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THE HUMAN MAST CELL: FUNCTIONS IN PHYSIOLOGY AND DISEASE

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1. ABSTRACT

Mast cells are multifunctional, tissue-dwelling cells capable of secreting a wide variety of mediators. They develop from bone marrow-derived progenitor cells, primed with stem cell factor (SCF), which mediates its actions by interacting with the SCF receptor or *c-kit* on the cell surface. Mast cells continue their maturation and differentiation in peripheral tissue, developing into two well described subsets of cells, MC_T and MC_{TC} cells, varying in content of tryptase and chymase as well as in immunobiology. Mast cells are activated by numerous stimuli, including antigen (acting via the high affinity IgE receptor, FcεRI), superoxides, complement proteins, neuropeptides and lipoproteins resulting in activation and degranulation. Following activation, these cells express mediators such as histamine, leukotrienes and prostanoids, as well as proteases, and many cytokines and chemokines, pivotal to the genesis of an inflammatory response. Recent data suggests that mast cells may play an active role in such diverse diseases as atherosclerosis, malignancy, asthma, pulmonary fibrosis and arthritis. Mast cells directly interact with bacteria and appear to play a vital role in host defense against pathogens. Drugs, such as glucocorticoids, cyclosporine and cromolyn have been demonstrated to have inhibitory effects on mast cell degranulation or mediator release.

2. INTRODUCTION

Paul Ehrlich was the first to describe cells in connective tissue that stained reddish-purple (metachromasia) with aniline dyes. He used the term "mästzellen" to describe these cells, a German term referring to feeding (1). Metachromasia is now known to be due to interaction of dyes with acidic heparin, a constituent of mast cell granules. Ehrlich also described the association of mast cells with inflammation as well as with blood vessels and neural tissue. Since then, several developments have occurred including the discovery of histamine, mast cell growth factors and more recently, the role of mast cells in inflammatory disease and host defense.

The mast cell expresses the high affinity receptor for IgE and is involved in immediate type hypersensitivity reactions (2-4). In such reactions, antigen cross-links two IgE molecules occupying the FcεRI resulting in a cascade of rapid sequence signaling events, leading to degranulation and elaboration of mediators. These mediators include preformed mast cell granule contents as well as newly synthesized mediators such as histamine, proteases, lipid products, cytokines and chemokines. Mast cells are located perivascularly and in sentinel locations in order to respond to noxious stimuli. This immediate response of the mast cell accounts for a pivotal component of the host immune

Table 1. Subtypes and heterogeneity of mast cells

Feature	MC_{TC} Cell	MC_T Cell
Mediators		
• Preformed Granules		
Histamine	+++	+++
Chymase	++	–
Tryptase	++	++
Carboxypeptidase	++	–
Cathepsin G	++	–
• Newly Generated		
LTC4	++	++
PGD2	++	++
TNF-alpha	++	++
IL-4, IL-5, IL-6, IL-13	++	++
Tissue distribution		
Skin	++	–
Intestinal submucosa	++	+
Intestinal mucosa	+	++
Alveolar wall	–	++
Bronchi	+	++
Nasal mucosa	++	++
Conjunctiva	++	+
Structural aspects		
Grating/Lattice granule	++	–
Scroll granules	Poor	Rich
Effects of HIV Infection	Unchanged	Decreased
On cell populations		numbers

Please refer to text for explanations of abbreviations

defense response and may be responsible for leukocyte recruitment, endothelial activation and vasodilatation. Though much of the initial information on mast cell biology was obtained from animal models and mast cell-deficient mice, more recent data suggest that human mast cells are capable of many of the functions ascribed to the murine counterpart. Moreover, while initially considered as crucial to the manifestation of an allergic reaction, mast cells have now been implicated in the pathogenesis of immune complex reactions, tissue remodeling and in host defense. The purpose of this review is to summarize salient features of mast cell immunobiology and to describe their associations with human disease.

3. IMMUNOBIOLOGY OF HUMAN MAST CELLS

3.1. Mast cell development

Mast cells develop from progenitor cells that in turn arise from uncommitted hematopoietic stem cells in the bone marrow (5, 6). Basophils arise like the mast cells from bone marrow progenitor cells, however they complete their maturation and differentiation within the bone marrow. In contrast, mast cells, undergo terminal differentiation in tissues. It is now becoming clear that mast cells express the receptor for stem cell factor (SCF receptor or c-kit) that binds to SCF, a specific growth factor for mast cells (5-7). The interactions between SCF and c-kit are crucial for the growth and development of mast cells (8). Mutations of c-kit and elevated levels of the c-kit proto-oncogene have been associated with mastocytosis (9, 10). Kirshenbaum and colleagues have described $CD34^+$, $c\text{-}kit^+$ and $CD13^-$ precursors that develop into mast cells in the presence of specific growth factors (11, 12). Mast cell progenitors have been described in peripheral blood, and represent a distinct pool of cells separate from leukocytes or mononuclear cells (13). As summarized later, two mast cell subtypes have been described in tissue- the mucosal (MC_T) or connective tissue (MC_{TC}) mast cell. The factors that regulate the differentiation into one or other subtype of mast cell are unknown at this time. SCF has multiple effects on mast cells, including modulation of differentiation and homing, prolonging viability, inducing mast cell hyperplasia and enhancing mediator production (7). Mast cells deprived of SCF undergo apoptosis (14) probably mediated by down regulation of Bcl-2 and Bcl-XL (15). The effects of SCF on rescuing mast cells from apoptosis are inhibited by transforming growth factor beta1 (TGF beta1). Interleukin 6 (IL-6) and nerve growth factor (NGF) appear to enhance mast cell development from hematopoietic stem cells, whereas glucocorticoids and IL-4 appear to have the opposite effects (5). Fibroblasts through cell surface expression of SCF, secretion of NGF or by contact mechanisms, contribute to further differentiation and maturation of mast cells in tissue (16, 17). Recent studies also suggest that the eosinophil chemotaxin, eotaxin, enhances mast cell development (18). Patients with HIV infection and AIDS have preservation of MC_{TC} mast cells suggesting these can continue to develop in a T cell-independent manner.

3.2. Mast cell subtypes and heterogeneity

In humans, two types of mast cells, MC_T and MC_{TC} subsets of mast cells have been described, based on structural, biochemical and functional data. (3, 19-21). These aspects are described in Table 1. The murine counterparts of these subtypes have been referred to as mucosal or connective tissue mast cells. The MC_T mast cell expresses tryptase predominantly and is usually localized to mucosal surfaces in close relationship to T cells, especially of the Th2-type. The MC_T is increased in allergic and parasitic diseases and diminished numbers are seen in HIV-infected patients (3). Structurally, granules from MC_T are scroll-rich. The MC_{TC} mast cell, on the other hand, expresses tryptase, chymase, carboxypeptidase and cathepsin G. It predominates in the gastrointestinal tract as well as in skin, synovium and subcutaneous tissues. Increased numbers of MC_{TC} mast cells are seen in fibrotic diseases while numbers are relatively unchanged in allergic or parasitic diseases and in HIV infection. MC_{TC} mast cells have lattice and grating structures and are scroll-poor. Thus, MC_{TC} mast cells may be more important to tissue remodeling and angiogenesis, for example, while MC_T mast cells are central to inflammation. Both types of mast cells and basophils express FcεRI and are capable of mediating allergic type responses. In contrast to these subtypes of mast cells, however, basophils do not express much tryptase, chymase or cathepsin G. Disease classification based on whether MC_T and/or MC_{TC} mast cells predominate is likely to shed light into the molecular pathogenesis of several inflammatory diseases.

3.3. Structural aspects of the human mast cell

The general ultrastructure of the human mast cell has been well–described in numerous publications (22, 23). The nucleus is small, and round to oval in shape. The cell surface demonstrates slender filiform cytoplasmic

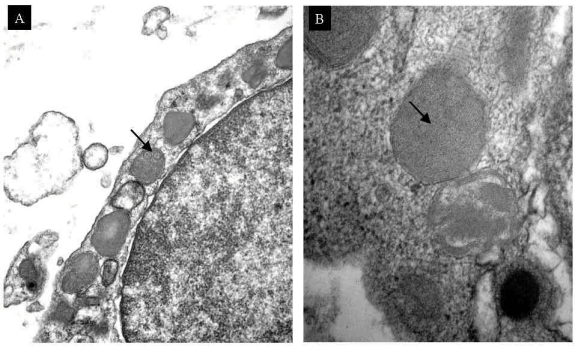

Figure 1. Transmission electron microscopy of human mast cells showing characteristic scroll granules. 1 A: A colonic mucosal mast cell. One granule demonstrates the complete discrete scroll formations (34,000 x). 1 B: A colonic submucosal mast cell. The granules demonstrate grating substructures (105,000 x)

projections or undulating folds (Figure 1). The cytoplasm contains filaments, microtubules, rough endoplasmic reticulum, Golgi vesicles, free ribosomes, mitochondria, lysosomes, and lipid bodies. In addition, the cytoplasm is dominated by the presence of numerous membrane-bound mast cell granules. The granules, and the mast cells containing them, can be subtyped into scroll-rich and scroll-poor morphologies (24, 25). Both morphologies may demonstrate granules with amorphous material, finely granular electron-dense material, non-discrete scroll formations that merge with one another, loosely-organized internal lamellae, or some peripheral coiled parallel lamellae (23, 26). However, the scroll-rich morphology is characterized by the presence of granules containing multiple discrete complete membranous scroll formations (Figure 1), resembling scrolls of papyrus (a less common form of granule associated with the scroll-rich morphology has a beaded, coarsely particulate, or reticulated appearance). The scrolls can be tightly or, more often, loosely wound. They may enclose cores of central electron-lucent or electron-dense material (23, 26). On the other hand, the scroll-poor morphology is characterized by the general absence of granules with discrete scrolls. Additionally, some of the electron-dense granules seen in cells with scroll-poor morphology may contain crystalloid substructures with a grating or lattice appearance (24, 25).

The substructures can demonstrate variable periodicities. Granules associated with the scroll-poor morphology tend to be more numerous, larger, and more uniform in shape (23, 24). Lipid bodies, large round non-membrane-bound cytoplasmic structures with internal lucencies, are less frequent in cells with scroll-poor morphology (22). In general, the scroll-rich morphology (discrete scrolls) indicates an MC_T cell, and the scroll-poor morphology (grating or lattice patterns) indicates an MC_{TC} cell (23). However, there has been controversy over the reliability of this distinction, and controversy over whether intermediate morphologic forms exist. Interpretation of granule morphology can be complicated by the effects of fixation, variable planes of sectioning, and the tendency of various authors to use similar descriptive terms to mean different things. Comparison between papers is better accomplished by close attention to photographs rather than verbal descriptions. Also, the presence of nonspecific non-discrete scroll formations may be misinterpreted as evidence of the scroll-rich morphology. Problems aside, the discrimination of mast cell subtype by granule morphology appears to be good but not perfect. In one study, 340 mature MC_{TC} cells were examined by electron microscopy, and only 10 of these cells were found to contain granules with (a few) complete discrete scrolls (26). Interestingly, the discrete scrolls were associated with focal absence of chymase, as demonstrated by an immunogold electron microscopic technique. In another study (24), 39 of 502 mast cells demonstrated granules showing at least one complete discrete scroll and granules showing grating/lattice substructures (sometimes both occurred in a single granule). Mast cells cultured from peripheral blood have been shown to have minimal chymase activity in the presence of a scroll-poor ultrastructure (27). Mast cell functional diversity is more complex than a simple division into MC_T and MC_{TC} phenotypes can account for. An MC_C subtype has been demonstrated (25). Also, mast cells from different body sites show marked variability in their response to non-immunologic stimulation by substances such as protamine, morphine, compound 48/80, C5a, and substance P. For example, skin MC_{TC} cells respond to substance P, but cardiac MC_{TC} cells do not (28). The morphologic correlates, if any, of these phenotypic variations have not been well-characterized. Additional aspects of morphologic diversity in mast cells have been described. For example, mast cells from breast parenchyma contain large granules and show evidence of granule fusion or division. Differences in mast cell granule size and appearance can be demonstrated between black and white skin (29). Dendritic mast cells have been identified in lesions of cutaneous prurigo nodularis (30). Mast cell ultrastructure can be affected by the degree of maturity and by degranulation. Immature mast cells demonstrate a smaller size, a higher nuclear/cytoplasmic ratio, a paucity of granules, and the presence of granules with dense central nucleoids embedded in granule matrix (22, 31). Anaphylactic-type degranulation can result in swollen or frayed lucent amorphous or filamentous granules, and the formation of large degranulation channels or labyrinths that communicate with the extracellular space (31, 32).

3.4. Mast cell activation and signaling mechanisms

Human mast cells and basophils express the high affinity receptor for IgE, FcepsilonRI [FcεRI] (2). The FcεRI, in contrast to FcεRII, binds IgE with high affinity. FcεRII has been detected on eosinophils, mononuclear cells, lymphocytes and platelets. FcεRI is a multimeric complex composed of four chains, α, β and two disulfide-linked γ chains (33, 34). The IgE-binding domain is located on the α chain. Multivalent antigen binds to IgE that in turns binds by it's Fc portion to the α-chain of FcεRI. This leads to receptor aggregation and internalization, followed by signaling. The β and γ chains of FcεRI have immune receptor tyrosine-based activation motifs (ITAMs) that are essential to signal transduction. 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. Syk

Table 2. Selected preformed and newly synthesized mast cell mediators

Mediator	Biological Functions
PREFORMED	
Histamine	Vasodilation, endothelial activation, pulmonary fibrosis, eosinophil chemotaxis
Heparin	Anti-coagulant, inhibition of platelet aggregation and lymphocyte activation
Chondroitin sulfate E	Lipoprotein binding
Tryptase	Endothelial activation, fibrinogen cleavage, mitogenic for smooth muscle cells, activate pro-stromelysin
Chymase	Converts angiotensin I to II, remodeling, lipoprotein degradation
Carboxypeptidase	Metalloproteinase, remodeling
Cathepsin G	Protein degradation, tissue/vascular remodeling, converts angiotensin I to II
Tissue plasminogen activator	Dissolution of blood clot
NEWLY SYNTHESIZED	
LTC_4, LTB_4	Leukocyte chemotaxis, smooth muscle contraction
PGD_2, PGE_2	Leukocyte chemokinesis, vasodilation, inhibition of platelet aggregation
Platelet activating factor	Platelet activation, vasoconstriction
Thromboxanes	Platelet activation, coagulation

kinase then becomes activated sequentially, followed by involvement of phospholipase C γ (PLC γ) and mitogen activated protein kinases (MAPK) and phosphoinositol-3 kinase. Generation of inositol trisphosphate 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. This is also accompanied by transcription of cytokine genes leading to an evolution of an inflammatory cascade.

4. ROLE OF MAST CELLS IN HUMAN PATHOPHYSIOLOGY

4.1. Mast cells in inflammation

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-versus-host disease, fibrotic diseases, sarcoidosis, asbestosis, ischemic heart disease, keloid scars and malignancy (3). In the instance of the airway pathology of allergy and bronchial asthma, a complex inflammatory cascade has been recognized to be associated with the development of disease. In these diseases, typical pathological findings include epithelial loss, sub-epithelial collagen deposition, edema and infiltration of the mucus membrane by inflammatory cells, including mast cells, macrophages, T cells and eosinophils. This is accompanied by the elaboration of lipid mediators and various cytokines (35, 36). In addition, mast cells reside in peripheral tissues, all vascularized tissue, and the submucosa of the respiratory and gastrointestinal tract (37, 38). At these locations mast cells are in a key position to act as effector cells in the inflammatory cascade. As mentioned in the previous section, mast cells are activated through aggregation of IgE, antigen, and the high affinity FcεRI receptor on the mast cell surface membrane, or by various stimuli (39). Once activated, mast cell effector functions are initiated. These can be divided into acute phase, late-phase, and chronic inflammatory states. Acute phase anaphylaxis is characterized by the appearance of signs and symptoms such as vascular collapse, respiratory distress, pruritus, and urticaria with or without angioedema within seconds or minutes after administration of the allergen to a previously sensitized individual. This is an IgE- mediated phenomenon in which FcεRI aggregation with allergen bound IgE activates and degranulates mast cells resulting in secretion of the contents of preformed granules, synthesis of lipid mediators derived from stored precursors, and expression and secretion of cytokines. All these mediators and cytokines further provoke a profound immunological and inflammatory process.

4.1.1. Mediator and protease expression by mast cells

Allergen binding to or cross-linking of mast cell surface IgE which is bound to the high affinity IgE-receptor, FcεRI, leads to the rapid release of inflammatory mediators (40). Mast cells can also be activated to degranulate by a variety of stimuli including; opiates, components of the complement cascade (41-43), neuropeptides (vasoactive intestinal peptide, calcitonin gene-related peptide and substance P), superoxide anion, radio-contrast media, oxidized low density lipoproteins (Ox-LDL), histamine releasing factors, chemokines (monocyte chemotactic proteins-1, -2 and -3 [MCP-1, -2, -3], and monocyte inflammatory peptide 1 alpha [MIP-1 α]), regulated upon activation normal T-cell expressed and secreted (RANTES), connective tissue activating peptide, pathogenic bacteria (44, 45), parasites (46, 47), enterotoxin B (48), cholera toxin (49), or changes in osmolality (50, 51). This indicates the occurrence of multiple pathways of mast cell activation, and suggests a role for mast cells in many physiopathological processes that go beyond the traditional role of these cells in causing allergy. Mediators secreted by mast cells are usually subdivided into those that are preformed and secretory granule-associated, and those that are newly synthesized following activation (3, 52). Preformed mediators (Table 2) include histamine, proteoglycans (heparin, chondroitin sulfate E), serotonin, proteases (such as tryptase, chymase, ∃-Hexosaminidase, ∃-Glucuronidase, ∃-D-galactosidase, cathepsin G and carboxypeptidase), some cytokines, and growth factors (basic fibroblast growth factor, bFGF) and tumor necrosis factor alpha (TNF-α). The mast cell also elaborates several newly generated mediators after activation (Table 2). These include the lipid mediators (prostaglandin D_2 and

Table 3. Selected cytokines expressed from human mast cells

FAMILY	FACTOR	ACTIONS	REFERENCE
CYTOKINE	TNF-alpha	Local inflammation, endothelial activation, cytotoxic toward cancerous cells	(59),(60),(61),(62),(64),(63)
	IL-1 beta	Fever, T cell activation, macrophage activation	(65)
	IL-3	Synergistic action in hematopoiesis	(66),(67),(68),(69),(70)
	IL-4	B cell activation, IgE switch	(71),(72),(48),(73),(68),(74),(79),(80), (81)
	IL-5	Eosinophil growth, differentiation	(73),(68),(74),(75),(76),(79),(80)
	IL-6	T and B cell growth and differentiation, acute phase reaction	(77),(61),(78)
	IL-10	Suppression of macrophage functions (cytokine synthesis inhibition factor)	(91)
	IL-13	B cell growth and differentiation, inhibits macrophage inflammation, cytokine production	(92),(93),(94),(95),(96),(97)
	IL-16	Chemoattractant for T cells	(99),(100)
CHEMOKINE	IL-8	Chemoattractant for neutrophils and T cells, activates T cells and basophils	(82),(83),(66),(71),(84),(85),(86),(87), (88),(89)
	MCP-1,2,3	Chemoattractant for monocytes, lymphocytes, basophils, and NK cells	(104)
	MIP-1 alpha	Chemoattractant for monocytes, T cells and eosinophils	(101),(85)
	RANTES	Chemoattractant for monocytes, T cells, eosinophils, basophils, NK cells and dendritic cells	(85)
	EOTAXIN	Chemoattractant for Eosinophils	(103)
GROWTH FACTOR	TGF-beta 1	Inhibits cell growth, anti inflammatory	(106),(107)
	basic FGF	Promotes growth of fibroblasts, endothelial cells, chondrocytes, smooth muscle cells, melanocytes and others, promotes adipocyte differentiation	(105)
	NGF	Nerve growth	(109)
	VEGF	Promotes vascular endothelial cell growth	(110)
	PDGF-A	Chemoattractant and mitogenic for fibroblasts	(106)
HEMATOPOIETIC FACTOR	GM-CSF	Promotes growth and differentiation of myelomonocytic lineage cells	(108),(62)

leukotrienes, generated from arachidonic acid), thromboxanes ($TXAB_2$), 5,12-hydroxyeicosatetraenoic acid, nitrogen radicals, oxygen radicals, inflammatory cytokines and chemokines.

4.1.2. Mast cells as sources of immunoregulatory cytokines

Human mast cells are capable of secreting a wide variety of cytokines, chemokines and growth factors (53-55). The initial demonstration that mast cells possess the capacity to secrete cytokines was demonstrated in the seminal paper of Plaut *et al*., who described induction of transcripts for IL-4, IL-5 and IL-6, a classic Th2 profile, in murine mast cells activated by calcium ionophores or by crosslinkage of FcεRI (56). Since then, the work of many laboratories has shown that both murine and human mast cells are capable of expressing a wide repertoire of cytokines in response to many stimuli. Both *in vivo* and *in vitro* data have suggested that human mast cells are capable of expressing tumor necrosis factor alpha (TNF-α), IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, IL-16, granulocyte macrophage colony stimulating factor (GM-CSF), SCF, basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF β), chemokines such as macrophage inflammatory protein 1 alpha (MIP-1 alpha), monocyte chemotactic protein 1 (MCP-1) and several metalloproteinases. These cytokines allow the mast cells to potentially orchestrate a wide variety of inflammatory responses and also simultaneously modulate host defense, angiogenesis and tissue remodeling. The following sections describe *in vitro* and *in vivo* evidence of human mast cell cytokine expression. Table 3 lists the cytokines known to be expressed by human mast cells and their putative function in an inflammatory cascade.

In vitro and *in vivo* evidences of mast cell production of cytokines comes from the work of various laboratories. Autocrine production of SCF by mast cells is of great interest as it allows their own differentiation and maturation (57). Zhang and coworkers showed that human skin and lung mast cells express stem cell factor (57).

Human cardiac mast cells also express SCF, as demonstrated in mast cells purified from hearts of patients undergoing cardiac transplantation by protein A/gold staining (58). Mast cells express TNF-α. The initial data that this TNF-α is functional came from Walsh *et al*., who showed that TNF-α made by human dermal mast cells induced adhesion molecules on endothelial cells (59). The work of Bradding and coworkers suggests that airway mast cells in the nose and lung express TNF-α (60, 61). TNF-α expression by lung mast cells may also account for eosinophil activation seen in asthma, as the release of eosinophil mediators by mast cell supernatants was blocked up to 68% by anti-TNF-α antibody (62). TNF-α is also released from skin mast cells in response to Substance P-mediated activation (63). TNF-α is also detectable in mast cells infiltrating atheromatous plaques (64), where they may assist in activating metalloproteinases in macrophages. IL-1 β may be a product of human mast cells (65). There is evidence that IL-3, a pleuripotential growth factor, is expressed by human mast cells. The human mast cell leukemia cell line, HMC-1, expresses IL-3 transcripts (66, 67). Naive human mast cells developed from bone marrow mononuclear cells and lung-derived mast cells express IL-3 (68, 69). Wallaert *et al*., showed that mast cells express IL-3 *in vivo*, in the lungs of patients with asthma (70). There is quite a bit of data confirming the production of IL-4 and

IL-5 in mast cells, both *in vitro* and *in vivo*. The mast cell line, HMC-1, expresses IL-4, shown by us and others (48, 71, 72). FcεRI-mediated mast cell activation induces IL-4 and IL-5 production (68, 73, 74). Jaffe *et al*., showed expression of IL-5 mRNA transcripts temporally in human lung mast cells following IgE-mediated activation (75). IL-5 production is also a feature of intestinal mast cells (76). Co-expression of IL-4, IL-5 and IL-6 in mast cells has been shown in biopsies of lung (61, 77) and nose (78) of patients with asthma and rhinitis, respectively. 53% and 29% of mast cells in the late phase skin reaction stained for IL-4 and IL-5 respectively (79). Ying *et al*., showed that while the majority (>70%) of mRNA signals for IL-4 and IL-5 localized to the T cells in the lungs of patients with asthma, both mast cells and eosinophils also demonstrated expression of these transcripts (80). Other investigators have suggested the mast cell may be a major source of IL-4 in atopic asthma (81). Human mast cells also express the α-(CXC) chemokine, IL-8, a major neutrophil chemoattractant (66, 71, 82, 83). Both HMC-1 cells as well as skin mast cells produce IL-8 (84, 85). Induction of IL-8 in HMC-1 cells was shown in response to adenosine A2b receptors, mediated by mitogen activated protein kinases (86, 87).

Adhesion to extracellular matrix or activation by stromal cell-derived factor 1α may provide additional stimuli for IL-8 expression in mast cells (88, 89). Since the IL-8 receptors, CXCR1 and CXCR2 are expressed on human mast cells, an autocrine effect of this chemokine on mast cell chemotaxis may be possible *in vivo* (90). Human mast cells have also been shown to express IL-10, a negative regulator of inflammation and cytokine expression (91). Human lung mast cells (92, 93), HMC-1 cells (94) and cord blood-derived mast cells (95, 96) express IL-13, a cytokine that shares functions with IL-4. Stem cell factor may be essential to IL-13 production from human mast cells (97). Both IL-4 and IL-13 are capable of switching B cells to IgE production in the presence of costimuli (98).

Rumsaeng *et al*., showed expression of the lymphocyte chemoattractant, IL-16, from human mast cells (99). More recently, *in vivo* evidence of IL-16 expression by mast cells in asthma has been presented (100). Human mast cells express the chemokines, macrophage inflammatory protein 1 alpha (MIP-1 α), **R**egulated on **A**ctivation, **N**ormal **T** cell **E**xpressed and **S**ecreted (RANTES), eotaxin and monocyte chemoattractant protein-1 (MCP-1). Human mast cells express MIP-1 α in response to chemoattractant receptor ligation (101), phorbol esters (85) or FcεRI-mediated signaling (102). Both RANTES (85) and eotaxin (103) may be expressed by human mast cells. Recent data suggests that human lung mast cells express the β (CC)-chemokine, MCP-1 in response to FcεRI-mediated signaling and SCF-mediated activation (104). Human mast cells may also be additional sources of pivotal growth factors essential to remodeling and reparative processes. For example, basic fibroblast growth factor is a mast cell product and has been localized to mast cell secretory granules (105). TGF β1 and platelet-derived growth factor-A (PDGF-A) have been reported to be produced by human mast cells (106). This may have implications for wound healing and fibrotic diseases (107). The hematopoietic factor, GM-CSF, can be produced by mast cells and is capable of activating eosinophils, in conjunction with TNF-α and IL-5 (62, 108). Nerve growth factor (NGF) (109) and vascular endothelial growth factor (VEGF) (110), a cytokine that regulates angiogenesis, have also been localized to mast cells. We demonstrated expression of multiple transcripts for inflammatory cytokines in HMC-1 cultured cells, including IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF and TNF-α in response to phorbol esters and calcium ionophore. HMC-1 cells also expressed proteins for IL-4, IL-6, IL-13, GM-CSF and IL-8, suggesting they are able to both transcribe and translate genes for many pro-inflammatory cytokines (71). There is also some data to suggest that heterogeneity of human mast cells exist in regards to cytokine expression *in vivo*. In their study, Bradding *et al*., demonstrated the existence of this heterogeneity in mast cells from bronchial biopsies of patients with asthma. By immunocytochemistry, it was noted that the MC_{TC} cells expressed predominantly IL-4, while the MC_T cells expressed both IL-5 and IL-6 (77). 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, following activation. The production of these cytokines in cord blood-derived mast cells was further enhanced by the addition of the monokines, IL-1β, in a dose-dependent manner, suggesting a role for macrophage-mast cell cross-talk in allergic inflammation. On the other hand, dexamethasone inhibited production of these cytokines from these cells, suggesting a differential regulation. These data indicate a mast cell-eosinophil axis may exist *in vivo* that may be susceptible to pharmacological manipulation.

4.1.3. Role of mast cell mediators and cytokines in the inflammatory response

The mediators released by mast cells can independently, and in synergy with macrophage- and T-cell-derived cytokines, induce much of the inflammatory pathology seen in inflammation and serve to orchestrate a complex immune response (Figure 2). The functions of mast cell mediators released upon degranulation are shown in Table 1. Histamine binds cells expressing histamine receptors and produces effects that are tissue specific. Other contents of mast cell granules have effects on the coagulation cascade (see below) or are involved in local tissue destruction. Lipid mediators, which include LTB_4, LTC_4, PAF, and PGD_2, have direct effects on peripheral tissues. Direct tissue effects caused by activated mast cells help other inflammatory cells in the circulation reach the appropriate site. Tryptase, chymase and TNF-α from mast cells may be capable of activating fibroblasts leading to collagen deposition and fibrosis. Mast cell-derived TNF-α is essential for NF-κB-dependent induction of endothelial adhesion molecule expression *in vivo* (59). The mast cell granules potentiate endotoxin-induced IL-6 production by endothelial cells. All point to the process of an acute phase of inflammation.

Mast cell-derived cytokines and chemokines further regulate IgE synthesis and cell migration, basophil histamine release, smooth muscle proliferation and

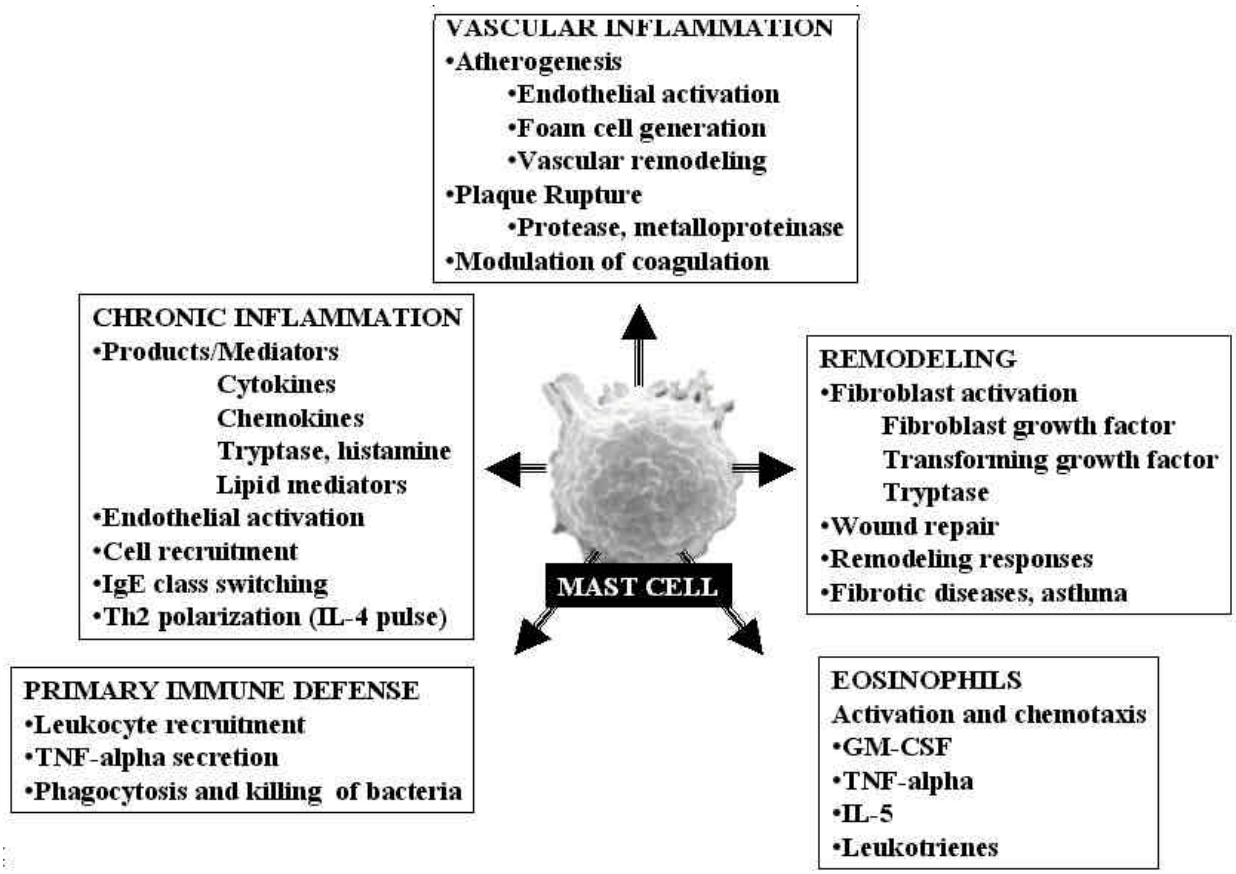

Figure 2. Biological functions of human mast cells: Mediator and cytokine synthesis and regulation of human physiological and pathological processes

endothelial chemotaxis and proliferation. IL-4 and IL-13 can also class switch B-cells to induce IgE synthesis (111, 112). IL-5, another product of Th2 cells and of mast cells, can also serve to activate eosinophils and accentuates IgA production from B cells. Eosinophils further accentuate chronic allergic inflammatory responses by themselves secreting IL-5 and other toxic mediators such as major basic protein (113). Chemokines (such as IL-8) and leukotrienes (specifically LTC_4) released by mast cells can recruit neutrophils and eosinophils to inflamed airways which can further potentiate damage (3). Mast cells have been postulated to provide the IL-4 pulse that allows the development of Th2 cells that selectively secrete IL-4 and IL-5 on activation (114). Exciting recent data also suggest that certain mast cell-derived chemokines, especially MIP-1 α, can potentiate a shift of T cells towards a Th1-phenotype, while others, such as MCP-1, can shift these cells functionally to a Th2-phenotype (115). There is a close association between mucosal mast cells and T cells (116) and several T cell-, mesenchymal- and/or macrophage-derived cytokines, such as IL-3, IL-4, GM-CSF and SCF are required forproliferation of mast cells. 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. In addition, cell-derived mediators and cytokines can modulate airway smooth muscle tone, vascular permeability, stimulate mucus production, activate neuronal function and induce many of the pathological changes observed as part of the inflammatory response (35, 36).

4.2. Role of mast cells in the coagulation cascade and atherosclerosis

Mast cells are uniquely positioned around capillary vessels to effect coagulation via the release of mediators, such as heparin and proteases, and the potential roles of these mediators are just beginning to be elucidated with regard to their impact on the coagulation cascade. They may thus play crucial roles in vascular injury and atherosclerosis (4). There are indications that mast cell granule components, released upon activation, could have both anti-coagulant and thrombogenic functions. Szczeklik *et al*., reported delayed generation of thrombin in atopic patients, and protection from cardiac death after myocardial infarction, associated with elevated serum IgE, increased bleeding time and depressed platelet aggregation, similar to the effects of aspirin (117, 118). Additionally, Kauhanen *et al*., found that individuals with urticaria pigmentosa had reduced clotting times (119). However, increased numbers of mast cells have been found in atherosclerotic plaques where they appear to be associated with plaque rupture which initiates thrombosis (120). Subsequently, Johnson *et al*. showed a correlation between extracellular tryptase activity in atherosclerotic plaques and active matrix metalloproteinase levels (121). Kovanen *et al*., 1995 found

increased numbers of mast cells at the site of atheromatous rupture in patients that had died of acute myocardial infarction and that mast cell degranulation was 200-fold higher at the site of rupture than in adjacent, unaffected intima (122). Therefore, it appears that general mast cell activation, as in allergies, may provide some measure of protection from thrombosis, whereas mast cell activation in atherosclerotic plaques may contribute to atheroma formation and/or plaque rupture. Some of the effects of mast cells on the coagulation cascade may be effected by mediators expressed by these cells.

Although purified heparin is a useful clinical anti-coagulant, which functions via the activation of inhibitors of coagulation pathway proteases, there is little evidence that heparin released from mast cells functions as an anticoagulant *in vivo*. Mast cell heparin is complexed with granules components, including proteases and histamine. Histamine apparently dissociates from heparin when the acidic mast cell granules enter the neutral extracellular fluid. Heparin stabilizes the active, tetrameric structure of tryptase (123) and excess heparin seems needed to maintain the tryptase-heparin complex (124). Consequently, the amount of mast cell heparin available to function as an anti-coagulant is unknown and mast cell heparin may have more to do with protease storage than with anti-coagulation.

Tryptase, which is present in all human mast cells (125), has been reported to activate pro-stromelysin (matrix metalloproteinase-2) (126) and the activation of matrix metalloproteinases in atherosclerotic plaque was correlated with tryptase activity, but not with chymase activity (121). Matrix metalloproteinases 1 & 3 were found to be the principal MMPs present in atherosclerotic plaque (121) and caseinolytic and gelatinolytic activities measured by *in situ* zymography were increased when atherosclerotic plaque tissue was treated with compound 48/80, a mast cell degranulation agent. Mast cells were predominantly in the shoulder regions and fibrous caps of the plaques and degranulation was observed in 78% of these mast cells. There has long been an association between mast cells and fibrosis. Tryptase causes fibroblast proliferation and increased collagen synthesis (127), which could contribute to formation of fibrin caps over atherosclerotic plaques. The fibroblast response apparently occurs via tryptase activation of protease-activated receptor-2 [PAR2] (128).

Chymase has been found in atherosclerotic plaques. Cathepsin G, which is the primary chymotrypsin-like protease of neutrophils, has also been found in mast cells (129). But mast cell cathepsin G has not been studied with regard to atherosclerosis and coagulation. Chymase and cathepsin G have been shown to convert angiotensin I to angiotensin II, which is a potent vasoconstrictor (130). Uehara *et al*. found that chymase was the only angiotensin II forming activity in human atherosclerotic internal thoracic arteries (131). Human mast cells have also been reported to express gelatinase B (MMP-9) (132). Human chymase presumably activates these matrix metalloproteinases, produced by mast cells themselves or by other cells in the vicinity of degranulating mast cells. Kovanen and coworkers found that mast cell chymase cleaves apolipoprotein B-100 of LDL, which facilitated lipoprotein aggregation,and uptake by macrophages (133). Additionally, this group has shown that chymase degrades apolipoprotein A of HDL, which would reduce cholesterol efflux and increase lipid deposition (134).

Thus, an alternative mechanism for LDL macrophage uptake (and foam cell formation) that does not require prior formation of oxLDL is provided by mast cells. Mast cell degranulation produces neutral proteases, such as chymase, and granules. The released granules bind LDL and this LDL is also degraded and fused by the released proteases. *In vivo* evidence suggests that these non-oxidative modifications of LDL promote its phagocytosis by macrophages leading to foam cell formation in the human arterial intima (135). Moreover, mast cell chymase may act on high density lipoprotein (HDL) and reduce its ability to remove cholesterol from foam cells (136). These finding suggest that mast cell proteases contribute to atherosclerosis by various means.

4.3. Mast cell proteases and fibrinolysis

Mast cells have been reported to produce tissue plasminogen activator (tPA) (137). Although tPA which initiates the dissolution of blood clots is produced as a precursor like other serine proteases, tPA is inherently active and its activity increases upon binding to fibrin. While this finding suggests an anti-coagulant function, stimulated mast cells have also been found to synthesize plasminogen activator inhibitor-1 (138). Pro-urinary plasminogen activator (pro-uPA) must be proteolytically converted to a two chain active form (uPA) and mast cell tryptase has been shown to activate pro-uPA (139). Several cells, including cardiac mast cells (140), have urinary plasminogen activator receptors (uPAR) that bind both pro-uPA and uPA, and this binding allows uPA to function as a cellular plasminogen activator. Fibrinogen cleavage by tryptase and the resulting slowed coagulation, was first reported by Schwartz *et al*., (141). It is therefore conceivable that tryptase decreases the risk for atherosclerotic disease by lowering the level of "functional" fibrinogen, because increased fibrinogen concentrations are associated with increased risk for atherosclerotic disease. Mast cell tryptase also was shown to cleave high molecular weight kininogen, resulting in a reduction of this protein's ability to stimulate coagulation via activation of factor XII. Subsequently, the cleavage site in high molecular weight kininogen was identified as Arg431 in the histidine-rich region of the heavy chain (142).

Mast cells seem capable of slowing clotting via the secretion of heparin and via tryptase mediated inactivation of fibrinogen and high molecular weight kininogen. Additionally, secretion of tPA, and activation of pro-uPA, could result in plasmin mediated fibrinolysis. However, mast cells may also contribute to atherosclerotic plaque formation via chymase cleavage of LDL and tryptase may stimulate fibrin cap formation via activation of PAR2 on fibroblasts. Additionally tryptase, chymase and cathepsin G may activate matrix metalloproteinases, resulting in plaque rupture and thrombus formation.

Obviously, the resulting outcome depends on the balance between anti-coagulant and thrombotic functions.

4.4. Role of mast cells in host defense

Mast cells lie at key positions in the body to play a critical role in immune surveillance and contribute to host defense. Mast cells are a heterogeneous group of cells whose characteristics are governed by growth factors present in a particular microenvironment (52). Mast cells obtained from different sites have different responses to stimulation and different morphology (41). Mast cells migrate to body sites as uncharacterized precursors and then undergo differentiation once they take up residence in a particular tissue (47). Mature mast cells are further regulated by such factors as SCF and IL-4 (143). Once in there final location, mast cells serve as highly refined defenders at key positions. At their various positions mast cells can be activated by a number of host and foreign stimuli. Mast cells can then initiate both innate and acquired immune reactions (50, 144). They can phagocytose foreign particles and also express receptors such as intercellular adhesion molecule-1 (ICAM-1) and ICAM-3, CD 43, CD 80, CD 86, and CD 40L allowing interaction with T and B lymphocytes. Mast cells enhance the development of Th2 cells and allow B cells to class switch to IgE. By influencing both humoral and cell mediated immune mechanisms, mast cells regulate host defense. Moreover, it should be recognized that complement products as well as neuropeptides can induce mast cell degranulation, thereby allowing interaction with the innate immune system and neuroimmune mechanisms. Mast cells can secrete cytokines and chemokines that activate lymphocytes such as IL-1, IL-5, IL-8, and particularly TNF-? (44, 145). They produce lipid mediators and histamine that can have profound effects on vascular endothelium allowing other circulating immune cells to migrate into the tissues. Most of these roles are tissue independent but clearly there are some site-specific roles for macrophages. Mast cells play a very important role in host defense at the site of the lung. Here, mast cells reside in an intraepithelial location or near blood vessels, bronchioles, and mucous secreting glands (44). It has been shown that in mast cell-deficient mice, pathogenic bacteria survived ten-fold more than in mice with mast cells (146). There is good evidence that mast cells are capable of phagocytosis of a large range of bacteria (145). In addition, mast cells release prestored TNF-? which serves as a powerful neutrophil chemoattractant (147, 148). A role as antigen presenting cells has also been proposed for mast cells (149). These antibacterial properties of mast cells are present independent of the tissue they reside in. In addition to functions in the lung, mast cells play important roles in the GI tract. Here, the immune system must protect the host from pathogens while being tolerant to the normal flora and a wide array of dietary antigens (150) Overall, mast cells are key players in host defense with roles in immune surveillance, phagocytosis, and immune activation. They are critical at sites such as the lung and GI tract for prevention of bacterial infection. They may have other effects such as antitumor effects that have yet to be fully appreciated.

4.5. Roles of mast cells in tissue remodeling and fibrosis

Mast cells are increased in numbers in many fibrotic diseases and may play a crucial role in development of fibrosis (151). Liebler *et al*., found mast cell hyperplasia during the later reparative stages of the lungs of patients with the adult respiratory distress syndrome but not in the early stage (152). The percentages of mast cells in bronchoalveolar lavage fluid from patients with sarcoidosis or interstitial fibrosis are greater than from control individuals (153). Patients with idiopathic interstitial pulmonary fibrosis show evidence of mast cell degranulation and elevated mast cell numbers (154). In patients with IgA nephropathy, mast cell numbers correlate with the degree of interstitial fibrosis and with creatinine clearance and express tryptase and basic fibroblast growth factor (bFGF) (155). In this study, mast cells were shown to be in close association with fibroblasts. Inoue and coworkers also demonstrated that the mast cell was the dominant source of bFGF in patients with fibrotic lung disease (156). 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 (157). Thus it appears that mast cells play a pivotal role in fibrotic disorders (158, 159). The dominant mechanisms behind the regulation of fibroblast function and proliferation by human mast cells are uncertain. It is clear that mast cell products such as tryptase and cytokines (TNF-α, bFGF) induce fibroblast proliferation (156, 160, 161). On the other hand, fibroblasts appear to enhance mast cell survival (162). Thus a bidirectional relationship between mast cells and fibroblasts has been proposed (3). Fibroblasts are closely opposed to mast cells in fibrotic diseases, suggesting the additional possibility of cognate, cell-cell interaction (163). Whether this is mediated by cell surface molecules such as CD40-CD40 ligand interactions, blockade of which could modulate fibrosis, are unclear at this point (164). To further complicate the story, mast cells are themselves capable of laying down some forms of collagen and mast cell tryptase can activate collagenases capable of matrix degradation. Thus mast cells play important roles in tissue remodeling and the development of fibrosis (37).

5. ROLE OF MAST CELLS IN HUMAN DISEASES

Human mast cell hyperplasia and dysfunction have been documented in various pathological states. Allergic inflammation including rhinitis, asthma, anaphylaxis and urticaria are all classical disorders associated with mast cell activation and these disorders have reached epidemic proportions (165-167). In allergic disease, polarization of T cell responses leads to an increased Th2-type cytokine burden, with IgE production, mast cell activation, eosinophil recruitment and chronic inflammation (35, 168-172). In systemic anaphylaxis, mast cell activation is associated with the elaboration of β-tryptase that is detectable in the circulation as a diagnostic marker (173, 174). Another disorder associated with mast cell hyperplasia and excessive activation is systemic mastocytosis. In this disease, mutations of c-kit (Asp 816 Val mutation) have been shown to exist (8, 175-177). Systemic

mastocytosis is characterized by a pathological increase in mast cell numbers in affected tissue (178). In this disease, skin lesions (urticaria pigmentosa) and infiltration of the liver, spleen, lymph nodes and bone marrow may occur (178, 179). Some patients have indolent disease, while others have systemic disease with hematological complications or aggressive disease culminating in mast cell leukemia, especially those patients with the c-kit mutation (10, 180, 181). Hematological disorders noted in patients with mastocytosis include myeloproliferative syndromes or myelodysplasia and lymphoreticular malignancy (182). Cutaneous manifestations include urticaria pigmentosa, diffuse and erythematous mastocytosis, mastocytoma and telangiectasia macularis eruptiva perstans (183). ? -tryptase is elevated in the serum of patients and provides an excellent diagnostic marker (184). Mast cells have also been found to infiltrate unstable plaques in patients with coronary artery disease (64). An evolving role for mast cells and IgE-mediated pathology has been reported in HIV infection (185). The chemokine receptor, CCR3, is expressed on mast cells and may provide one explanation for the chemotactic effects of tat protein on mast cells (185). In one study, increased adventitial mast cell numbers were noted in the arteries of patients dying of cocaine toxicity (186, 187). However, the role of mast cells in HIV and cocaine-induced vascular pathology is unclear (187).

Mast cells may play a role in rheumatological diseases and anaphylactic release of mast cell mediators such as alpha- and beta-tryptase and histamine has been demonstrated in various forms of arthritis (188, 189). In osteoarthritis, mast cells counts and tryptase and histamine levels are elevated in synovial fluid (190, 191). Mast cells are seen in rheumatoid lesions and may be activated and responsible for the inflammatory response (192-194). Mast cell chemotactic activity and mast cell expression of vascular endothelial growth factor (VEGF) have been demonstrated from rheumatoid synovium (195, 196). In early rheumatoid arthritis, MCT mast cells are expanded while in later disease, the dominant subtype is the MCTC mast cell (197). It also appears that antibodies to IgE and to Fc? RI occur in several autoimmune diseases suggesting one additional mechanism of mast cell activation in these disorders (198). Skopouli et al., reported on mast cell infiltration in the minor salivary glands of patients with Sjogren's syndrome and showed their association with fibrosis and c-kit expression (199). Patients with fibromyalgia demonstrate higher dermal deposits of IgG and increased dermal mast cell numbers, but the significance of these findings is unclear (200). By inducing angiogenesis, secretion of VEGF and bFGF, elaboration of collagenases, mast cells can contribute to tumor pathology and invasiveness (201-203). Osteoporosis is often a feature of mastocytosis and mast cells may contribute to bone resorption (204). Mast cells are found in intimate contact with myofibroblasts in keloid scars suggesting they may play a role in fibroblast activation and scar formation (205). Thus, besides allergic disease, mast cells may play an important role in a variety of other inflammatory, rheumatolgical and neoplastic diseases.

6. PHARMACOLOGICAL MODULATION OF MAST CELL FUNCTION

Since mast cells play such crucial roles in inflammation, host defense and tissue remodeling, modulation of mast cell function allows a therapeutic approach to human disease. A variety of pharmacological agents have been demonstrated to inhibit mast cell growth, activation and production of histamine and/or cytokines. Glucocorticoids are commonly used for the therapy of human inflammatory and allergic diseased. Studies in various laboratories have shown inhibitory effects of glucocorticoids on mast cell function (71, 206-210). Inhibition of cytokine production (IL-4, IL-5, IL-6 and IL-8) have been shown in human mast cells by glucocorticoids (71, 206). Glucocorticoids also inhibit mast cell-dependent wheal and flare responses and SCF-dependent mast cell survival (211-213). Cyclosporine and tacrolimus have been shown to have inhibitory effects on mast cells (214). For example, cyclosporine inhibits PA-I gene expression in mast cells (138). Accordingly, cyclosporine and glucocorticoids have therapeutic effects in aggressive, systemic mastocytosis (215). In one study, cyclosporine was shown to inhibit mast cell activation in atopic dermatitis (216). Cyclosporine A and FK-506 inhibit SCF-mediated histamine secretion from mast cells (217). In another study, cyclosporine A inhibited histamine release from human synovial mast cells (218). Warbrick *et al*., reported that cyclosporine A and dexamethasone inhibited cytokine gene expression by the human mast cell line, HMC-1 (67). Human skin mast cells treated with cyclosporine A produce less PGD_2 when challenged with anti-IgE (219). In contrast, human synovial mast cells and HMC-1 cells appear to be resistant to the effects of methotrexate (67, 218). Drugs referred to as "mast cell stabilizers" inhibit IgE-mediated mast cell degranulation. These include amlexanox, sodium cromoglycate and tranilast, which appear to bind to calcium-binding proteins (220). Yanni *et al*., showed that nedocromil sodium and olapatidine but not cromolyn inhibit histamine release from conjunctival mast cells activated with IgE and anti-IgE (221). Antihistamines such as azelastine, cetirizine, loratidine and ranitidine also inhibit cytokine release from activated HMC-1 cells (222). Certain cytokines have inhibitory effects on mast cells and have been used therapeutically for this reason. Interferons inhibit mast cell growth and differentiation (223). Interferon alpha-2b has been used to treat patients with mastocytosis (224).

7. 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. Several drugs with anti-inflammatory function mediate

their effects by altering mast cell degranulation and mediator release. The role of mast cells in asthma, atherosclerosis, 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 the true biological roles of these ubiquitous cells.

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