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\(_T\) and MC\(_{TC}\) 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 Fc\(\varepsilon\)RI), 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+, c-kit+, and CD13- 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
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-
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$_T$ cells are diminished in individuals infected with human immunodeficiency virus (HIV) (3). Structurally, granules from MC$_T$ are scroll-rich (Fig. 2B demonstrates a typical scroll-like granule in mast cells developed from umbilical cord blood mononuclear cells).

The MC$_{TC}$ 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$_{TC}$ 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$_{TC}$ cells could help explain why patients with HIV infection continue to have allergic reactions (e.g., to medications). MC$_{TC}$ mast cells have lattice and grating structures and are scroll-poor.

Table 1
Mast Cell Subtypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>MC$_{TC}$ cell</th>
<th>MC$_T$ cell</th>
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<tbody>
<tr>
<td>Structural features</td>
<td></td>
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<tr>
<td>Grating/lattice granule</td>
<td>+++</td>
<td>–</td>
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<tr>
<td>Scroll granules</td>
<td>Poor</td>
<td>Rich</td>
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<tr>
<td>Tissue distribution</td>
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<tr>
<td>Skin</td>
<td>++</td>
<td>–</td>
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<tr>
<td>Intestinal submucosa</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Intestinal mucosa</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Alveolar wall</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Bronchi</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Nasal mucosa</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Mediator synthesized</td>
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<tr>
<td>Histamine</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Chymase</td>
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<td>–</td>
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<tr>
<td>Tryptase</td>
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<td>++</td>
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<tr>
<td>Carboxypeptidase</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>LTC$_4$</td>
<td>++</td>
<td>++</td>
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<tr>
<td>PGD$_2$</td>
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<td>++</td>
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<tr>
<td>TNF-α</td>
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<td>IL-4, IL-5, IL-6, IL-13</td>
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3. Mast Cell Activation and Mediator Production

Human mast cells and basophils express the receptor for IgE, FcεRI (2). FcεRI (in contrast to the other receptor for IgE, FcεRII) binds IgE with high affinity (22). The other receptor for IgE, FcεRII, has been detected on eosino-

Fig. 2. (A) Tryptase immunostaining of human cord blood-derived mast cells (×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.
phils, mononuclear cells, lymphocytes, and platelets. FcεRI is a multimeric complex composed of four chains, designated as α (which has the IgE-binding domain), β, and the two disulfide-linked γ chains (23, 24). Typically, multivalent antigen binds to IgE, which in turn binds by the Fc portion to the α-chain of FcεRI, leading subsequently to receptor aggregation and internalization and culminating in receptor-mediated signaling. The β and γ chains of FcεRI 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 β and γ 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 γ, 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 FcεRI-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 FcεRI, 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 α [MIP-1 α]), 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, β-hexosaminidase, β-glucuronidase, β-D-galactosidase, cathepsin G,
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and carboxypeptidase), some cytokines (tumor necrosis factor [TNF]-α), and basic fibroblast growth factor (bFGF). The newly generated products include the lipid mediators (prostaglandin D2 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. Autocrine 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\textsubscript{TC} cells predominantly expressed IL-4, the MC\textsubscript{TC} 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\textbeta 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\textsubscript{4}, LTC\textsubscript{4}, PAF, and PGD\textsubscript{2} may have multiple effects on inflammatory cell recruitment (eosinophils), smooth muscle hyperplasia, and vascular dilatation (80,81). Tryptase, chymase, and TNF-\alpha from mast cells activate fibroblasts, leading to collagen deposition and fibrosis. Mast cell-derived TNF-\alpha regulates NF-\kappaB-dependent induction of endothelial adhesion molecule expression on endothelial cells in vivo (49). Mast cell granules and tryptase 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\textsubscript{4}) 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
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selectively secrete IL-4 and IL-5 on activation (84). Exciting recent data also suggest that certain mast cell-derived chemokines, especially MIP-1α, 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-α, 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, α-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 (α- and β-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


