

Mast Cell Modulation of the Immune Response

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Current Allergy and Asthma Reports 2009, **9**:353–359
Current Medicine Group LLC ISSN 1529-7322
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Mast cells are present in nearly all vascularized tissues, but not the blood. They are best known for the prominent role they play in atopic disease. However, our current understanding of their direct and indirect roles in the immune response offers a more nuanced picture of both villain and hero. Although they are implicated in many inflammatory disorders, they also defend us from bacterial pathogens, prevent dangerous overreactions by the immune system, and even protect us from snake venom. Perhaps there is more to these maligned cells than we thought.

Introduction

Mast cells have been accused and convicted—rightly so—for their well-documented role in allergy and asthma. Given that atopic disease is an established epidemic in many developed nations, their ability to elicit inflammation in response to dog dander and oak pollen makes these cells the target of much frustration. However, atopy and its best-known culprit are understood only after examining intent. Although mast cells harbor powerful mediators of the vasculature, respiratory, and gastrointestinal tracts, as well as the immune system, when and why they choose to use these weapons is more complicated than first thought. The old theory that mast cells have held sway in evolution because of the pressures of parasitic infection are likely correct, but today we also appreciate that these granulated denizens of the connective tissue and mucosa do much more than chase worms. New evidence supports a more detailed picture of a cell that rapidly takes up arms against venoms and bacteria and can even halt inflammation. Unfortunately, these strong-arm tactics are brought to bear not just in allergy, but perhaps in autoimmunity as well. This review presents the evidence for and against a complicated member of the immune system.

Culpability Starts With Location

If crime starts with opportunity, mast cells are situated to get into trouble. They begin their development in the bone marrow, branching off the hematopoietic stem cell at a very early stage. The earliest mast cell-committed precursor is derived from a multipotential progenitor prior to the common myeloid or common lymphoid progenitor stage. This precursor expresses c-Kit, T1/ST2 (the receptor for interleukin [IL]-33), and integrin β_7 and lacks Sca-1, Ly6c, and defined lineage markers (ie, it is Lyn-negative) [1]. Thus, whereas mast cells bear functional and genetic similarities to granulocytes, these lineages are distant cousins in ontogeny.

Importantly, mast cells do not complete their development in the marrow but leave as progenitors that differentiate in the connective and mucosal tissues. Although IL-3 is a strong proliferative factor for rodent mast cells, stem cell factor is the defining stimulus for mast cell development and survival [2]. Mature mast cells are found virtually everywhere, except in the bloodstream. They are prevalent in the dermis and mucosal lining of the respiratory, genitourinary, and intestinal tracts. Thorough searches have also shown mast cells in nearly all vascular tissues, including the lymphoid organs and central nervous system (CNS) [3]. Tissue-wide dissemination is not the entire story: within these locations, mast cells are often found adjacent to nerves and blood vessels, partially explaining their rapid and profound effects on so many organs. This broad distribution is reminiscent of dendritic cells. As detailed subsequently, this is no accident. Like dendritic cells, mast cells appear as part of an early alert network that controls inflammation. With such opportunity, it is no wonder that mast cells often go astray.

How Mast Cells Are Activated

Their distribution is not the only factor making it inevitable that mast cells are involved in many inflammatory conditions. True to their role as early-activated innate immune cells, mast cells can be triggered by myriad stimuli, including IgE (with or without antigen), IgG, immunoglobulin light chain, complement components, neuropeptides, cytokines, microbial products, and physical stimuli (including heat, cold, and pressure) [4•]. Although each of these deserves attention, we address

recent advances in IgE and IgG signaling, as they have the most overt clinical linkage.

Mast cells express the high-affinity IgE receptor FcεRI. This heterotetrameric structure, composed of an IgE-binding α chain, a signal-amplifying β chain, and a disulfide-linked dimer of γ chains, is studied in great detail and is the most clinically relevant of mast cell activators [5,6]. Since the 1970s, it has been noted that IgE greatly increases FcεRI expression—more than 10-fold in vitro—by stabilizing the receptor and slowing its rate of turnover [7]. Although there is debate regarding the ability of monomeric IgE to activate FcεRI in the absence of antigen, a conservative view of this work is that small amounts of IgE–FcεRI aggregates form on the cell surface, providing a weak but important mast cell-activating potential. The result is that atopic patients with elevated serum IgE levels have mast cells bearing very high FcεRI levels and are poised for activation. In addition to IgE, other stimuli can regulate surface FcεRI levels, including cytokines such as transforming growth factor (TGF)-β and IL-10 that suppress IgE receptors [8], and the Rab5-interacting protein Rabaptin-5 that is required to maintain FcεRI surface stability [9•].

IgG-mediated mast cell activation was studied for some time but is now better appreciated, as mast cells are linked to autoimmune disease. There are differences in rodent and human systems, with mouse mast cells expressing the activating IgG receptor FcγRIII, whereas at least some human mast cell populations may only express FcγRI as an activating receptor. Both populations express the inhibitory IgG receptor FcγRIIb [4•]. The activating receptors share β and γ subunits with FcεRI and likely elicit similar downstream signaling events. Likewise, FcγRIIb can be co-aggregated with IgE as well as IgG receptors, suppressing either pathway [10].

Receptor Signaling Events

The pathways leading to mast cell activation from IgE and IgG receptors are orchestrated by the presence of immunoreceptor tyrosine-based activation motifs (ITAMs) found on the β and γ chains. Antigen-mediated interactions with the receptor trigger aggregation that activates the Src family kinase Lyn, which phosphorylates ITAMs on their tyrosine residues. The receptor subunits then become docking sites for other kinases, and a signaling cascade ensues. This signal transduction pathway has been examined in great detail in recent reviews [11,12], but an overview of these events is warranted here. After Lyn, the tyrosine kinases Syk and Fyn are recruited to the receptor. Syk is known to bind the γ chains, whereas Fyn may interact with the β subunit. These two enzymes organize overlapping but somewhat distinct cascades that can be (somewhat simplistically) summarized as follows.

Syk phosphorylates the key adapter protein linker of activated T cells, which activates the enzyme phospholipase C γ (PLCγ). PLCγ cleaves phosphatidylinositol 4,5

bisphosphate (PIP₂) into inositol trisphosphate and diacylglycerol, which collectively promote calcium release from the endoplasmic reticulum (and, subsequently, calcium flux across the cell membrane). Calcium promotes both degranulation and cytokine production. Fyn kinase phosphorylates the adapter Grb2-associated binding protein (Gab2), which leads to the recruitment and activation of phosphatidylinositol 3'-kinase (PI3K). Like PLC, PI3K targets PIP₂, but rather than cleavage, PI3K elicits phosphorylation, producing PIP₃. Kinases in the Tec family bind PIP₃, particularly Bruton's tyrosine kinase and Akt. These kinases phosphorylate several downstream mediators, with Bruton's tyrosine kinase feeding into the calcium flux cascade, while Akt activates the inhibitor of κ-binding kinase. Collectively, these events, like Syk signaling, lead to degranulation and cytokine production. Degranulation events are organized by membrane fusion proteins in a family termed *soluble N-ethyl-maleimide-sensitive-factor-attachment proteins*. Cytokine production is controlled at the transcriptional level by several families of proteins, including nuclear factor-κB, nuclear factor of activated T cells, and signal transducers and activators of transcription [9•].

It is not surprising that these activating signals are held in check by antagonistic inhibitory events. Although they are generally less understood than the activating cascades, recent advances have shed new light on mast cell inhibition. Although Lyn kinase initiates signaling at the receptor, it appears to rapidly recruit negative regulators that subsequently dampen mast cell activation. In this sense, Lyn may be the fulcrum on which the mast cell response pivots. Lyn activates—directly or indirectly—the ubiquitinating protein Cbl, as well as the inositol phosphatase SHIP-1 (Src homology inositol phosphatase) and the tyrosine phosphatase SHP-1 (Src homology tyrosine phosphatase) [13]. These proteins collectively suppress activating signals by promoting protein degradation (Cbl) or by undoing the phosphorylating events started by kinases (SHIP, Shp). An important caveat to these findings is that Lyn's negative functions are most overt in some strains of mice (eg, the 129 strain clearly shows negative regulation by Lyn, whereas C57BL/6 mice show mostly positive signals) [14]. This leaves one to wonder if human populations may bear some resemblance, with differences in Lyn expression or function among atopic versus nonatopic patients. A second powerfully negative mediator of mast cell signaling is the IgG binding receptor FcγRIIb (CD32). Instead of an ITAM, CD32 contains an immunoreceptor tyrosine-based inhibitory motif, which binds the SHIP phosphatase. Along with Lyn, CD32 suppresses mast cell activation. It is interesting to note that loss of either Lyn or CD32 expression in mice leads to a collection of pathologic events, including autoantibody production and glomerulonephritis, that mimic human lupus. Mast cells from these mice

are also hyperresponsive [15,16]. Although many cell types can be altered by the loss of Lyn or CD32, a role for mast cells in lupus should be considered.

Mast Cell Interactions in the Immune Response

When considering how mast cells function in health and disease, their intersections within the immune network are a logical starting point. Because the immune response is a chain of events, we should begin at the beginning. Protective immunity is initiated with antigen trapping by dendritic cells in the periphery, which occurs simultaneously with recognition of the infectious agent by tissue-bound macrophages and mast cells, both of which promote inflammatory infiltration. Dendritic cells travel to a draining lymph node and present processed antigen to a naïve T cell. This interaction activates the T cell, possibly polarizing it to a cytokine-producing subset, such as T-helper (Th) type 1, Th2, or Th17. The newly activated T cell then initiates a response involving B-cell activation and furthers the recruitment of innate immune cells (neutrophils, eosinophils, or macrophages) to the area of infection. Over a period of a few days, this response should clear the infection and then subside, restoring tissue homeostasis. Pathology comes from too little or too much immune response; this is where the mast cell can get into trouble.

Let us first consider the innate response, especially leukocyte infiltration into the tissue. Mast cells are best linked to atopy. Atopic diseases typically involve the recruitment of eosinophils, which subsequently promote tissue damage and remodeling. Mast cells are well established as eliciting allergic disease and release many products capable of attracting eosinophils, including cytokines (eg, IL-5, IL-13), chemokines (eg, CCL-3), and arachidonic acid metabolites (eg, leukotriene [LT]B₄) [17]. Eosinophil migration is critical to resistance to parasitic infection. Mast cells are implicated in immunity to helminthic parasites in part because of their ability to recruit eosinophils [6]. However, eosinophils are not the only innate immune cells attracted by mast cells. As noted in several bacterial infection models, mast cells are potent and critical activators of the neutrophil response. Much of this activity is ascribed to mast cell-derived tumor necrosis factor (TNF) secretion, although some TNF-independent effects are cited. In the absence of mast cells, mice succumbed to bacterial infection in several models [18]. Hence, it is apparent that mast cell modulation of the innate response is a matter of when and why. In this context, atopic disease represents the misdirected use of a normally protective mast cell response.

Mast Cells and the Adaptive Immune Response

A role for mast cells in innate immunity is logical given their rapid response mechanisms, but their importance in adaptive immunity is gaining support. New evidence indi-

cates that mast cells interact with dendritic cells, offering a plausible link to lymphocyte activation. We consider how mast cells alter dendritic cells and T cells, as dendritic cell-T-cell interactions set the stage for the adaptive response. The effects of mast cells in the adaptive response were reviewed recently, and we refer the reader to these reviews for a more complete set of references [4•,18].

The most overt data supporting a role for mast cells come from murine models of bacterial infection. In either peptidoglycan or *Escherichia coli* infection models, mast cell-deficient mice demonstrate defective lymph node hyperplasia, an indication of diminished T-cell clonal expansion. This defect is associated with poor dendritic cell migration to the draining lymph nodes. Coculturing dendritic cells with activated mast cells leads to dendritic cell activation, as judged by increased expression of CD80, CD86, CD83, CCR7, major histocompatibility complex (MHC) I, and MHC II. These effects are likely caused in part by histamine released during mast cell activation. Dendritic cells express all four known histamine receptors, and histamine is shown to enhance antigen uptake and presentation, as well as dendritic cell chemotaxis. However, mast cell-derived TNF also activates dendritic cells. One confusing aspect of the literature in this area is the apparent ability of mast cells to affect dendritic cell-mediated T-cell polarization to the Th1 or Th2 lineages. For example, mast cell products such as thymic stromal lymphopoietin, histamine, prostaglandins, and LTs can alter dendritic cell function to promote Th2 differentiation, perhaps by suppressing IL-12 production. At least one study found that mast cell activation, with histamine release in vivo, enhanced dendritic cell-mediated induction of Th2 development [19]. However, Gregory et al. [20] found that mast cell-derived IL-4 enhanced dendritic cell-mediated Th1 development, a result that is at first counterintuitive. A plausible explanation is that IL-4 suppresses dendritic cell-mediated IL-10 production [21], a cytokine that can prevent IL-12 secretion; hence, the presence of IL-4 actually promotes IL-12 secretion indirectly. The effects of mast cells on dendritic cells clearly are contextual, much like T-cell polarization. It is worth noting that mast cell activation is not an all-or-nothing event. Instead, mast cells can degranulate in a piecemeal fashion and can selectively secrete newly synthesized mediators [18]. Thus, the various effects of mast cells on adaptive immunity in general and dendritic cells in particular could rely on the strength and means by which mast cells are triggered.

A role for mast cells in T-cell activation also should be considered. Studies dating to the late 1990s have presented in vitro evidence that mast cells express functional MHC II and can present antigen [4•]. There is also evidence that surface FcεRI can facilitate antigen uptake and that subsequent mast cell apoptosis allows these cells to be phagocytized and the ingested antigen presented [22]. In addition to MHC II, mast cells express several “signal 2” costimulatory mediators, including CD80, CD86,

CD153, 4-1BB, CD40L, and OX40L, and can produce the cytokines known to polarize T-cell differentiation to Th1 (interferon- γ , IL-12), Th2 (IL-4, IL-13), Th17 (IL-6, TGF- β), or T-regulatory cells (Tregs; IL-2, TGF- β) [4•,18].

Some of the more intriguing new data in this area relate to mast cell–Treg interactions. Tregs are powerfully suppressive and represent a means by which autoimmunity may be controlled [23]. Lu et al. [24] recently showed that skin graft tolerance required not just the presence of Tregs in the grafted tissue but mast cell migration as well. Treg-derived IL-9 may be the stimulus attracting mast cells to the grafted tissue [24]. The means by which mast cells contribute to graft tolerance or immunosuppression are not entirely clear. In this regard, two additional articles should be mentioned. Treg-mediated suppression of mast cell degranulation, with no change in IgE-mediated cytokine secretion, was recently demonstrated [25]. These data are in contrast to an article from our group showing Treg-mediated enhancement of IgE-induced cytokine production [26]. Both assay systems showed that cell–cell contact was required and that OX40 expression on Tregs was necessary to suppress degranulation in the former article. A key difference in the two systems was timing. Our group studied mast cells cocultured with T cells for 4 days, a time point chosen because we have frequently found mast cell feedback signals at this interval [8]. In contrast, mast cell suppression was noted when Tregs were added to mast cells at the time of antigen challenge, or at most 16 hours beforehand [25]. It will be interesting to decipher how this timing may alter signaling events. Gri et al. [25] found that Treg-enhanced mast cell cyclic adenosine monophosphate levels may have suppressed IgE-mediated signals. Our group found enhanced Stat5 activation in mast cells cocultured with Tregs [26], likely explaining the increased cytokine production [27]. T-cell interactions, especially those between mast cells and naïve Th cells or Tregs, are a potentially critical means by which mast cells may alter the adaptive response. We look forward to new advances in this area.

Mast Cells and Inflammatory Disease

With their entire inflammatory armament and an ability to modify the adaptive response, it is no surprise that mast cells contribute to inflammatory disease. Rather, the depth of their involvement has proven more striking than previously appreciated. Certainly the role of mast cells in type I hypersensitivity is well established [17]. Mast cell activation via IgE–antigen interactions contributes both to the initiation of early events—via histamine, protease, and arachidonic acid metabolite secretion—and to the delayed inflammatory infiltrate through the production of cytokines and chemokines. Although murine models of airway hyperresponsiveness have shown that airway inflammation can occur without mast cells [28], mast cells likely have a prominent role in humans. Recent evidence from a murine model also

showed that mast cells contribute to Th17-driven, neutrophil-mediated airway inflammation [29]. In the realm of asthma, allergic rhinitis, atopic dermatitis, and food allergy, mast cells are logical and important players, but does the story end there?

New evidence, mostly from murine model systems, impugns the mast cell from seemingly every immunologic angle, fingering these cells as a culprit in types II, III, and IV hypersensitivity. Sayed et al. [4•] recently published an articulate and detailed review of this subject that included data suggesting that mast cells worsen the inflammatory response in autoimmune arthritis, multiple sclerosis (MS), bullous pemphigoid, Graves' ophthalmology, inflammatory bowel disease, Guillain-Barré syndrome, type 1 diabetes, and systemic sclerosis. Most of the support for a role for mast cells in these models is compelling, if somewhat circumstantial. This includes the presence of mast cells (often in increased numbers in inflammatory lesions), evidence of mast cell activation prior to disease onset, and diminished symptoms after treatment with mast cell–stabilizing agents (which can have additional actions outside the mast cell compartment). A simple view of this situation is that mast cells are powerful initiators of the immune response and are likely involved in at least the early stages of many inflammatory diseases. A wonderful benefit from the long history of mast cells in atopic disease is that we have considerable means to suppress mast cell activation, including antagonists of histamines and LTs, steroid-based cytokine/chemokine suppression, antigen-specific immunotherapy, and anti-IgE-mediated suppression. These tools may be useful in diseases not previously considered within the purview of mast cell biology.

Barring a full discussion of all the inflammatory diseases in which mast cells participate, we would like to focus on the role of mast cells in MS, for which evidence has persisted for two decades. With mast cells being located in the CNS and with an ability to respond to many stimuli, recruit and activate dendritic cells, and modify T-cell function, they are a logical participant in MS. In fact, MS patients were found to have elevated cerebral spinal fluid titers of histamine and tryptase [30,31], and CNS plaques analyzed by genome screening show expression of tryptase and Fc ϵ RI [32]. A link between mast cells and MS was noted using the animal model experimental autoimmune encephalomyelitis (EAE) since 1989 [33]. These early reports generally showed that mast cells were present in or near EAE lesions, that their numbers or activation changed with disease onset, and that mast cell–stabilizing agents could delay symptoms [33–35]. These data were bolstered more recently by evidence that mast cell–deficient Wv mice have a late onset of EAE and a near 50% reduction in disease scores [36], as well as reduced CD4 and CD8 T-cell numbers in the CNS [37]. Mast cell expression of the activating IgG receptor Fc γ RIII was required for full disease induction [38], suggesting a role for immune complexes. Importantly, mast

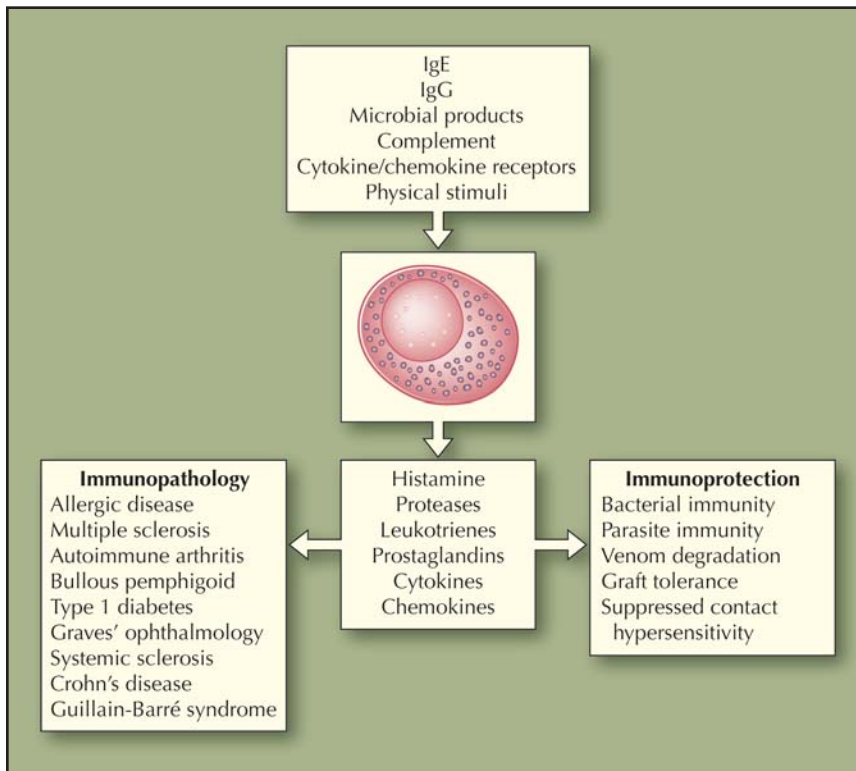


Figure 1. The role of mast cells in immune regulation. Mast cells are activated by many stimuli, allowing them to function as early activators of the immune response. Their biphasic response, first releasing preformed mediators and arachidonic acid metabolites and followed by cytokines and chemokines, can be selective. Coupled with the range of factors they produce, mast cells have the ability to augment or suppress immune function. They are linked, at least circumstantially or through animal models, to several important inflammatory or immuno-protective responses.

cell reconstitution of Wv mice restored the normal course of EAE but did so without repopulating mast cells in the CNS [39]. Thus, it appears that at least in the EAE model, the essential role for mast cells may lie outside the CNS, perhaps in immune activation at the lymph node. This hypothesis fits with evidence that mast cells promote dendritic cell trafficking and are required for lymph node hyperplasia [40]. It is not completely clear that mast cell blockade after EAE is established would be protective. In fact, early reports showed that mast cell stabilizers slowed disease onset but did not ultimately alter severity [33–35]. Given the early responder role of the mast cell, its most plausible role is in disease induction, meaning that mast cell-directed therapies may not provide significant relief to patients with active MS. However, many MS patients develop a relapsing–remitting form of the disease [41]. One wonders if mast cell-directed agents used during remission would prevent or delay disease recurrence.

Mast Cells and Immune Tolerance

Recent data offer a view of mast cells quite contrary to the one to which we have become accustomed during the past 40 years. Rather than just driving inflammation, mast cells sometimes suppress it (Fig. 1). Animal models now show that mast cells suppress the immune response to UV-B light [42,43]; mosquito bites [44]; skin grafts [24]; and some forms of contact hypersensitivity, including a common culprit, poison ivy [45•]. Additional and exciting findings include the demonstration that mast cell proteases degrade the sarafotoxins in bee and snake venoms [46]. Although this latter finding shows a prominent role

for carboxypeptidase A3 [47], most suppressive effects may be attributed to production of inhibitory cytokines, such as IL-10 and TGF- β_1 [8]. In fact, mast cell-derived IL-10 is required for contact hypersensitivity suppression in at least one animal model [45•]. These data illustrate that mast cells maintain a functional duality (they are “tunable,” to borrow a phrase from Galli et al. [6]).

Conclusions

Mast cells are not simple allergy antagonists. It has been 20 years since we first fully appreciated that these IgE-responsive sacs of histamine also make cytokines [48], complicating our view of their life and livelihood. We now know they are present in nearly all tissues, respond to many stimuli besides IgE, and can shift the immune response with impressive agility. Fully understanding the mast cell life cycle may provide fundamental insights that will yield progress in myriad areas of immunology. Controlling their migration, proliferation, activation, suppression, and death will offer tools that can likely be used at least in the initial stages of many inflammatory diseases. The most recent data demonstrate that mast cells are productive and important members of the immunologic society. What we need is a means to reduce mast cell recidivism—the knowledge to keep these cells out of trouble and put them to good use.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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- Of major importance

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One of a handful of articles demonstrating the suppressive role of mast cells in disease, this article focuses on the production of IL-10 and offers surprising results.