

Mast Cells: Not Only in Allergy

Ido Bachelet, MSc^a, Francesca Levi-Schaffer, PhD^a,
Yoseph A. Mekori, MD^{b,c,*}

^a*Department of Pharmacology, School of Pharmacy, The Faculty of Medicine,
The Hebrew University of Jerusalem, Ein-Kerem, Jerusalem 91120, Israel*

^b*Department of Medicine B, Meir General Hospital, Kfar Saba 44281, Israel*

^c*The Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel*

Mast cells are known to be the central effector cells in the early phase and important in the late phase of IgE-mediated allergic inflammatory reactions [1]. Mast cells can be activated to secrete diverse preformed mediators and de novo synthesized lipid mediators and cytokines after cross-linking of Fcε receptor (FcεR) I-bound IgE with multivalent antigen [2]. The wide range of the biologic effects of the various mediators accounts for the role of mast cells in the induction of acute allergic responses as well as in the development of chronic allergic inflammation. The accumulation and activation of lesional mast cells as observed in several chronic inflammatory and fibrotic processes, such as multiple sclerosis [3], rheumatoid arthritis [4], sarcoidosis [5], Crohn's disease [6], chronic graft-versus-host disease [7], and scar tissue [8], suggest their involvement in other settings as well. In vitro and in vivo studies have demonstrated that mast cells or their products are pivotal in mediating leukocyte recruitment into inflammatory sites, are capable of presenting antigens to T cells, interact directly with and affect the function of cells of the adaptive immune system, and mediate tissue remodeling.

Therefore, the contribution of mast cells to physiologic and pathologic processes extends far beyond their accepted role in allergic disease. Several morphologic and functional features of mast cells enable them to contribute to nonallergic inflammatory processes. Mast cells are strategically poised at perivascular sites to regulate inflammatory responses [1]. They are also located for optimal interaction with the environment and for their putative functions in host defense [9]. Their predilection to occupy tissues that

* Corresponding author. Department of Medicine B, The Meir Hospital–Sapir Medical Center, Kfar Saba 44281, Israel.

E-mail address: ymekori@clalit.org.il (Y.A. Mekori).

interface with the external environment, including the skin and respiratory and gastrointestinal tracts, places them in a unique position to encounter invading organisms and orchestrate a response. Their close physical proximity with T cells in inflamed tissues has led investigators to propose a functional relation between these two cell populations that might facilitate the immune response.

Apart from activation by means of Fc ϵ RI, mast cells are also activated by a wide array of non-IgE-driven signals from their environment, such as cross-linking of surface FC γ receptor (Fc γ R) I and Fc γ RIII molecules [10]; anaphylatoxins [11]; a range of small peptides, including substance P and calcitonin gene-related peptide [12]; and β -chemokines, such as macrophage inflammatory protein (MIP)-1 α and monocyte chemoattractant protein-1 [13]. Furthermore, human and murine mast cells have been found to be activated and to release granule-associated mediators and cytokines by heterotypic adhesion to activated T cells [14,15]. This indicates the occurrence of multiple pathways of mast cell activation and suggests a role for mast cells in many pathophysiologic processes in addition to their traditional role in causing allergy.

Mast cells express a wide array of surface receptors that may be implicated in costimulation during innate or acquired immune responses [1]. Molecules like major histocompatibility complex (MHC) class I and II [16,17], intercellular adhesion molecule (ICAM)-1 [18], β 2-integrins [19], CD40L [20], and Toll-like receptors (TLRs) enable mast cells to interact with other inflammatory cells or with invading microorganisms, thus orchestrating an immune response [1]. Further, mast cells produce and release a broad spectrum of mediators, including vasoactive amines; products of arachidonic acid metabolism; and many proinflammatory, chemoattractive, and immunomodulatory cytokines that may contribute to immunologic reactions by affecting cell growth, recruitment, and function [21]. It is therefore reasonable to assume that the extent of mast cell involvement in allergic and non-allergic diseases as well as host defense is likely far greater than would be predicted strictly on the basis of studies of classic IgE-dependent immune responses.

The specific functions of mast cells in inflammatory processes *in vivo* are difficult to evaluate, because the immune responses as well as tissue changes that can accompany them may involve the coordinated and potentially redundant and overlapping activities of several cell types. Further complicating the analysis of mast cell function *in vivo* is that mast cell activation results in the elaboration of several mediators, which may have diverse and sometimes opposing biologic effects [22]. It is therefore impossible to predict the net effect of mast cell degranulation in complex processes. These problems can often be readily addressed by using mice genetically deficient in mast cells, in which mast cell populations have been selectively reconstituted ("knock-in" mice) [23]. Such mast cells can be derived from bone marrow cells of the congenic wild-type mice or various (genetically compatible)

knockout mice or directly from embryonic stem cells. This approach permits a direct assessment of how the expression of biologic responses in vivo differs in the presence or absence of wild-type mast cells or mast cells with certain genetic alterations that affect mast cell phenotype or function. By using these mast cell knock-in mice, several groups have confirmed the role of mast cells in certain types of inflammatory conditions associated with innate immunity, autoimmunity, T-cell-mediated delayed-type hypersensitivity (DTH), and immune complexes (Table 1).

Host defense and innate immunity

Among their many properties, mast cells are strategically positioned in the body in places in which contact with pathogens is likely to occur: mucosal surfaces of the airways and gastrointestinal and urogenital tracts [37] as well as the connective tissue of the skin (dermis) [38]. This positioning makes them natural candidates for participation in host defense and innate immunity. Mast cells also exist in lower vertebrates, such as fish and amphibians [39–42], suggesting a function in primitive immune systems that lacked an adaptive branch.

The high-affinity IgE receptor FcεRI mediates important interactions between mast cells and bacteria in host defense. Patients with atopic dermatitis have been shown to express IgE antibodies against *Staphylococcus aureus* or its exotoxin [43–45], and IgE against *Helicobacter pylori* was shown to exist in patients with gastritis and peptic ulcers [46,47]. Another intriguing IgE-dependent route of pathogen-induced mast cell activation is through

Table 1
Involvement of mast cells in inflammatory settings

Disease model	Putative mechanism	Important mediator	Reference
Late allergic response	Leukocyte infiltration	Histamine, proteases, TNFα	[24,25]
Immune complex-induced peritonitis	Neutrophil recruitment	TNFα	[26,27]
Contact sensitivity	Neutrophil recruitment, dendritic cell migration	TNFα, MIP-2	[28]
Multiple sclerosis	Peripheral effects in lymphatic organs	Not determined	[3,29]
Bullous pemphigoid	Neutrophil recruitment	IL-8	[30,31]
Rheumatoid arthritis	Neutrophil recruitment	Not determined (TNFα?)	[32,33]
Infection-induced lymphadenopathy	T-cell recruitment	TNFα	[34]
Fibrosis	Fibroblast stimulation, ECM deposition and angiogenesis	TGFβ, NGF, VEGF, ECM enzymes, tryptase (PAI-1?)	[35,36]

Abbreviations: ECM, extracellular matrix; IL, interleukin; MIP, macrophage inflammatory protein; NGF, nerve growth factor; PAI, plasminogen activator inhibitor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

pathogen-derived proteins serving as immunoglobulin superantigens [45,48]. It has been shown that the *S aureus Cowan-1*-derived protein A and *Peptostreptococcus magnus*-derived protein L cross-link Fc ϵ RI-bound IgE through interaction with its V_H3 region [48]. The HIV-1 gp120 induces mast cell and basophil activation through the same mechanism [49]. Moreover, endogenous Fv protein released from the liver during hepatitis may also function as a superallergen for mast cells [49].

IgE mediates further functions of mast cells in host defense. Mast cells have been associated with parasitic infections based on observations reporting that mast cell numbers and their tissue deployment change during the course of infection [24,50]. It has been reported that mast cells take active part in the clearance of enteric pathogens, such as *Schistosoma mansoni* and *Salmonella typhi*, that undergo phagocytosis through interaction with the complement receptor CR3 [51–53].

Several studies have shown that mast cells recognize bacteria through the fimbrial antigen FimH expressed by several gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae* [54,55]. This interaction was later shown to be mediated by CD48 [56]. CD48 is a glycosyl-phosphatidylinositol-anchored membrane protein highly expressed on the leukocyte surface and displays an inducible phenotype. Engagement of this protein by FimH-expressing bacteria induces a strong activation response in mast cells characterized by tumor necrosis factor- α (TNF α) production and phagocytosis of the bacterial particles [57,58]. Moreover, phagocytosis enables the mast cell to process and present antigens to T lymphocytes in an MHC class I- or class II-restricted and costimulatory molecule-dependent fashion [16,59]. The in vivo TNF α response to enterobacteria has been shown to be critically dependent on mast cells. Mast cell-deficient mice, also found to have decreased reactive levels of TNF α , failed to recruit neutrophils and clear bacteria from the infected site, a response that was restored on reconstitution of the mice with mast cells or on the addition of exogenous TNF α [60,61].

Only recently, it has been demonstrated that mast cells express members of the TLR family, key molecules of innate immunity [9,62], which enable them to respond to various pathogen-derived signals. TLR-4 has been shown to be critical for an effective TNF α response to bacterial lipopolysaccharide (LPS) in mice. Expression of TLR-4 (and its cosignaling molecule CD14) in human mast cells is still controversial [63–65], although it is clear that they respond to LPS stimulation. Other than TLR-4/CD14, mast cells have been shown to express TLR-2 and TLR-9 [66]. TLR-2 can dimerize with TLR-1 or TLR-6 to form receptors for lipopeptides in the former case or for bacterial peptidoglycan and yeast zymosan in the latter. Together, TLR-2 and TLR-4 might constitute a critical sensing module for bacterial pathogens. TLR-9 contributes to this module by recognizing bacterial and cytosine (connected by phosphodiester bond to) guanine (CpG) DNA. It is now known that TLR-9 is able to modulate T helper

(Th) 2 reactions, such as asthma, by introducing synthetic CpG oligonucleotides via TLR-9 [67], and this method shows promising results in this aspect. Mast cells have also been reported to express TLR-1, TLR-3, TLR-6, and TLR-7, implying that they are able to respond to an enormous spectrum of pathogen-associated patterns, bolstering their role in innate immunity (Table 2; Fig. 1).

Chronic inflammation, fibrosis, tissue remodeling, and angiogenesis

Studies in mast cell-deficient and -reconstituted mice show that mast cells are essential for virtually all the augmented vascular permeability and tissue swelling associated with IgE-dependent skin responses, such as passive cutaneous anaphylaxis. Furthermore, clinical and animal studies indicate that mast cell activation contributes to the leukocyte infiltration associated with late-phase responses. This effect is mediated through increased vascular permeability and the expression of specialized adhesion molecules on endothelial cells required for leukocyte migration into the site of inflammation. Mast cells can also affect the behavior of structural cells—namely the fibroblasts—within the inflammatory site [35,75,76]. Although these events are regulated temporally as well as functionally, repeating or unrestrained mast cell activation critically contributes to the development of chronic inflammatory and fibrotic disorders.

As immune effector cells, mast cells are finely kept in balance between activating and inhibiting signals. In recent years, data have been accumulated regarding the expression and function of immune inhibitory receptors in

Table 2
Mechanisms of mast cell host defense functions

Molecule	Ligand/Function	Reference
CD48	FimH: bacterial phagocytosis, degranulation and TNF α production	[56]
IgE	Recognition of targeted pathogens Activation by superantigens through the V _H 3 region	[45,48,68]
CR3	Clearance of enteric pathogens	[69]
TLR-1/2 dimer	Pam ₃ Cys (lipopeptides)	[70]
TLR-2/6 dimer	Bacterial peptidoglycan and yeast zymosan: production of TNF α and IL-6	[71]
TLR-3	dsRNA: production of IFN α , TNF α , and IL-6	[72,73]
TLR-4/CD14	Bacterial lipopolysaccharide: production of TNF α and IL-6	[64,70,74]
TLR-7	ssRNA/resiquimod: production of TNF α , IL-6, MIP-1 α , MIP-2, and RANTES	[66]
TLR-9	CpG oligodeoxynucleotides: production of TNF α , IL-6, MIP-1 α , MIP-2, and RANTES	[66]

Abbreviations: CpG, cytosine (connected by phosphodiester bond to) guanine; Cys, cysteinyl; dsRNA, double-stranded RNA; IFN, interferon; IL, interleukin; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T-cell expressed and secreted; ssRNA, single-stranded RNA; TLR, Toll-like receptor; TNF, tumor necrosis factor.

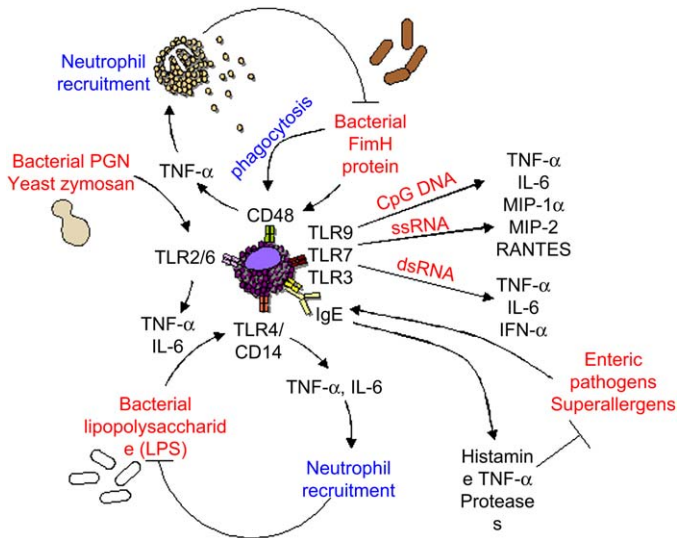


Fig. 1. Major interactions of mast cells in innate immunity and host defense. Five major pathways are depicted in this schematic diagram: (1) FimH recognition via CD48; (2) foreign nucleic acid recognition via TLR-3, TLR-7, and TLR-9; (3) enteric pathogens and superallergens via IgE; (4) LPS response via TLR-4/CD14; and (5) PGN and zymosan response via TLR-2. IFN, interferon; PGN, peptidoglycan; RANTES, regulated on activation, normal T-cell expressed and secreted.

mast cells [77]. These receptors negatively regulate mast cell responses; therefore, impaired function of these molecules might lead to augmented unrestrained mast cell activity. A recently identified susceptibility locus for atopic dermatitis and rheumatoid arthritis on chromosome 17q24.25 is in close linkage with a gene cluster called CMRF35H containing two identified inhibitory receptors on mast cells [78–80]. The possibility that exaggerated mast cell activity in these diseases derives from a malfunctioning inhibitory receptor is intriguing and requires further investigation.

Within the site of inflammation, there is a continuous interplay between mast cells and fibroblasts. It has been shown that a reciprocal relation exists between these two cell types: mast cells modulate fibroblast phenotype, and fibroblasts provide important signals for mast cell differentiation, survival, and activation. For example, activation of mast cells by eosinophil major basic protein is mediated by a membrane-bound form of stem cell factor expressed on fibroblasts [81]. It has been demonstrated that mast cells can be sustained for long periods and acquire responsiveness to IgE-independent stimuli when cocultured with fibroblasts [82–85]. These interactions form a functional basis for mast cell involvement in fibrotic disorders. Indeed, mast cells have been associated with numerous fibrotic conditions, such as idiopathic lung fibrosis, bleomycin- or radiation-induced lung fibrosis, asthma, scleroderma, chronic graft-versus-host disease, and liver cirrhosis.

In all these conditions, mast cell hyperplasia is evident, with a high percentage of the mast cells seen degranulated in situ.

Mast cells may exert a bidirectional effect on matrix turnover. Trypsase and chymase have been shown to activate in vitro the zymogen forms of matrix metalloproteinases and procollagenase, thereby promoting matrix degradation [25,86]. Conversely, mast cell degranulation and proliferation have been documented in fibrotic processes in vivo, and certain mast cell mediators (ie, chymase, trypsin, TNF α , basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor- β [TGF β]) have been found to exert fibrogenic effects by causing fibroblast proliferation or increased collagen synthesis [35,87]. Thus, mast cells are specialized to receive the appropriate signals to initiate an immune response by recruiting and activating relevant effector cells in a process that subsequently culminates in tissue repair. Indeed, it has recently been shown that mice deficient in the mast cell protease chymase expressed impaired matrix turnover and collagen elimination, thus indicating a key role for this enzyme in matrix modulation [88]. It is conceivable that these functions also underlie mast cell involvement in related physiologic settings, such as wound healing. Studies with mast cell-deficient mice show the contribution of mast cells to normal wound healing [89,90], although unbalance in this process may again lead to fibrosis and *functio laesa*.

Chronic inflammatory and fibrotic diseases are characterized by a component of tissue remodeling. A hallmark feature of chronic asthma, for example, is a gradual thickening of the airway wall, whereas narrowing of the airway lumen leads to limited airflow [91], which may ultimately render the disease unresponsive to conventional therapeutic measures. Mast cells contribute to these changes through release of mediators that act directly on structural cells or indirectly stimulate other effector cells, such as eosinophils [92–94]. It has recently been reported that mast cells are a rich source of plasminogen activator inhibitor (PAI)-1, the main inhibitor of the fibrinolytic cascade known to play an essential role in tissue remodeling [92,95]. Asthmatic PAI-1-deficient mice displayed less matrix deposition and tissue remodeling than asthmatic wild-type mice [95,96]. Genetic analysis revealed that a PAI-1 allele called 4G is associated with higher plasma PAI-1 and that its frequency was significantly higher in patients with asthma [97,98].

A crucial component of tissue remodeling is the formation of new blood vessels, a process known as angiogenesis. Angiogenesis contributes to the perpetuation of chronic inflammation by promoting the migration of inflammatory cells to the inflammatory site. Tissue hypoxia is an important signal for inflammatory cells to synthesize angiogenic factors. Specifically, mast cells are capable of producing such proangiogenic factors as prostaglandin E₁ and E₂, interleukin (IL)-8, heparin, vascular endothelium growth factor (VEGF), nitric oxide, and platelet-activating factor as well as TGF- β 1 [36,99,100]. Angiogenesis has long been linked with chronic inflammatory diseases. The synovial tissue in rheumatoid arthritis undergoes

extensive neovascularization, and angiogenesis is crucial for normal wound healing [100,101].

As cells bearing remarkable proangiogenic capabilities, mast cells may contribute to other states involving angiogenesis, especially cancer. It is likely that angiogenic factors released from mast cells promote tumor growth through vessel formation. For example, it was recently demonstrated that mast cell-derived angiopoietin-1 is critically involved in neovascularization, promoting growth of plasma cell tumors *in vivo* [102]. In human beings, it has been reported that angiogenesis in endometrial cancer is facilitated by mast cell tryptase [103]. Still, the question as to whether they actually promote the tumor, eliminate it, or are simply innocent bystanders remains open (Fig. 2).

Autoimmunity and the T-cell interplay

Numerous observations have suggested mast cell involvement in autoimmune disorders based on microscopic studies showing mast cell presence, hyperplasia, and activity. Recent findings shed light on mechanistic links between mast cells and autoimmunity. Although the exact functions and

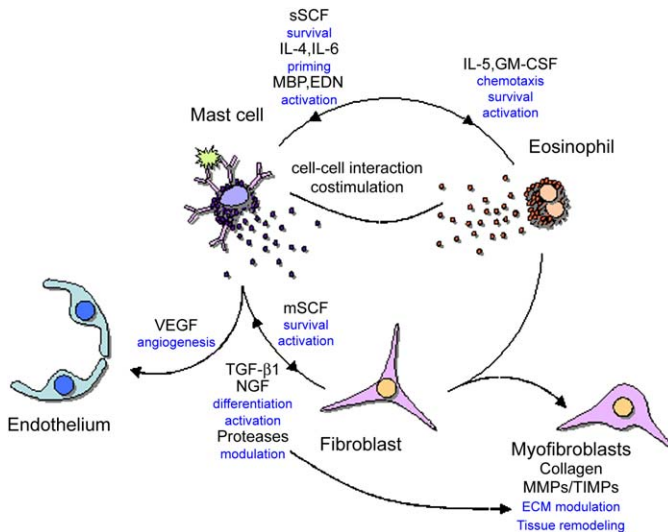


Fig. 2. Major interactions of mast cells in late allergic responses and fibrosis. (1) Eosinophils: mast cells recruit eosinophils, prime them, and promote their survival, contributing to late allergic responses. (2) Fibroblasts: mast cells induce fibroblast differentiation to myofibroblasts, thereby inducing tissue fibrosis. (3) Endothelium: mast cells secrete proangiogenic mediators attracting endothelium, causing angiogenesis and tissue remodeling. ECM, extracellular matrix; EDN, eosinophil-derived neurotoxin; GM-CSF, granulocyte-macrophage colony-stimulating factor; MBP, eosinophil major basic protein; MMP, matrix metalloproteinase; mSCF, membrane-bound form stem cell factor; NGF, nerve growth factor; sSCF, soluble form stem cell factor; TIMP, tissue inhibitor of matrix metalloproteinase; VEGF, vascular endothelial growth factor.

interplays of mast cells in autoimmune diseases are still not completely understood, studies using mast cell-deficient mice have provided important insights as to the specific conditions dependent on mast cells for their development.

In rheumatoid arthritis, synovial mast cell hyperplasia is a constant feature of the disease [32,33]. The synovial fluid of patients with arthritis displays high levels of stem cell factor, consequently produced by synovial fibroblasts after stimulation with mast cell-derived $\text{TNF}\alpha$ [104,105]. Synovial mast cells are constantly activated during the disease course. A disease resembling inflammatory arthritis develops spontaneously in *K/BxN* mice but can also be induced by injection of antibodies recognizing glucose-6-phosphate isomerase into healthy mice [106]. Mast cell activation was found only in the inflamed synovium a short time after the injection of the arthritogenic antibodies and before the recruitment of neutrophils. These observations prompted the conclusion that mast cells might have an early coordinating role in this model of rheumatoid arthritis [106]. It is likely that synovial mast cells are activated by articular autoimmune complexes suggestive of an immune complex hypersensitivity reaction in the synovium. Indeed, mast cells have been found to be important for the induction of neutrophil influx in immune complex-mediated responses. This effect has been attributed to mast cell $\text{TNF}\alpha$, because $\text{TNF}\alpha$ levels were significantly reduced in the *W/W^v* mice in association with a decrease in neutrophil accumulation. Mast cell reconstitution normalized $\text{TNF}\alpha$ levels and neutrophil mobilization. This induction of immune complex-mediated mast cell-dependent inflammation was shown to involve $\text{Ig}\gamma$ -Fc or C3/C5a receptors [107]. Ligation of these receptors has been shown to be a potent activator of mast cell function in vitro and in vivo. Thus, mast cells may provide the cellular target of autoantibodies, the complement network, and Fc receptors in the subsequent development of inflammatory responses, such as rheumatoid arthritis.

Mast cell hyperplasia as well as elevated cerebrospinal fluid levels of mast cell mediators has been found in experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis. Mast cells have also been found to be responsible for the severity and disease incidence of EAE in vivo [29]. In this model system, mast cell-deficient (*W/W^v*) mice exhibited significantly reduced disease incidence and decreased clinical scores when compared with their normal littermates. Reconstituting the mast cell population in the *W/W^v* mice could eliminate this difference. Interestingly, it has recently been shown that mast cells exert their effect in lymphatic tissues outside the central nervous system (CNS) in this animal model of multiple sclerosis, pointing to a direct influence on B- and T-cell responses known to occur in this microenvironment [108].

Bullous pemphigoid (BP) is a subepidermal blistering disease caused by autoantibodies against two hemidesmosomal proteins, BP180 and BP230. Mast cells in BP lesional skin are evidently degranulated, and the upper

dermis is infiltrated with various inflammatory cells. Injection of anti-BP180 into wild-type BALB/c neonatal mice reproduces the key features of BP. Injection of anti-BP180 into T-cell or T-cell/B-cell-deficient mice generated BP; however, mice deficient in mast cells, neutrophils, and macrophages were resistant to antibody-induced BP [109]. Mice deficient only in mast cells developed a response that was significantly weaker than that of the fully deficient mice, suggesting two separate pathways for neutrophil recruitment—dependent and independent of mast cells [30]. Experiments with macrophage-deficient mice showed that mast cells play the key role in leukocyte recruitment but that macrophages enhance mast cell activation. These findings demonstrate the orchestration between the important effector cells in this *in vivo* disease model.

Other autoimmune disorders have recently been associated with mast cells. These include Sjögren's syndrome, a destructive autoimmune disease of the salivary glands in which mast cells invade the gland at early stages of the disease [110,111]; autoimmune thyroiditis [112]; and systemic sclerosis [38,113], although mast cells are possibly involved in other autoimmune disorders as well.

The role of mast cells in autoimmunity is tightly linked to their ability to interact with T cells. Many reports describe mast cells and T cells in close vicinity at sites of inflammation, such as parasitic infection, contact hypersensitivity, and autoimmune processes [59,114]. The induction of DTH in mice is critically dependent on mast cells, specifically on mast cell-derived $\text{TNF}\alpha$ and MIP-2 (functionally analogous to human IL-8), because mast cell-deficient mice displayed impaired leukocyte recruitment in cutaneous DTH [115,116]. The combination of these two mediators is crucial for cell recruitment, because $\text{TNF}\alpha$ and MIP-2 provide two qualitatively different but synergistic signals. Mast cell-derived $\text{TNF}\alpha$ has been shown to induce adhesion molecule expression required for lymphocyte and polymorphonuclear attachment to endothelial cells, whereas MIP-2 establishes a chemotactic gradient required for diapedesis and directed migration [28,117].

The induction of MIP-2 and $\text{TNF}\alpha$ was strictly dependent on the presence of mast cells and local activation of memory T cells, which shows that the infiltrating T cells deliver signals that induced $\text{TNF}\alpha$ and MIP-2 production by mast cells. Although the nature of these signals *in vivo* has not yet been defined, it seems reasonable to suggest that direct cross-talk between these two cell populations exists, because recent *in vitro* studies indicated that mast cells may be triggered to degranulate and release cytokines on heterotypic adhesion to activated but not resting T cells [14,15].

T-cell–mast cell interaction has been shown to be bidirectional. Activated mast cells can modulate T-cell function through several mechanisms. As mentioned previously, mast cells are able to present antigens to T cells, resulting in their activation, in an MHC class I- or class II-restricted and costimulatory molecule-dependent fashion [16,118]. Furthermore, mast cell-derived cytokines, such as IL-4 and histamine, have been found to polarize T cells to

differentiate preferentially into the Th₂ subset [1]. Mast cells express ligands for costimulatory molecules on T cells, thereby enhancing T-cell activation, such as the ICAM-1/leukocyte function associated antigen-1 axis, through which mast cells are also enhanced by T cells. Mast cells provide T-cell chemotactic signals in a polarized manner by the chemokines, IL-16 (attracting CD4+ T cells), lymphotactin (attracting CD8+ T cells), and leukotriene B₄ (general) or by inducing expression of specific adhesion molecules on endothelial cells that facilitate T-cell migration to the site of antigen challenge [59]. It is therefore likely that mast cell–T-cell crosstalk plays an important role in T-cell–mediated responses and autoimmune disorders.

Atherosclerosis

Cardiovascular diseases and atherosclerosis are among the main causes of death in Western countries. Atherosclerosis is a fibrotic condition of the blood vessels in which cholesterol-fed macrophages induce the build-up of plaques connected to the vessel walls [119]. These plaques often erode, detach, and drift in the circulation. Once there, they might block important arteries in the brain or heart and cause lethal infarctions. The reasons for plaque erosion and rupture are diverse, and include death of smooth muscle cells that maintain the fibrous cap holding the plaque in situ (a process referred to as anoikis), oxidation of cap proteins leading to a fragile structure, and an autoimmune process targeted at plaque constituents. It has recently been suggested that mast cells may contribute to plaque instability.

Mast cells have long been linked with atherosclerosis. As early as in the 1950s, it was shown that sections of thrombotic arteries revealed the presence of degranulated mast cells within the plaque regions [120,121]. Nevertheless, it was not until the past decade that it was clearly demonstrated that mast cell mediators may profoundly modulate the process of atherosclerosis from its onset until the plaque rupture stage. The first stage in atherosclerosis, the formation of foam cells, was shown to be dramatically facilitated by the presence of mast cell granule remnants in vitro, in a process first involving binding of low-density lipoprotein (LDL) particles to granule heparin and later degradation of the apolipoprotein component by neutral proteases [122–124]. Moreover, mast cell activation led to cholesteryl ester synthesis and accumulation in macrophages [119,125]. Mast cell chymase was then shown to weaken the matrix structure of the fibrous plaque cap by activating collagen-degrading enzymes and inhibiting collagen deposition by fibroblasts [126,127]. Furthermore, chymase actively induced anoikis by degrading the smooth muscle basement layer [128]. Recently, the chymase inhibitor SUN-C8257 was observed to inhibit lipid accumulation in hamster aorta [129], thus demonstrating a role for chymase in the atherosclerotic process.

Another important mediator of atherosclerosis is angiotensin-II through diverse effects on cell proliferation, migration, induction of adhesion molecule expression, leukocyte activation, and matrix production [130]. The

expression of angiotensin-converting enzyme (ACE), the enzyme thought to mediate most physiologic formation of angiotensin-II, is induced in stenotic aortic valves [131] and coronary arteries [132]. Nevertheless, as recently reported, multiple pathways for angiotensin-II formation exist independent of ACE. In the human heart and aorta in vitro, for example, the main pathway for generating angiotensin-II is by mast cell chymase [133]. On an equimolar basis, chymase is more potent than ACE in this regard [134]. Other pathways, such as kallikrein and cathepsin G (which also exists in large quantities in mast cells), might also contribute to angiotensin-II formation in a tissue-specific manner.

Chymase emerges as a key modulator of atherogenesis because of another novel function identified recently—the formation of a 31-amino acid form of endothelin-1 called ET-1(1-31) [135,136]. ET-1(1-31), similar to endothelin-1, elicits a vasoconstrictor effect and is mitogenic for vascular smooth muscle cells. ET-1(1-31) is increased in atherosclerotic lesions in hamster aorta [136], suggesting an as yet unclear involvement in the process.

Understanding the entire network through which mast cells promote atherogenesis and identifying key players in this process, such as chymase, may ultimately lead to novel approaches for treating this important condition (Fig. 3).

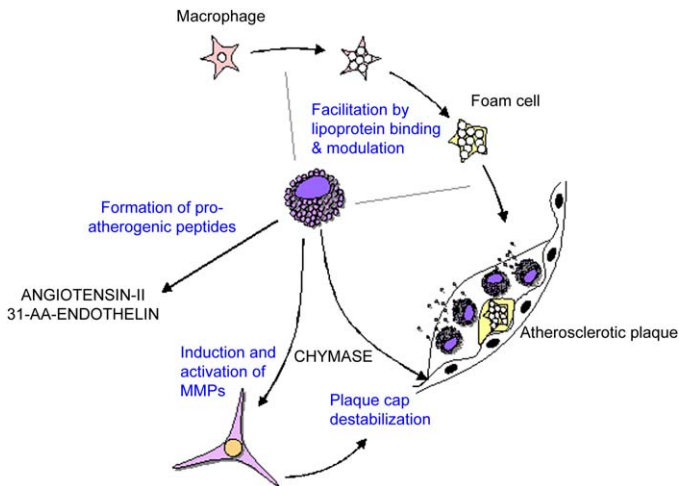


Fig. 3. Major pathways of mast cell involvement in atherogenesis. (1) Mast cells promote foam cell generation by lipoprotein degradation and modulation of cholesterol pathways and transport in macrophages. (2) Mast cells contribute to plaque erosion and instability by releasing matrix-modulating enzymes (especially chymase), activating matrix enzymes and collagenases, inhibiting collagen synthesis by fibroblasts, and inducing smooth muscle apoptosis. (3) Mast cell-derived proteases participate in generation of proatherogenic peptides like angiotensin-II and 31AA-endothelin-1. MMP, matrix metalloproteinase.

Summary

The past decade has confronted us with a striking abundance of novel findings regarding the roles of mast cells in immune responses in health and disease. Newly developed models and techniques have enabled clear-cut dissection of the mast cell contribution in these settings. We now understand that mast cells possess critical effector functions not only within the traditional context of allergic reactions. It is likely that mast cells played pivotal roles in primitive immune systems, yet these functions have been masked in the recent eras by newer immune functions, such as adaptive immunity. Conceivably, mast cells should be refocused on so as to obtain new insights about diverse pathologic conditions, ultimately leading to novel therapeutic approaches targeting these fascinating cells.

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