

The mastocyte: The “other” inflammatory cell in immunopathogenesis

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Mast cells are known to be the central effector cells in the elicitation of the early-phase and late-phase IgE-mediated allergic inflammatory reactions.^{1,2} These cells can be activated to secrete diverse preformed mediators and de novo synthesized lipid mediators and cytokines after cross-linking of FcεRI-bound IgE with multivalent antigen. The wide range of the biological effects of the various mediators accounts for the essential role of mast cells in the induction of acute allergic responses as well as the development of chronic allergic inflammation.¹⁻³ In addition to classical IgE-mediated allergic responses, mast cells have been implicated in a range of other inflammatory reactions. Both *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.¹⁻⁴

It is also now known that mast cell precursors arise from pluripotent bone marrow-derived stem cells, circulate in the blood and lymphatics, and migrate into tissues, in which they reach phenotypic maturation under certain microenvironmental influences.^{1,5} Elucidating the mechanisms that regulate the viability and maturation of mast cells, with IL-3 and the kit ligand (stem cell factor) the principal growth-promoting cytokines, has enabled us to define further and characterize conditions associated with mast cell hyperplasia or neoplasia as reviewed by Valent et al⁶ and as illustrated by Escribano et al⁷ in this issue of the Journal. This information has obvious implications not only for understanding the etiology and control of mast cell proliferation in various pathologic processes but also for designing specific pharmacologic treatments for these conditions, as proposed by Akin et al.⁸

Because of such new information, it is becoming increasingly evident that the contribution of mast cells to

Abbreviations used

DC: Dendritic cell

DTH: Delayed-type hypersensitivity

MIP: Macrophage inflammatory protein

both physiologic and pathologic processes extends far beyond their accepted role in allergic disease. The accumulation and activation of lesional mast cells as observed in several chronic inflammatory and fibrotic processes such as multiple sclerosis, rheumatoid arthritis, sarcoidosis, Crohn's disease, chronic graft-versus-host disease, and scar tissue suggest their involvement.¹⁻³ Several morphologic and functional features of mast cells enable them to contribute to nonallergic inflammatory processes (Table I). Mast cells are strategically poised at perivascular sites to regulate inflammatory responses. They are also located for optimal interaction with the environment and for their putative functions in host defense. Their predilection to occupy tissues that interface 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 relationship between these 2 cell populations that might facilitate the immune response.³

Apart from activation by means of FcεRI, mast cells are also activated by a wide array of non-IgE-driven signals from their environment such as cross-linking of surface FcγRI and FcγRIII molecules, anaphylatoxins, a range of small peptides including substance P and calcitonin gene-related peptide, and β-chemokines such as macrophage inflammatory protein (MIP)—1α and monocyte chemoattractant protein 1.^{2,3} Furthermore, both human and murine mast cells have been found to be activated and to release both granule-associated mediators and cytokines by heterotypic adhesion to activated T cells.^{9,10} 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.¹¹ Molecules such as MHC

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class I and II, intercellular adhesion molecule 1, B7, β 2-integrins, CD40L, and Toll-like receptor enable mast cells to interact with other inflammatory cells or with invading microorganisms, thus orchestrating an immune response. 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.^{12,13} It is therefore reasonable to assume that the extent of mast cell involvement in both allergic and nonallergic diseases, as well as host defense, is likely far greater than would be predicted strictly on the basis of studies of classical IgE-dependent immune responses.¹³ Indeed, as reviewed by Marshall and Jawdat,¹⁴ there is more than circumstantial evidence that the mast cell's biology is well suited to perform an important role in innate immune responses against various microorganisms. The ability of mast cells to release proinflammatory and chemotactic mediators on interaction with microorganisms gives them a significant role in the innate immune response against these offending elements.

It is difficult to be certain of the mast cell's specific functions in inflammatory processes *in vivo* because immune responses as well as the tissue changes that can accompany them may involve the coordinated and potentially redundant and overlapping activities of several cell types. For instance, many mast cell–associated mediators are also produced by other cells. As a result, evidence that one of these mediators has a critical role in a particular biological response is not by itself sufficient proof that mast cells are important in that response. A similar argument may be made about pharmacologic experiments using antagonists of specific mast cell–derived mediators or inhibitors of mast cell activation. As valuable as this approach is for evaluating the function of each individual mast cell mediator, resulting data may provide incomplete or, in some cases, misleading information of the role of the intact mast cell, because other target cells, as well as mast cells, may be implicated.¹ 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 biological effects.¹⁵ It is therefore difficult to predict the net effect of mast cell degranulation in complex processes. Finally, mast cell heterogeneity, which includes variations not only in morphology but also in mediator content and response to secretagogues and drugs, makes it difficult to offer succinct generalization about mast cell function and biological responses.

These problems can often be readily addressed by using genetically mast cell–deficient mice in which mast cell populations have been selectively reconstituted. Such mast cells can be derived from bone marrow cells of either the congenic wild-type mice or various (genetically compatible) knockout mice, or directly from embryonic stem cells. This approach permits one to assess directly

TABLE I. Mast cell features facilitating their contribution to nonallergic inflammatory processes

- Located around blood vessels in tissues exposed to the external environment
- Found to reside in physical proximity to T cells in inflamed tissues
- Activated by several non–IgE-driven signals
- Express many surface molecules important in costimulation during both innate and adaptive immunity
- Release a wide range of mediators known to exert immunomodulatory effects

how the expression of biological 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.¹² 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 II).

Studies in mast cell knock-in mice show that mast cells are essential for virtually all of the augmented vascular permeability and tissue swelling associated with IgE-dependent skin responses such as passive cutaneous anaphylaxis. Furthermore, both clinical and animal studies indicate that mast cell activation contributes to the leukocyte infiltration associated with late-phase responses.^{1-3,12} The contribution of mast cells to the development of asthma has also been demonstrated in an asthma model in mast cell–deficient and reconstituted mice. In this model system, mast cells were found to contribute to airway hyperresponsiveness and to increase eosinophil infiltration and the numbers of proliferating cells in the airway epithelium.¹⁶ Another way by which mast cells contribute to the development of asthma may be related to recent findings in human beings demonstrating mast cell infiltration in airway smooth muscle cells. The possible relevance of this finding to the pathophysiology of asthma is discussed in this issue of the Journal by Robinson.¹⁷ Also, as suggested elsewhere by Crummy et al,¹⁸ the differential physiologic effects of adenosine-induced mast cell degranulation in the lungs of asthmatic subjects compared with nonasthmatic subjects have been similarly attributed to the specific localization of mast cells within the bronchial smooth muscle fibers in asthma. Thus, mast cells may contribute to bronchoconstriction in asthma by a direct interaction with the adjacent bronchial muscle fibers.

Mast cells have also been found to be responsible for both severity and disease incidence in a murine model of multiple sclerosis. In this model system, mast cell–deficient mice (W/W^v) exhibited significantly reduced disease incidence and decreased clinical scores compared with their normal littermates. Reconstituting the mast cell population in the W/W^v mice could eliminate this difference.¹⁹ Interestingly, it has recently been shown that mast cells exert their effect in lymphatic tissues

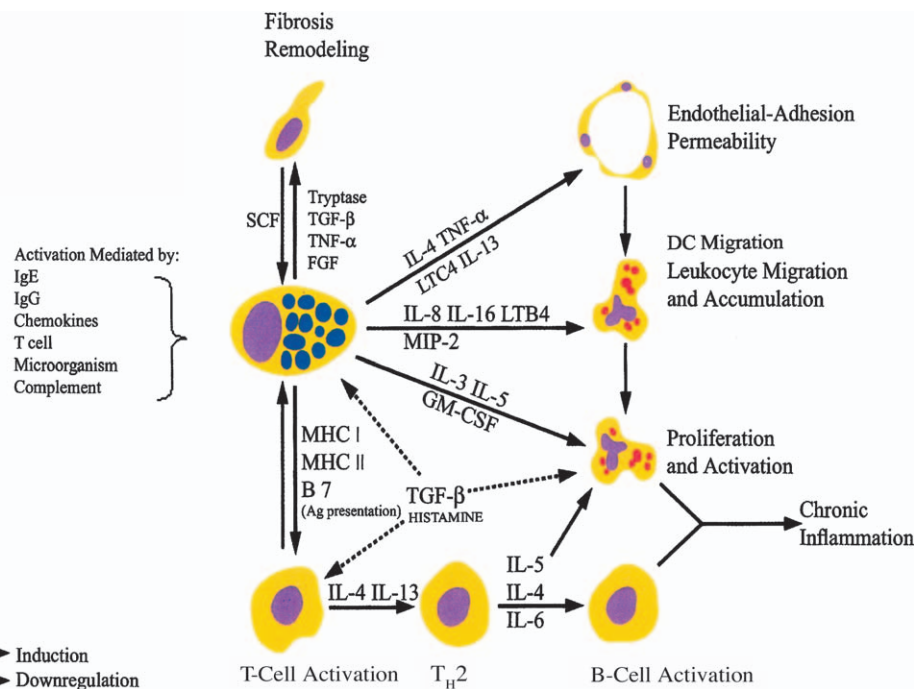


FIG 1. Biological effects of the mast cell within the nonallergic inflammatory context. Mast cells may be activated by several inflammatory signals such as immune complexes binding to Fc γ R, C3a and C5a binding to specific complement receptors, T cells interacting with surface adhesion molecules, and microorganisms (or their products) binding to receptors such as Toll-like receptor or CD48. On encountering these stimuli, mast cells are activated and release a diversity of mediators (representative mediators are depicted). The biological effects of these mediators include increased vascular permeability and increased endothelial adhesiveness facilitating homing of leukocytes to the site of antigen challenge. Chemokines, cytokines such as IL-16, and LTB4 provide the necessary chemotactic stimulus driving leukocyte accumulation in the inflammatory site. These leukocytes are also activated by mediators released from the mast cells, thus perpetuating the inflammatory response. Mast cells can also affect the sensitization phase of immune responses by influencing DC migration and activation. Mast cells are capable of presenting antigens to T cells and polarizing T cells toward the T_H2 phenotype through the effects of IL-4 and IL-13. Mast cell mediators are also involved in remodeling connective tissue. Several mediators are known to exert inhibitory effects. These include TGF- β , known for its inhibitory effects on both mast cells and lymphocytes, and histamine through its H2-receptor.

TABLE II. Mast cell involvement in inflammatory reactions *in vivo* as demonstrated in mast cell-deficient and reconstituted mice

Disease model	Putative mechanism	Involved cytokine	Reference
Late allergic response	Leukocyte infiltration	Proteases, biogenic amines, TNF- α	12,16
Immune complex-mediated peritonitis	Neutrophil recruitment	TNF- α	28
Contact sensitivity	Neutrophil recruitment; DC migration	TNF- α , MIP-2	23,32
Multiple sclerosis	Peripheral effects in lymphatic organs	Not determined	19,20
Bullous pemphigoid	Neutrophil recruitment	IL-8	22
Rheumatoid arthritis	Neutrophil recruitment	Not determined	21
Bacterial infection (innate response)	Neutrophil recruitment	TNF- α	4
Infection-induced lymphadenopathy	T-cell recruitment	TNF- α	25
Fibrosis	Increased α_1 -collagen	TNF- α , TGF- β	39

outside the central nervous system in this animal model of multiple sclerosis, pointing to a direct influence on B-cell and T-cell responses known to occur in this microenvironment.²⁰ By using the same experimental approach,

other groups have shown that mast cells are essential in mediating autoantibody-induced arthritis²¹ and the neutrophil infiltration that characterizes experimental bullous pemphigoid and T-cell-mediated cutaneous DTH.²²⁻²⁴

Mast cells appear to affect both the induction and elicitation phases of inflammatory processes by various mechanisms including cellular recruitment to inflamed tissues, induction of lymphocyte function, antigen presentation, T-cell polarization, and tissue remodeling^{1-3,24} (Fig 1). The effect of mast cells on lymphocyte and PMN recruitment into sites of inflammation has been established in both *in vitro* and *in vivo* systems. *In vivo*, by using W/W^v mice that were reconstituted with mast cells obtained from TNF^{-/-} mice, it could be shown that TNF- α and MIP-2 (the functional murine analogue of human IL-8) were essential for appropriate PMN recruitment during T-cell-induced cutaneous DTH reactions. Both cytokines were dependent on the presence of mast cells.²³ The combination of these 2 mediators is crucial for cell recruitment because TNF- α and MIP-2 provide 2 qualitatively different but synergistic signals. Mast cell-derived TNF- α has been shown to induce adhesion molecule expression required for both lymphocyte and PMN attachment to endothelial cells, whereas MIP-2 establishes a chemotactic gradient required for diapedesis and directed migration.³

The induction of MIP-2 and TNF- α 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 both TNF- α and MIP-2 production by mast cells.²³ Although the nature of these signals *in vivo* has not yet been defined, it seems reasonable to suggest that a direct cross-talk between these 2 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.^{9,10}

By using the same experimental approach, other investigators have shown that nodal T-cell recruitment during infection is mediated by mast cell-derived TNF- α , an effect that was associated with upregulation of vascular cell adhesion molecule expression in these lymph nodes.²⁵ Furthermore, mast cell-derived TNF- α may contribute to cell migration into sites of inflammation by priming sensory nerves, which in turn induce vascular hyperpermeability.²⁶ Other mast cell-derived mediators, such as IL-4, IL-13, and LTC₄, may further contribute, in a synergistic manner with TNF- α , to the stimulation of adhesion molecule expression by endothelial cells or fibroblasts.³

Mast cells have been found to be a source of several mediators shown to have a direct chemotactic effect on PMNs and T lymphocytes, including lymphotactin, IL-8, IL-16, MIP-1 β , and LTB₄. Interestingly, it has recently been reported that mast cell-derived LTB₄ differently affects subpopulations of CD8⁺ T cells. Thus, activated mast cells induced chemotaxis of effector, but not central memory, CD8⁺ T cells through production of LTB₄, indicating that mast cells may have a role in recruitment of effector CD8⁺ T cells to sites of inflammation.²⁷ Increased vascular permeability induced by mast cell-derived vasoactive amines, and degradation of extracellular matrix components by enzymes such as matrix metalloproteinase

9, which has also been shown to be released from mast cells on activation by T cells,¹⁰ may further facilitate cell migration through barriers such as the vascular wall and the blood-brain barrier.

A potential role for mast cells in autoantibody-induced arthritis has also been highlighted recently. Mast cell-deficient mice were resistant to development of joint inflammation, and susceptibility was restored by mast cell reconstitution.²¹ 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.^{21,24} 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 TNF- α , because TNF- α levels were significantly reduced in the W/W^v mice in association with a decrease in neutrophil accumulation.²⁸ Mast cell reconstitution normalized TNF- α levels and neutrophil mobilization. This induction of immune complex-mediated mast cell-dependent inflammation was shown to involve either IgG Fc or C3/C5a receptors.²⁹ Ligation of these receptors have been shown to be a potent activator of mast cell function *in vitro* and *in vivo*.^{30,31} 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 cells may also exert some immunoregulatory effects during the induction (sensitization) phase of nonallergic immune responses such as T-cell-mediated DTH or autoimmune processes.^{24,32} IgE, independent of exposure to a specific antigen, can promote optimal sensitization in experimental contact sensitivity by enhancing expression of mast cell-associated mediators that contribute to dendritic cell (DC) migration.³² This study demonstrates once again that mast cell-deficient mice have attenuated contact sensitivity. However, it should be noted that several groups have reported intact contact sensitivity responses in mast cell-deficient animals.³³ The reasons for the differences in the results obtained in the different studies are not yet fully understood. One possibility is that mast cell contributions to immune responses become most evident under specific conditions characterized by a low level of stimulation as found in the presence of low antigen exposure, less irritant vehicles, or vehicles with less or no adjuvant.^{16,32} Also, mast cells have been found to be differentially involved in DTH reactions induced by different antigens.³⁴

Mast cells are able to present antigens to T cells, resulting in their activation, in either a MHC class I or class II-restricted and costimulatory molecule-dependent fashion. Moreover, at the site of antigen entry, local release of mast cell cytokines and exosomes may influence both T-cell and B-cell function as well as DC maturation.^{35,36}

In addition to cytokines, granule-associated mediators such as histamine and tryptase are capable of regulating T-cell function, as manifested by differential effects on cytokine production.^{15,37} Further, mast cell derived cytokines such as IL-4 have been found to polarize T cells to differentiate preferentially into the T_H2 subset.³ On the other hand, T cells or their cytokines are capable of activating mast cells or controlling their numbers as well as altering some mast cell effector properties.^{3,38} Thus, T cell–mast cell interactions are bidirectional, fulfilling regulatory or modulatory roles affecting specific aspects of the immune response. On encountering antigens or activated T cells, mast cells can serve as antigen-presenting cells and release mediators that may activate other local inflammatory cells and recruit circulating cells into sites of antigen challenge.

Extending into another area of inflammation, several lines of evidence suggest that mast cells are involved in fibrotic processes and in tissue remodeling.^{1,2} Mast cells may exert bidirectional effect on matrix turnover. Tryptase and chymase have been shown to activate *in vitro* the zymogen forms of matrix metalloproteinases and procollagenase, thereby promoting matrix degradation.¹⁰ On the other hand, mast cell degranulation and proliferation have been documented in fibrotic processes *in vivo*, and certain mast cell mediators (ie, chymase, tryptase, TNF- α , b fibroblast growth factor, platelet derived growth factor, and TGF- β) have been found to exert fibrogenic effects by causing fibroblast proliferation and/or increased collagen synthesis.^{1,2,39} Mast cells are themselves capable of laying down some forms of extracellular matrix glycoproteins, thereby mediating matrix regeneration. Thus, mast cells are specialized to receive the appropriate signals to initiate an immune response by recruiting and activating relevant effector cells, and in a process that subsequently culminates in tissue repair.

One of the difficulties in determining mast cell function is the absence of a human disease characterized by the total absence of mast cells. However, this information is persuasive in developing an argument that mast cells are well engineered, highly developed, and critical to the induction of several specific and diverse immunologic processes in addition to allergic reactions. Thus, mast cells are no longer in the private domain of the allergists, and their role in various nonallergic inflammatory diseases may no longer be ignored. Elucidating the role of mast cells in health and disease will provide the necessary tools for the development of new therapeutic modalities focusing on attenuating mast cell disease–related proinflammatory effects without compromising their beneficial protective function.

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