677–683.
135. Renoux, M., Hilliquin, P., Galoppin, L., Florentin, I., and Menkes, C. J. (1996) Release of mast cell mediators and nitrites into knee joint fluid in osteoarthritis—comparison with articular chondrocalcinosis and rheumatoid arthritis. *Osteoarthritis Cartilage* **4**, 175–179.
136. Renoux, M., Hilliquin, P., Galoppin, L., Florentin, J., and Menkes, C. J. (1995) Cellular activation products in osteoarthritis synovial fluid. *Int. J. Clin. Pharmacol. Res.* **15**, 135–138.
137. Woolley, D. E. and Tetlow, L. C. (2000) Mast cell activation and its relation to proinflammatory cytokine production in the rheumatoid lesion. *Arthritis Res.* **2**, 65–74.
138. He, S., Gaca, M. D., and Walls, A. F. (2001) The activation of synovial mast cells: modulation of histamine release by tryptase and chymase and their inhibitors. *Eur. J. Pharmacol.* **412**, 223–229.
139. Bridges, A. J., Malone, D. G., Jicinsky, J., et al. (1991) Human synovial mast cell involvement in rheumatoid arthritis and osteoarthritis. Relationship to disease type, clinical activity, and antirheumatic therapy. *Arthritis Rheum.* **34**, 1116–1124.
140. Olsson, N., Ulfgren, A. K., and Nilsson, G. (2001) Demonstration of mast cell chemotactic activity in synovial fluid from rheumatoid patients. *Ann. Rheum. Dis.* **60**, 187–193.
141. Yamada, T., Sawatsubashi, M., Yakushiji, H., et al. (1998) Localization of vascular endothelial growth factor in synovial membrane mast cells: examination with “multi-labelling subtraction immunostaining.” *Virchows Arch.* **433**, 567–570.
142. Skopouli, F. N., Li, L., Boumba, D., et al. (1998) Association of mast cells with fibrosis and fatty infiltration in the minor salivary glands of patients with Sjogren’s syndrome. *Clin. Exp. Rheumatol.* **16**, 63–65.
143. Enestrom, S., Bengtsson, A., and Frodin, T. (1997) Dermal IgG deposits and increase of mast cells in patients with fibromyalgia—relevant findings or epiphenomena? *Scand. J. Rheumatol.* **26**, 308–313.



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