Current perspectives

Mast cells in innate immunity

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Mast cells have been most extensively studied in their traditional role as an early effector cell of allergic disease. However, in the majority of individuals, it might be the role of this cell as a sentinel in host defense that is most important. Mast cells have been repeatedly demonstrated to play a critical role in defense against bacterial infections, and evidence for their involvement in early responses to viral and fungal pathogens is growing. Mast cells are activated during innate immune responses by multiple mechanisms, including well-established responses to complement components. In addition, novel mechanisms have emerged as a result of the explosion of knowledge in our understanding of pattern-recognition receptors. The mast cell shares many features with other innate immune effector cells, such as neutrophils and macrophages. However, a unique role for mast cells is defined not only by their extensive mediator profile but also by their ability to interact with the vasculature, to expedite selective cell recruitment, and to set the stage for an appropriate acquired response. (J Allergy Clin Immunol 2004;114:21-7.)

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Abbreviations used
LT: Leukotriene
TLR: Toll-like receptor

EVIDENCE FOR MAST CELLS HAVING A ROLE IN INNATE IMMUNITY

The activation of innate immune responses occurs as a result of tissue injury or in response to more selective recognition of pathogen-associated products. As resident cells within the tissues that interface with the external environment, such as the skin, airways, and intestine, mast cells are well placed to initiate and enhance early responses to a variety of challenges. Acute mast cell activation is a feature of many types of tissue injury, as well as responses to a number of nonpathogen-associated inflammatory stimuli. It has been known for many years that pathogen products can also activate mast cells. Initially, studies focused on mast cell degranulation, and a number of parasite and bacterial products were shown to induce such responses, including structural components, toxins, and immunoglobulin-binding proteins. More recently, similar properties have been shown to be shared by a number of viral proteins or host proteins upregulated as part of the antiviral response.[1,2]

Direct evidence of a role for mast cells in host defense against bacterial pathogens did not become available until the mid-1990s after studies that indicated that mast cells could produce cytokines in response to LPS without degranulation.[3] In both a model of cecal ligation and puncture[4] and a model of *Klebsiella pneumonia*–induced peritonitis,[5] mice with normal numbers of mast cells survived bacterial challenge, whereas mast cell–deficient W/Wv mice succumbed to infection. When mast cells were selectively reconstituted in the peritoneal cavity, the ability to overcome infection was restored. The presence of mast cells was closely linked to the ability to rapidly recruit neutrophils to the site of infection, adding to the concept that the mast cell serves as a critical mobilizer of innate immune responses through early mediator production. The importance of TNF in this process was confirmed by studies in which mice were treated with anti-TNF antibodies. It was suggested that the mast cell was the

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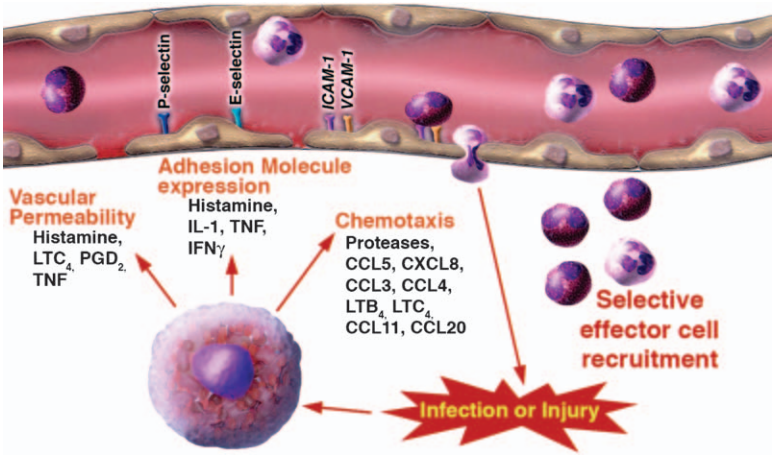

FIG 1. Mast cells induce effector cell recruitment through multiple interactions with the vasculature. After mast cell activation as a result of pathogens, their products, or other mediators associated with tissue damage, mast cells selectively produce some of a wide range of potential mediators with effects on the vasculature. These include those capable of increasing vascular permeability and enhancing adhesion molecule expression and some that are directly chemotactic for specific types of effector cells, such as neutrophils or eosinophils. Mediators from each of these classes can be produced in response to pathogen products without a requirement for classical mast cell degranulation to occur. However, preformed mast cell mediators, such as histamine and proteases, can also be critical contributors to the process of cell recruitment.

major source of early TNF, which is in keeping with observations of neutrophil recruitment after IgE-mediated mast cell activation.[6] However, other effector cells, such as macrophages, might also contribute to local TNF production in these models in response to early mast cell mediators, such as histamine or leukotrienes (LTs).[7]

In the context of viral infection, there is much less known regarding the implications of mast cell activation to host defense *in vivo*. However, recent studies with human mast cells have demonstrated that they can respond to a number of viruses and viral products to produce mediators essential to innate immunity. Not only has mast cell degranulation been observed in response to proteins derived from HIV and other viruses,[1] but also active infection of human mast cells with dengue virus has been associated with the production of a specific profile of chemokines and cytokines, including IL-1β, IL-6, CCL3, CCL4, and CCL5, with the ability to activate endothelial cells and potentially recruit effecter cells to the site of infection.[8] In the airways respiratory syncytial virus[9,10] and Sendai virus[11] have both been associated with changes in mast cell numbers or function, which might be indicative of pathogen-induced mast cell activation, perhaps in the absence of classical degranulation.

EFFECTOR MECHANISMS OF MAST CELLS

The ability of mast cells to substantially enhance the recruitment of neutrophils in the context of bacterial infection has been well documented. Mast cell production of TNF, initially through limited preformed stores and then rapidly newly generated, plays a critical role in this process.[4] However, other aspects of mast cell activation are likely to contribute to the appropriate and rapid local response to infection (Fig 1). A number of preformed mast cell mediators act on the vasculature to enhance cell recruitment. Histamine is well documented to have multiple effects leading to increased vascular permeability and enhanced adhesion molecule expression, such as upregulating P-selectin, which mediates neutrophil adhesion and recruitment.[12] Mast cell proteases have also been elegantly demonstrated to play critical roles *in vivo* in the recruitment of both neutrophils and eosinophils to sites of inflammation.[13,14] Changes in vascular permeability induced by early release of preformed mediators and lipid mediators enhance the availability of complement components and some initial inflammatory cells to the site of infection. The mast cells' early production of TNF,[15] IL-1α,[16] IL-1β, and other major proinflammatory cytokines is the basis of the ability of these cells to enhance the adhesion molecule expression necessary for effective cell recruitment. In addition, the mast cells' selective and sequential production of a variety of chemokines and chemotactic lipid mediators provides a key stimulus for the initial migration of cells out of the vasculature. Mast cells are likely to be particularly effective in aiding cell recruitment in view of their strategic association with blood vessels, an anatomic relationship that occurs throughout the body. An examination of the time course of different mediators produced by mast cells in response to complex pathogens reinforces this concept. In the initial few minutes after mast cell exposure to certain types of bacteria, TNF, histamine, and proteases are released that enhance vascular permeability and increase adhesion molecule expression. In response to some pathogens and their products, LTB_4 and LTC_4 will also be generated with the ability to enhance these processes and act as chemotactic agents for neutrophils and eosinophils. Even in the absence of degranulation, certain bacteria, such as *Pseudomonas aeruginosa*, and certain viral

infections have been demonstrated to induce multiple cytokines and chemokines from human mast cells, including TNF, IL-1β, IL-6, CCL5, and CCL20.[17] Although some of these cytokines are produced early, others, including CCL20, are more associated with the long-term recruitment of immature dendritic cells and T cells because they are produced over a longer time course of 24 to 48 hours or more.

The role of mast cells in innate immunity is not, however, limited to the direct recruitment of effector cells. Mast cell–dependent alterations in vascular permeability provide an optimal environment for the effective functioning of the complement cascade in the extravascular environment and for access of other innate effector mechanisms. Mast cell–dependent physiologic changes in the airways, such as bronchoconstriction, increased intestinal motility, and epithelial sloughing, might represent other aspects of early innate defense mechanisms. In addition, under some circumstances, mast cells might respond through pathogen phagocytosis,[18] a mechanism that might be enhanced by local complement fixation.

The production of antimicrobial peptides by mast cells is another potentially important aspect of their function in innate host defense. Cathelicidins and defensins are major families of antimicrobial peptides in mammals. Their function is to disrupt the integrity of the microbial membrane, which is mediated by their cationic and amphipathic properties, which enable them to bind to negatively charged microbes and insert into their membranes. The human cathelicidin (LL-37) and the murine cathelicidin-related antimicrobial peptide (CRAMP) are both expressed by mast cells.[19] Murine mast cells also express mRNA for β-defensin-4, an antimicrobial peptide that shares greatest homology with human β-defensin-2, which is abundantly present in inflamed skin. LPS activation of mast cells has been shown to induce CRAMP mRNA more than 6-fold, as well as to increase secretion at the protein level. The importance of CRAMP to the antimicrobial activity of mast cells was demonstrated by using mast cells deficient in the *CRAMP* gene ($Cnlp^{-}$), which had a 50% reduction in their ability to kill group A streptococci. Whether mast cells predominantly release cathelicidin extracellularly or kill the microbe intracellularly after uptake still needs further investigation.

Patients with atopic dermatitis have been shown to lack LL-37 expression, which might provide an explanation for the increased susceptibility of these patients to skin infections.[20] However, the contribution of the mast cell to this deficiency has not been examined. In addition to their antimicrobial effects, cathelicidin LL-37 has been shown recently to have chemotactic effects on mast cells, which might aid in the migration and accumulation of mast cells at the site of inflammation in several diseases.[21] Cathelicidin LL-37 has also been shown to induce mast cell degranulation and the release of histamine and prostaglandin D_2,[22] which could help in the recruitment of neutrophils to the site of inflammation and subsequent bacterial clearance.

SETTING THE STAGE FOR AN OPTIMAL ACQUIRED RESPONSE?

Like other cells involved in the innate immune response, mast cells appear to have a role in enhancing and influencing the nature of the acquired immune responses. The ability of mast cells to influence the maturation and function of dendritic cells is of particular interest in this context. Mast cells and dendritic cells are both frequently located at sites exposed to the external environment and sometimes in close proximity to each other. However, dendritic cells lack the close relationship with the vasculature exhibited by mast cells. One recent study reported that mast cell exosomes induce maturation of dendritic cells through the upregulation of MHC class II, CD80, CD86, and CD40 molecules.[23] They also demonstrated that antigen-containing exosomes could elicit an effective immune response in naive mice across an MHC-II barrier. The mechanism of action of exosomes was reported to be dependent on heat shock proteins. Here it is notable that heat shock proteins have also been demonstrated to be effective activators of Toll-like receptors (TLRs). Some mast cell effects on immature dendritic cells might also be mediated by histamine, which induces the expression of CD86, as well as upregulating the expression of accessory molecules.[24] Histamine treatment of dendritic cells has been shown to aid in T-cell polarization toward a T_H2 response.[25]

Another recent study has demonstrated that mast cell activation by bacteria or other degranulating stimuli induces the swelling of local lymph nodes.[26] This process involves the production of TNF by local mast cells and results in the increased accumulation of T cells in the draining nodes. This finding has important implications for the ability of mast cells to assist in providing a favorable environment for effective antigen presentation, particularly when viewed in the context of potential mast cell contributions to the mobilization and maturation of dendritic cells. It is clear that mast cell–deficient mice are capable of mounting normal antibody and T-cell responses after antigen administration. However, detailed studies examining the ability of mast cells to modify the speed, effectiveness, and polarization of acquired immune responses might be important now that we have a better understanding of the potential for mast cells to become activated and selectively produce mediators in the context of pathogen exposure or tissue injury.

SELECTIVE MEDIATOR PRODUCTION IN RESPONSE TO DIFFERENT PATHOGENS AND THEIR PRODUCTS

Although early mast cell TNF production is certainly the best-studied mechanism in the context of innate immunity, the range of responses that mast cells are capable of is impressive. In addition to their potential for degranulation, associated with the release of a plethora of preformed mediators, such as highly bioactive proteases,

histamine, and proteoglycans, mast cells also produce a wide range of cytokines and chemokines.[27] Both human and rodent mast cells also produce lipid mediators, such as LTC_4 and LTB_4, in response to bacterial activation.[7,28] Existing evidence suggests that the profile of mast cell mediators produced is tightly controlled with respect to the type and amount, as well as temporal sequence. Although some pathogen products induce the release or generation of preformed mediators, lipid mediators and cytokines have a more selective effect.[28] LPS will induce inflammatory cytokine production from rodent mast cells or IL-4/IFN-γ–pretreated human mast cells without substantial degranulation. Other bacterial products, such as *Staphylococcus aureus*–derived peptidoglycan or the yeast cell-wall component zymosan, will induce LTC_4 production from human mast cells without significant degranulation. The profiles of cytokines and chemokines induced also vary widely. For example, human mast cells treated with dengue virus in the presence of subneutralizing concentrations of antibody produce large amounts of CCL5 and smaller IL-1β, IL-6, and CCL3 responses but have no significant GM-CSF or CXCL8 response.[8] Similarly, mast cells treated with bacterial peptidoglycan, zymosan, or a tripalmitoylated synthetic lipopeptide all have profound GM-CSF and IL-1β responses but only produce limited amounts of CCL5 and IL-6.[28] The extent to which such differential mediator responses by mast cells alter the effectiveness of the innate immune response and the polarization of the subsequent acquired response remains to be determined. However, understanding the molecular basis for such selective mast cell activation might provide opportunities to modify mast cell behavior therapeutically in the context of vaccine development or allergic disease.

MECHANISMS OF MAST CELL ACTIVATION IN INNATE IMMUNITY

TLRs

There has been enormous recent progress in our understanding of the mechanisms by which innate immunity is mobilized.[29,30] The TLR family of pattern-recognition receptors has been demonstrated to have a pivotal role in many host defense mechanisms. This highly conserved group of proteins functions within a multimolecular complex, which usually consists of a TLR homodimer or heterodimer, as well as a number of coreceptors and intracellular, as well as extracellular, adaptor molecules. Different TLR family members are activated by different pathogen-associated or endogenous proteins. A variety of Toll activators have been defined, which include products from all classes of mammalian pathogens, as well as endogenous proteins, some of which are known to activate mast cells (Table I).[1,31-46] For example, TLR4 has been shown to mediate responses to most types of LPS, as well to a number of other pathogen products, and to heat shock protein 60, which might be released on cell stress. In contrast, TLR2 mediates responses to peptidoglycan from many gram-positive bacteria and the yeast cell-wall component zymosan, whereas TLR9 mediates responses to CpG motifs found within bacterial DNA.[40,41]

The mast cell uses selected TLRs, as well as a number of other receptor systems, to respond to pathogens. By using TLR-deficient mice, it has been demonstrated that both *in vivo* and *in vitro* murine mast cells respond to LPS through TLR4 and bacterial peptidoglycan through TLR2.[47-49] The effective response to LPS is dependent on a source of soluble CD14 because, in contrast to monocytes and macrophages, mast cells generally lack expression of this critical coreceptor molecule. The lack of mast cell CD14 expression might provide a partial explanation for the observation that much greater (10- to 100-fold) concentrations of LPS are required to activate mast cells than are optimal for macrophage activation or neutrophil priming. Some human mast cell populations have very low or absent levels of TLR4 expression and function.[28] LPS-mediated human mast cell activation has been best demonstrated after pretreatment with either IL-4 or IFN.[50,51] Expression of TLR4 by human mast cells *in situ* has not yet been shown. It remains possible that TLR4-mediated human mast cell activation might only occur after appropriate cytokine priming during infection or inflammatory disease.

TLR2-mediated mast cell activation occurs at doses of activators similar to those demonstrated to be effective in other cell types. The mast cell response to peptidoglycan derived from *S aureus* has been studied with particular interest in view of the potential importance of this organism in the pathogenesis of atopic dermatitis. In some studies peptidoglycan has been suggested to induce mast cell degranulation, with a mast cell–dependent eosinophilic inflammatory response observed in mice after peptidoglycan treatment.[48] Both peptidoglycan and zymosan, which use a TLR2/TLR6 heterodimer, have been shown to induce an LTC_4 response from mast cells. However, not all TLR2 activators have this effect. For example, the TLR2/TLR1-activating lipopeptide Pam $_3$CysSerLys$_4$ does not induce LTC_4 production from human mast cells. These differences in response could result from differences in TLR use or occur as a result of changes in activation of coreceptors or alternate receptor systems. Currently, we lack direct evidence that TLR-mediated signaling is responsible for lipid mediator production from mast cells in response to known TLR activators, although both degranulation and cytokine production from mast cells has been shown to be TLR dependent in murine[47-49] and human[50,51] models.

Complement

The recent excitement regarding TLRs and other newly defined innate pathways needs to be considered in the context of existing evidence regarding mast cell activation by inflammatory mediators produced during infection. Most notably, complement fixation is a feature of the innate response to many types of infections and tissue damage and has been recognized to alter mast cell function. Human mast cells express multiple receptors

TABLE I. Examples of pathogen receptor systems known to be capable of activating mast cells

Receptor	Ligand	References
TLR1	Lipopeptide (Pam3Cys Ser Lys4)	31
TLR2	Peptidoglycan (*S aureus*), zymosan, LTA, Lipopeptide (Pam3CysSer Lys4), LPS	32-34
TLR3	Poly I:C (dsRNA)	35
TLR4	LPS, RSV protein F, *Mycobacteria tuberculosis*	32,36,37
TLR6	Peptidoglycan (*Staphylococcus aureus*), zymosan,	38,39
TLR9	Bacterial DNA (CpG DNA)	40,41
Unknown carbohydrate	Mannose-binding protein SM60 (*Schistosoma mansoni*)	42
CD48	FimH protein (Fimbriated *Escherichia coli*)	43
FcγR/IgG	Protein A (*S aureus*)	44
FcεRI/IgE	GP120 (HIV-1)	1,45
FMLP receptors	GP41 (HIV)	46

for complement components, including CD11b (CR3), CD11c (CR4), and functional receptors for C3a and C5a.[53] In a mast cell–dependent murine model of bacterial infection, it has been demonstrated that complement also has a key role. Both C3- and C4-deficient mice demonstrated increased susceptibility to infection and reduced mast cell activation.[54] Complement-dependent signals are likely to be an important component of the mechanisms by which mast cells are activated during infection. The ability of complement components to selectively induce cytokines or lipid mediators from mast cells has not been extensively studied, but it is clear that many mast cell populations, including human skin mast cells, will degranulate in response to complement product activation. In addition, C3a and C5a have been shown to be chemotactic for mast cells,[53] potentially recruiting further mast cells to sites of infection. Some apparent differences between *in vitro* and *in vivo* studies of mast cell responses to pathogens might be explained by the lack of complement-mediated signals in cell-culture systems.

Pathogen-associated mannose-binding proteins

Pathogen-associated mannose-binding proteins have been demonstrated to induce mast cell activation, usually assessed through mast cell degranulation. In the context of innate immunity, the best studied of these is the FimH protein found on fimbriated *Escherichia coli*, which has been demonstrated to use CD48 to activate mast cells, inducing both degranulation and TNF production.[43] In addition, FimH-expressing bacteria have been demonstrated to undergo mast cell phagocytosis and killing through superoxide anion–dependent mechanisms, whereas bacteria lacking FimH are less susceptible.[55] Another mannose-binding protein from *Schistosoma mansoni* has also been shown to induce mast cell degranulation. In both cases mast cell–dependent neutrophil migration has been demonstrated in response to the actions of these mannose-binding proteins. The ability of CD48 to activate mast cells is particularly intriguing because it is a glycosylphosphatidylinositol-anchored protein that lacks signaling capacity. The ability of FimH to activate mast cells is not dependent on functional TLR4, but it is possible that CD48 might act as a coreceptor for another TLR or alternate pattern-recognition receptor.

Immunoglobulin-binding proteins

In vivo, under normal circumstances, mast cells express several Fc receptors, such as FcεRI and FcγRII, and can be activated through cross-linking of these receptors in the traditional manner by antigen to produce a full range of mediators. During inflammation and infection, particularly under circumstances in which the local cytokine milieu might include higher than usual levels of IFN-γ, the range of Fc receptors might change to include FcγRI.[56] In the context of an acquired immune response, the role of such receptors is obvious.

However, mast cell–bound immunoglobulin might also play a role in innate immune responses to pathogens that contain proteins capable of cross-linking occupied immunoglobulin receptors in a nonantigen-specific manner. Early examples of this type of response include the activation of human mast cells with protein A derived from *S aureus*, but other bacterial and important viral pathogens have been shown to share this effect, including Gp120 from HIV-1.[1] Endogenous proteins produced during viral infection might share these abilities, as suggested in recent studies of viral hepatitis.[2]

Other receptor systems

There are a variety of other receptor systems that have been implicated in the mast cell's innate response to pathogens. A recent and intriguing example is the ability of FMLP receptors to mediate the activation and chemotaxis of mast cells in response to synthetic peptides derived from the GP41 molecule of HIV.[46] A number of coreceptors for the TLR system have signaling capacity in their own right and might be important in mast cell activation to selected pathogens. Potential further examples include Dectin-1, mannose-binding protein, and other lectin-like receptor molecules implicated in other aspects of innate immune responses, as well as a number

of adhesion molecules with shared roles in innate immunity, such as CD11 family members.

BETTER DEFINING THE UNIQUE ROLE OF THE MAST CELL

Many of the mast cell receptors associated with pathogen recognition and responses, as well as the mediators produced after mast cell activation, are shared with other cell types, such as macrophages and neutrophils. Despite this apparent redundancy of function, *in vivo* mast cell deficiency is associated with a substantial impairment of certain aspects of innate immune function, particularly to bacterial pathogens. One reason for the mast cell's importance might be the rapidity with which mast cell mediators are produced when faced with the challenge of a rapidly dividing pathogen. Early TNF production by mast cells in response to pathogen stimulation also appears to be of critical importance. However, the close proximity of mast cells to the vasculature and the ability of mast cells to rapidly enhance all of the mechanisms necessary for effector cell recruitment through the combined effects of mediators that increase vascular permeability, upregulate adhesion molecules, and provide chemotactic stimuli for inflammatory cells, distinguishes mast cells from other innate immune cells. What we already know about the mast cell suggests that these cells might make useful targets in the development of novel adjuvant systems or for local modulation of immune and inflammatory responses. There are many puzzles remaining concerning the mechanisms of mast cell activation and their function in host defense. Through learning more about the role and regulation of this enigmatic cell type in host defense, we can begin to find better methods to harness the abilities of these cells for the treatment and prevention of disease and develop a greater understanding of critical mechanisms in innate immunity.

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