

Molecular mechanisms in allergy and clinical immunology

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Mast cell–T cell interactions

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In addition to being a major effector cell in the elicitation of allergic inflammation, mast cells have been found to be activated in various T cell–mediated inflammatory processes and to reside in close physical proximity to T cells. Such observations and the wide spectrum of mediators produced and secreted by mast cells have led investigators to propose a functional relationship between these 2 cell populations. Indeed, mast cell activation has been reported to induce T-cell migration either directly by the release of chemotactic factors, such as lymphotactin or IL-16, or indirectly by the induction of adhesion molecule expression on endothelial cells. Mast cells are also able to present antigens to T cells, resulting in their activation in either an MHC class I– or class II–restricted and costimulatory molecule–dependent fashion. Adhesion molecule–dependent intercellular contact or MHC class II cognate interactions between T cells and mast cells result in the release of both granule-associated mediators and cytokines from the latter. Also, T cell–derived mediators, such as β -chemokines, directly induce mast cell degranulation. On the other hand, mast cell–derived cytokines, such as IL-4, have been found to polarize T cells to preferentially differentiate into the T_{H2} subset. Thus T cell–mast cell interactions are bidirectional, fulfilling regulatory and/or modulatory roles affecting various aspects of the immune response. (*J Allergy Clin Immunol* 1999;104:517–23.)

Key words: Mast cell, T cell, adhesion, antigen presentation, chemotaxis, cytokines, degranulation, migration

Mast cells are known to be essential resident effector cells in the elicitation of the allergic response. IgE-sensitized mast cells, on encounter with specific antigen that is recognized by surface receptor (Fc ϵ RI)–bound IgE, secrete and generate bioactive mediators that facilitate the development of allergic inflammation.¹ Apart from activation by means of Fc ϵ RI, mast cells are also activated by cross-linking of surface Fc γ RIII molecules²; anaphylatoxins; a range of small peptides, including substance P and calcitonin gene–related peptide³; and β -chemokines, such as macrophage inflammatory protein

Abbreviations used

CTL:	Cytotoxic T cell
DTH:	Delayed-type hypersensitivity
ICAM:	Intercellular adhesion molecule
MCP-1:	Monocyte chemoattractant peptide-1
MIP-1:	Macrophage inflammatory protein-1
PAF:	Platelet-activating factor
VCAM:	Vascular cell adhesion molecule

(MIP)-1 α and monocyte chemoattractant peptide (MCP)-1.^{4,5}

In addition to classical IgE-mediated allergic responses, mast cells have been found to have a role in a range of other inflammatory reactions. For example, mast cells or their products have been shown to be pivotal in mediating leukocyte recruitment in vivo,^{6–8} to play a role in defense against bacterial infections,^{9,10} to exert immunoregulatory roles by interacting directly with cells of the adaptive immune system,¹¹ and to present exogenous antigen to T lymphocytes in vitro.¹² These effects may be attributed to the wide range of cytokines, vasoactive amines, and other mediators released from mast cells, as well as to direct contact with other immune cells.

Morphologic studies have documented an increase in the local density of mast cells and their activation during T cell–mediated inflammatory processes as observed in helminth infection, cutaneous delayed-type hypersensitivity (DTH), graft-versus-host reactions, sarcoidosis, and rheumatoid arthritis.¹³ Furthermore, morphologic studies have also revealed that mast cells reside in close physical proximity to T cells in inflamed allergic tissues and at sites of parasitic infections.^{14,15} This close apposition between T cells and mast cells has led investigators to propose a functional relationship between these 2 cell populations that might facilitate the elicitation of the immune response.¹² Consistent with this hypothesis, and using mast cell–deficient and reconstituted mice, it has been demonstrated that the mononuclear cell infiltration in the late allergic response is mast cell dependent.⁸

It has also been proposed that mast cell activation and degranulation may be an essential prerequisite for the induction and elicitation of cutaneous delayed hypersensitivity reactions.^{16,17} A T-cell regulation of mast cell proliferation and function has been argued for in this setting. Thus T cell–derived IL-3 induces mast cell proliferation in certain types of host responses to parasitic infec-

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tions,¹⁸ and histamine release from activated mast cells is significantly lower in athymic rats than in normal controls.¹⁹ In contrast, transforming growth factor- β was found to inhibit mast cell proliferation and induce apoptosis.²⁰ Taken together, these observations suggest a T cell-mast cell interaction that is bidirectional, fulfilling regulatory and/or modulatory roles affecting various aspects of the immune response.

MAST CELLS AND T-CELL RECRUITMENT

CD4⁺ T lymphocytes accumulate in tissues at sites of mast cell activation, where they are believed to play a critical role in the genesis of subsequent cellular events, such as those observed in the late-phase allergic response²¹ or in DTH responses.^{16,17} Several lines of evidence clearly document the important contribution of these T lymphocytes in chronic asthma and atopic dermatitis. Studies of bronchoalveolar lavage fluid or tissue biopsy specimens from asthmatic patients and studies with the ovalbumin-sensitized mouse model of asthma have consistently demonstrated significant infiltration of lymphocytes, which is usually maximal between 18 and 72 hours after antigen challenge.^{22,23} Marked accumulation of CD4⁺ T cells has been observed in the dermal eczematous lesions of patients with atopic dermatitis.²³ Mast cell activation in the skin and migration to lymph nodes is associated with the induction of contact sensitivity, a prototype T cell-mediated (DTH) immune response.¹⁷ Thus T cell-specific factor(s) generated by mast cells may be one mechanism by which mast cells initiate and contribute to late-phase events. Mast cells may affect T-cell recruitment to sites of inflammation by several mechanisms: direct release of chemotactic molecules, regulation of expression of adhesion molecules, and induction of cytokine release by endothelial cells.

No longer regarded simply as a passive barrier separating the blood and the surrounding tissues, endothelial cells are now recognized as being involved directly in the process of inflammation.²⁴ Activation of the endothelium by proinflammatory mediators stimulates the upregulation of cell surface adhesion molecules. This promotes the adherence of inflammatory cells to the vessel wall before migration into the inflammatory site.²⁵ Several families of adhesion molecules orchestrate the penetration of leukocytes into tissues. The group referred to as selectins precipitate initial slowing and rolling of leukocytes along the vessel wall.²⁵ These cells then tightly adhere to activated endothelium by interactions with immunoglobulin-like molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1.²⁶

Mast cells are strategically poised at perivascular sites to regulate inflammatory responses. The contribution of mast cells to neutrophil and mononuclear cell recruitment in IgE-induced late allergic responses has been verified by the use of mast cell-deficient mice.^{8,27} Unlike in normal mice, application of IgE-mediated stimuli in mast cell-deficient mice was not associated with a significant

cellular infiltration. This data is consistent with evidence that mast cell products released and generated during degranulation, including TNF- α , IL-1, IL-4, IL-6, IL-8, IL-13, platelet-activating factor (PAF), and leukotriene C4, are variously capable of affecting endothelial cells. Indeed, the antigen-dependent, IgE-mediated, mast cell-induced, late-phase cutaneous response, which includes a profound leukocyte influx into the skin 6 to 12 hours after degranulation, is significantly reduced by anti TNF- α antibody in a mouse model. This suggests that TNF- α contributes significantly to the delayed cellular infiltration in this response.²⁷

The capacity of mast cells to modulate endothelial cell function *in vivo* has also been supported by reports of increased E-selectin expression after dermal mast cell stimulation mediated largely by TNF- α .²⁸ Marked expression of both ICAM-1 and VCAM-1 is similarly observed 6 hours after intradermal allergen challenge in atopic individuals.²⁹ Increased bronchial ICAM-1 expression after allergen inhalation in a sensitized animal relates to cellular infiltration and bronchial hyperreactivity.³⁰ Also, allergen nasal challenge in allergic patients results in increased expression of VCAM-1 and E-selectin in the nasal mucosa.³¹

More recently, several studies have demonstrated that activated mast cells or their conditioned medium were capable of inducing T-cell adhesion to human endothelial cells or fibroblasts.^{29,32} This effect was associated with a significant increase in VCAM-1 and ICAM-1 expression, which was noted as early as 4 hours and which peaked 16 hours after exposure to mast cell degranulation products. The role of VCAM-1 and ICAM-1 in T-cell binding to endothelial cells was confirmed by the use of blocking antibodies. Antibodies to ICAM-1 or VCAM-1 both significantly reduced adherence, suggesting that lymphocytes required both receptors for maximal adherence. The ICAM-1 upregulation by mast cell-derived mediators was almost completely (>90%) neutralized by antibody to TNF- α , whereas the expression of VCAM-1 was only partially (70%) neutralized by this antibody. These data implicate mast cell-derived TNF- α as having an important role in mediating ICAM-1-induced inflammatory processes. Other mast cell-derived mediators, such as IL-4 and IL-13, may further contribute, in a synergistic manner with TNF- α , to the stimulation of VCAM-1 expression.³³

Mast cell-derived cytokine-induced expression of adhesion molecules should be a relatively slow process, requiring protein synthesis for detectable expression. However, mast cell-dependent rolling and adhesion have been observed as early as 10 minutes after reperfusion of postischemic intestine, invoking a role for early mast cell-associated leukocyte recruitment in this inflammatory process.⁶ Indeed, it has been shown that mast cell degranulation induced leukocyte rolling on and adhesion to mesenteric venule endothelium within 30 minutes. The increase in leukocyte flux was blocked with the H1 blocker diphenhydramine and an anti-P-selectin antibody. Adhesion, but not leukocyte flux, was decreased by

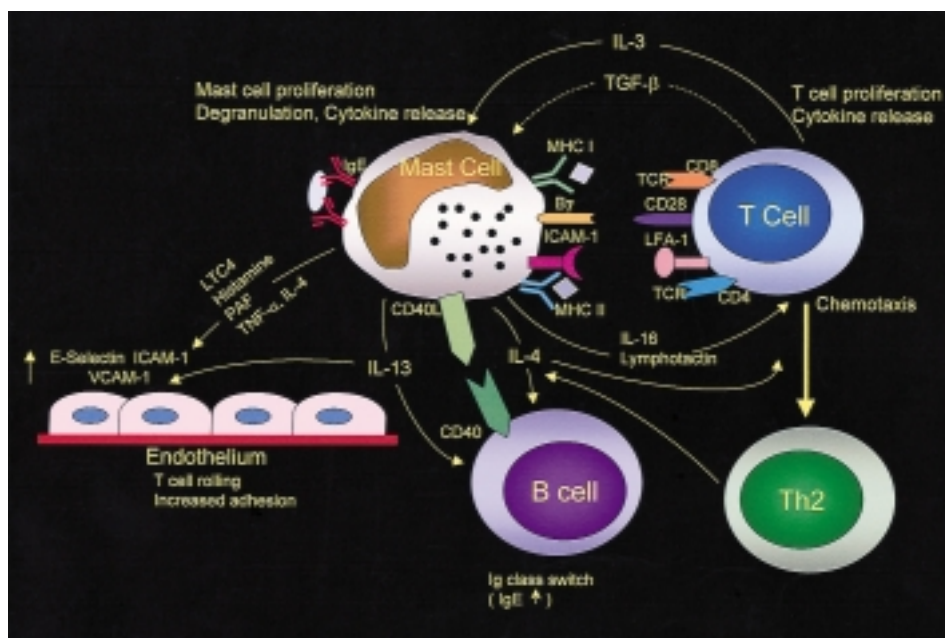


FIG 1. Mast cell-T cell interactions. Mast cells present antigen to T cells in either an MHC class I- or MHC class II-restricted and costimulatory molecule-dependent fashion. This results in T-cell activation, which in turn activates mast cells through cell-to-cell contact, leading to both degranulation and cytokine release. Certain T cells also produce and release IL-3 and transforming growth factor- β (TGF- β), which augment or inhibit mast cell proliferation, respectively. Mast cell degranulation products induce T-cell migration to sites of antigen challenge either directly through chemotactic molecules, such as IL-16 or lymphotactin, or indirectly by inducing the expression of adhesion molecules on endothelial cells. The expression of CD40 ligand (CD40L) on mast cells and their ability to release IL-4 and IL-13 contribute to IgE synthesis by proximal B cells. IL-4 released from mast cells polarizes T cells to preferentially differentiate into the T_H2 subset, which in turn promotes allergic inflammation. TCR, T-cell receptor; LTC4, leukotriene C4.

a PAF antagonist and an anti-CD18 (a ligand of ICAM-1) antibody. It has therefore been suggested that mast cells at perivascular sites have the capacity to initiate the early multistep process of leukocyte recruitment. This includes histamine-induced P-selectin-dependent leukocyte rolling and PAF-associated CD18-dependent leukocyte adhesion. Thus a proposed scenario may be that mast cell activation by a variety of secretagogues stimulates the leukocyte-endothelial interaction by the production and release of proinflammatory mediators. This in turn upregulates the expression of adhesion molecules necessary for cell migration from the intravascular compartment into sites of antigen challenge (Fig 1).

T-cell recruitment to sites of inflammation after encountering activated endothelial cells is further influenced by specific chemoattractants released by neighboring cells. Although mast cells clearly participate in this lymphocyte-recruiting process, and supernatants of activated mast cells are known to have lymphocytic chemotactic activity,³⁴ little has been known until recently of the specific molecules released by mast cells that are chemotactic for lymphocytes. Such studies have now demonstrated that activated human leukemic mast cells release IL-8, a chemokine reported to have some lymphotactic activity.³⁵ Mast cell-derived tryptase is known to similarly induce both messenger (m)RNA expression

and secretion of IL-8 from human umbilical vein endothelial cells.³⁶ Activated murine mast cells also release lymphotactin, a lymphocytic chemokine with preferential activity for CD8⁺ T cells.³⁷ More recently, it has been shown that human bone marrow-derived mast cells and human lung mast cells are a source of IL-16. On treatment with phorbol myristate acetate or the anaphylatoxin C5a, IL-16 mRNA levels increase. This is followed by the release of IL-16 protein. The secreted IL-16 is biologically active and is a chemoattractant for CD4⁺ T cells.³⁸ In other in vitro studies, histamine has been shown to cause IL-16 release from CD8⁺ T cells and bronchial epithelial cells.^{39,40} IL-16 was also detected in vivo in bronchoalveolar lavage fluid from asthmatic patients after antigen challenge.⁴¹ The release of histamine from activated mast cells may thus cause further IL-16 secretion from other sources in the tissue microenvironment. This complex interaction offers one explanation for the persistence of CD4⁺ T-cell infiltration at allergic sites.

T-cell adhesion to the extracellular matrix or to its glycoprotein components fibronectin and laminin is inhibited by supernatants obtained from activated mast cells. Histamine was shown to induce this inhibitory effect by increasing intracellular cyclic adenosine monophosphate and decreasing the calcium influx in T cells through the

H₂ receptor.⁴² Thus mast cell activation may also interfere with the later mobilization or migration of T cells from inflammatory sites.

During the sensitization phase of contact sensitivity and after application of the sensitizing hapten dinitrofluorobenzene in the mouse, mast cells migrate to peripheral lymph nodes. These mast cells serve as the predominant source of the chemokine MIP-1 β . Neutralization of MIP-1 β then partially inhibits T-lymphocyte recruitment.¹⁷

T cells, on the other hand, may similarly induce mast cell chemotaxis. However, the mechanisms responsible for such mast cell migration are poorly understood. Of the various molecules studied, the chemokines MCP-1, RANTES, platelet factor-4, and MIP-1 α ⁴³; the complement components C1q, C3a, and C5a⁴⁴; the angiogenic factors platelet-derived growth factor, vascular endothelial growth factor, and basic fibroblast growth factor⁴⁵; and the cytokines IL-3,⁴⁶ transforming growth factor- β ,⁴⁷ and c-kit ligand⁴⁸ have all been reported to be chemotactic for mast cells *in vitro*.

MAST CELL-INDUCED T-CELL ACTIVATION

Mast cells secrete cytokines in response to both immunologic and nonimmunologic stimulation. These include cytokines that influence both T-cell and B-cell development and function, including IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, IL-16, TNF- α , and certain chemokines.⁴⁹ Both IL-16 and TNF- α can be released rapidly from preformed stores. With more prolonged kinetics, additional cytokines are produced from transcripts expressed in response to appropriate activation of the cell.^{38,49} The physiologic significance of this unique property may include a pivotal role for mast cells in host defense against bacterial infections, as has been recently reported.^{9,10} The hypothesis is that mast cells represent a central component of host defense against bacterial infection. It has been shown that mast cell- and TNF- α -dependent recruitment of circulating leukocytes with bactericidal properties is crucial to a full response. The TNF- α released by mast cells is apparently in response to contact with a bacterial component, serving an important role in the generation of the associated influx of neutrophils to the site of infection and resulting in bacterial clearance.

Another potentially important observation is that mast cells are able to present antigens to T cells in either an MHC class I- or class II-restricted and costimulatory molecule-dependent fashion.^{12,50} Both rodent and human mast cells have been reported to express MHC class II molecules and process and present immunogenic peptides to CD4⁺ cells, inducing proliferation and cytokine production of the latter.⁵¹⁻⁵³ In addition, murine bone marrow-derived cultured mast cells and human mast cells were found to express B7-1, B7-2, and ICAM-1 molecules. These surface components are known to serve as accessory molecules in the costimulation of normal specific T cells.⁵²⁻⁵⁴ Thus mast cells may express characteristics that allow them to function as efficient antigen-pre-

senting cells and promote clonal expansion of T cells. These features include internalization and degradation of protein antigens into immunogenic peptides, expression of peptide-MHC class complexes on the cell surface, and delivery of costimulatory signals to T cells.¹²

Mast cells are also capable of processing antigens after phagocytosis of a number of pathogenic gram-negative enterobacteria for class I MHC presentation to CD8⁺ T cells.⁵⁰ This finding, and the ability of mast cells to produce IL-4, is of particular interest in the context of class I MHC-restricted presentation to cytotoxic T cells (CTLs). IL-4 has been shown to stimulate both proliferation and differentiation of CTL precursors and to enhance the CTL response to alloantigen in a mixed lymphocyte reaction.⁵⁵ Thus mast cells may be involved in the generation of CTL responses to bacterial antigens *in vivo*.

MAST CELL ACTIVATION BY T CELLS

Both T cell-derived cytokines and heterotypic adhesion involving direct contact between mast cells and T cells have been demonstrated to affect mast cell activation and mediator release. Cytokines influence mast cell degranulation by means of 2 different mechanisms. First, mediators, such as the β -chemokines MCP-1 and MIP-1 α , may directly induce degranulation of mouse or rat mast cells *in vitro* or *in vivo*.^{4,5,17} Electron microscopic examination of skin injected with these 2 chemokines thus revealed extensive mast cell degranulation by MIP-1 α and, to a lesser extent, by MCP-1.⁵ Human skin mast cells were, however, unresponsive to these 2 chemokines.⁵⁶ Second, by priming mast cells, cytokines may potentiate the effect of, and thus operate synergistically with, "classical" secretagogues, such as antigen, anti-IgE, or complement components.⁵⁷

More recently, we have reported that both human and murine mast cells are induced to release mediators on cell-to-cell contact with activated, but not resting, T cells.^{58,59} Coculture of murine (bone marrow cultured) or human (leukemic or primary cultured) mast cells with activated T cells resulted in significant histamine and TNF- α release. Also, Fc ϵ RI aggregation-induced degranulation was augmented when bone marrow-derived cultured mast cells were cocultured with activated T cells. Supernatants of activated T cells failed to exert the stimulatory effect, whereas separation of the 2 cell populations prevented degranulation. These observations indicate that mast cell activation was aggregation dependent. Indeed, the kinetics of histamine release paralleled the kinetics of the formation of heterotypic aggregates starting at 4 hours and peaking at 16 hours of coculture. This mast cell-T cell interaction was mediated, at least in part, by the adhesion molecules ICAM-1 and its ligand leukocyte function-associated antigen-1 because the addition of antibodies directed against these 2 molecules inhibited the adhesion-induced mast cell degranulation.⁵⁸

Other examples of heterotypic adhesion-induced mast cell activation have also been studied. Thus intercellular contact between mast cells and activated T cells has been

found to induce promoter activity of the (chemokine) *TCA3* gene in mast cells.⁶⁰ Similarly, it has been reported that incubation of human mast cell leukemia-1 cells with membranes purified from anti-CD3-activated T cells resulted in induction of IL-8 transcripts.⁶¹ Another pathway of IgE-independent mast cell activation has recently been described, which involves cognate interaction with CD4⁺ T cells.⁶² This is a T cell-dependent MHC class II-mediated mast cell activation resulting in IL-4 transcription and protein release.

The relatively slow kinetics of heterotypic adhesion-induced mast cell activation, as compared with rapid anaphylactic degranulation, may indicate that this pathway of activation involves induction of new proteins or other mediators that, in turn, generate a series of signals leading to mast cell activation and mediator release. It has also been shown that costimulation provided for anti-CD3-mediated proliferation of T cells involves an extended leukocyte function-associated antigen-1/ICAM-1 interaction, leading to signal transduction events that result in prolonged (>4 hours) inositolphospholipid hydrolysis and a sustained increase in free cytosolic calcium level.⁶³ This observation may be relevant to the relatively slow onset of the effects of T-cell contact on mast cell activation and mediator release observed in the above studies. Taken together with the morphologic studies showing mast cells in close physical proximity to T cells, these observations suggest a pathway through which mast cells are activated to release granule-associated mediators and produce cytokines when involved in T cell-mediated inflammation.

MAST CELL EFFECT ON T-CELL POLARIZATION

In addition to being potent effector cells, recent data suggests that mast cells may have important regulatory functions in the immune system. Relevant to the allergic response, mast cells have been shown to induce IgE synthesis by B cells and to affect T-cell differentiation toward the T_{H2} phenotype. Human mast cells also express CD40 ligand. This ligand for CD40 on B cells is an important cell surface antigen expressed by T cells and critically involved in T-B cell interactions that lead to immunoglobulin synthesis on stimulation with certain cytokines. Thus in the presence of IL-4, mast cells induced IgE synthesis by B cells, which was mediated by CD40 ligand.¹¹ This observation has recently been extended by using mast cells from allergic inflamed tissues.⁶⁴ Mast cells obtained from the nasal mucosa of allergic patients were found to contain both IL-4 and IL-13 and to secrete these cytokines when activated by the specific allergens. Moreover, these mast cells were able to induce IgE synthesis by purified tonsillar B cells in the presence of the specific allergen (Der f 2). In contrast, mast cells obtained from nonallergic tissues failed to induce IgE production. This study has also demonstrated that IgE production was mediated by the secreted IL-4 and especially by IL-13.⁶⁴ Thus mast cells, in addition to their effector role, may contribute to the allergic reaction

by promoting IgE synthesis within the local microenvironment.

Mast cells may be able to exert influences on T cells in addition to directing B-cell function. Mast cells are a major source of cytokines (eg, IL-4, IL-10, and IL-13), which can presumably signal naive memory T cells to preferentially differentiate into the T_{H2} subset. The early presence of IL-4 is the most potent stimulus for T_{H2} differentiation, whereas IL-12 and IFNs favor T_{H1} development.⁶⁵ Indeed, coculturing T cells with activated mast cells led to the development of IL-4-producing T_{H2} cells.⁶⁶ Anti-IL-4 antibody, when introduced to this system, abolished the mast cell-mediated T_{H2} development, indicating the role of this cytokine in skewing T cells toward the T_{H2} phenotype. This finding and the ability of mast cells to serve as antigen-presenting cells may indicate that through presenting antigen to T cells, mast cells can direct T cells into becoming polarized T_{H2} populations. In support of this argument, it has recently been reported that during antigen presentation by mast cells, activated T cells in turn induce MHC class II-dependent mast cell activation, resulting in IL-4 release.⁶² This mast cell-T cell interaction may perpetuate and augment allergic inflammation in that IL-4 may directly influence the polarization of allergen-reactive T cells toward the T_{H2} pathway. This in turn would lead to the local production of proinflammatory cytokines, which are involved in processes that promote IgE production and eosinophil recruitment and survival (eg, IL-4/IL-13 and IL-5, respectively (Fig 1). Interestingly, it has been shown that up to 90% of IL-4-secreting cells in normal or atopic nasal mucosa are mast cells.⁶⁷ The overall effect would thus be an increase in the immediate hypersensitivity response.

In summary, there is ample evidence for complex interactions between mast cells and lymphocytes within lymphoid tissues and at sites of inflammation. Such interactions are mediated by cytokines or by heterotypic aggregation. The end result appears to be a cooperative enhancement that potentiates the role of both cells in host defense and in the regulation of the inflammatory response.

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REFERENCES

1. Galli SJ. Complexity and redundancy in the pathogenesis of asthma: reassessing the role of mast cells and T cells. *J Exp Med* 1997;186:343-7.
2. Alber G, Kent UM, Metzger H. Functional comparison of FcεRI, FcγRII and FcγRIII in mast cells. *J Immunol* 1992;149:2428-36.
3. Columbo M, Horowitz EM, Kagey-Sobotka A, Lichtenstein LM. Substance P activates the release of histamine from human skin mast cells through a pertussis toxin-sensitive and protein kinase C-dependent mechanism. *Clin Immunol Immunopathol* 1996;81:68-73.
4. Alam R, Forsythe PA, Stafford S, Lett-Brown MA, Grant JA. Macrophage inflammatory protein-1α activates basophil and mast cells. *J Exp Med* 1992;176:781-6.
5. Alam R, Kumar D, Anderson-Walters D, Forsythe PA. Macrophage inflammatory protein-1α and monocyte chemoattractant peptide-1 elicit immediate and late cutaneous reactions and activate murine mast cells in vivo. *J Immunol* 1994;152:1298-303.

6. Gaboury JP, Johnston B, Niu XF, Kubes P. Mechanisms underlying acute mast cell-induced leukocyte rolling and adhesion *in vivo*. *J Immunol* 1995;154:804-13.
7. Kubes P, Kanwar S. Histamine induces leukocyte rolling in post-capillary venules. A P-selectin-mediated event. *J Immunol* 1994;152:3570-7.
8. Wershil BK, Furuta GT, Wang ZS, Galli SJ. Mast cell dependent neutrophil and mononuclear cell recruitment in immunoglobulin E-induced gastric reactions in mice. *Gastroenterology* 1996;110:1482-90.
9. Malaviya R, Ikeda T, Ross E, Abraham SN. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF- α . *Nature* 1996;3810:77-80.
10. Echtenacher B, Mannel DN, Hultner L. Critical protective role of mast cells in a model of acute septic peritonitis. *Nature* 1996;381:75-7.
11. Gauchat JF, Henchoz S, Maszcei G, Aubry JP, Brunner T, Blasey J, et al. Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* 1993;365:340-3.
12. Mecheri S, David D. Unraveling the mast cell dilemma: culprit or victim of its generosity? *Immunol Today* 1997;18:212-5.
13. Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol Rev* 1997;77:1033-79.
14. Friedman MM, Kaliner M. In situ degranulation of human nasal mucosal mast cell: ultrastructural features and cell-to-cell association. *J Allergy Clin Immunol* 1985;76:70-82.
15. Smith TJ, Weiss JH. Mucosal T cells and mast cells share common adhesion receptors. *Immunol Today* 1996;17:60-3.
16. Geba GP, Ptak W, Anderson GM, Paliwal V, Ratzlaff RE, Levin J, et al. Delayed-type hypersensitivity in mast cell deficient mice: dependence on platelets for expression of contact sensitivity. *J Immunol* 1996;157:557-65.
17. Wang H-W, Tedla N, Lloyd AR, Wakefield D, McNeil HP. Mast cell activation and migration to lymph nodes during induction of an immune response in mice. *J Clin Invest* 1998;102:1617-26.
18. Svetic A, Madden KB, Di Zhou X, Lu P, Katona IJ, Finkelman FD, et al. A primary intestinal helminth infection rapidly induces a gut-associated elevation of Th2-associated cytokines and IL-3. *J Immunol* 1993;150:3434-41.
19. Chen XJ, Enerback L. IgE receptors, IgE content and secretory response of mast cells in athymic rats. *Immunology* 1994;83:595-600.
20. Mekori YA, Metcalfe DD. Transforming growth factor- β prevents stem cell factor-mediated rescue of mast cells from apoptosis after IL-3 deprivation. *J Immunol* 1994;153:2194-203.
21. Tsiocopoulos A, Hamid Q, Haczku A, Jacobson MR, Durham SR, North J, et al. Kinetics of cell infiltration and cytokine mRNA expression after intradermal challenge with allergen and tuberculin in the same atopic individual. *J Allergy Clin Immunol* 1994;94:764-72.
22. Robinson D, Hamid Q, Bentley S, Ying S, Kay B, Durham SR. Activation of CD4⁺ T cells. increased Th2-type cytokine mRNA expression, and eosinophil recruitment in bronchoalveolar lavage after allergen inhalation challenge in patients with atopic asthma. *J Allergy Clin Immunol* 1993;92:313-24.
23. Leung DYM. Immunologic basis of chronic allergic diseases: clinical messages from the laboratory bench. *Pediatr Res* 1997;42:559-68.
24. Mantovani A, Bussolino F, Introna M. Cytokine regulation of endothelial cell function: from molecular level to the bedside. *Immunol Today* 1997;18:231-40.
25. Springer TA. Adhesion receptors in the immune system. *Nature* 1990;346:425-34.
26. Osborn L. Leukocyte adhesion to endothelium in inflammation. *Cell* 1990;62:3-6.
27. Wershil BK, Wang ZS, Gordon JR, Galli SJ. Recruitment of neutrophil during IgE-dependent cutaneous late phase responses in the mouse is mast cell dependent: partial inhibition of the reaction with antiserum against tumor necrosis factor- α . *J Clin Invest* 1991;87:446-52.
28. Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor α which induced endothelial leukocyte adhesion molecule 1. *Proc Natl Acad Sci USA* 1991;88:4220-4.
29. Meng H, Tonnesen MG, Marchese MJ, Clark RAF, Bahou WF, Gruber BL. Mast cells are potent regulators of endothelial cell adhesion molecule ICAM-1 and VCAM-1 expression. *J Cell Physiol* 1995;165:40-53.
30. Wegner CD, Gundel RH, Reilly PJ, Haynes N, Gordon Letts LR. Inter-cellular adhesive molecular-1 (ICAM-1) in the pathogenesis of asthma. *Science* 1990;247:456-9.
31. Lee BJ, Naclerio RM, Bochner BS, Taylor RM, Lim MC, Baroody FM. Nasal challenge with allergen upregulates the local expression of vascular endothelial adhesion molecules. *J Allergy Clin Immunol* 1994;94:1006-16.
32. Meng H, Marchese MJ, Garlick JA, Jelaska A, Korn JH, Gailit J, et al. Mast cells induce T-cell adhesion to human fibroblasts by regulating intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression. *J Invest Dermatol* 1995;105:789-96.
33. Bochner BS, Klunk DA, Sterbinsky SA, Coffman RL, Schleimer RP. Interleukin-13 selectively induces vascular cell adhesion molecule-1 (VCAM-1) expression in human endothelial cells. *J Immunol* 1995;154:799-803.
34. Center DM. Identification of rat mast cell-derived chemoattractant factors for lymphocytes. *J Allergy Clin Immunol* 1983;71:29-35.
35. Moller A, Lippert U, Lessmann D, Kolde G, Hamann K, Welker P, et al. Human mast cells produce IL-8. *J Immunol* 1993;151:3261-6.
36. Compton SJ, Cairns JA, Holgate ST, Walls AF. The role of mast cell tryptase in regulating endothelial cell proliferation, cytokine release and adhesion molecule expression: tryptase induces expression of mRNA for IL-1 β and IL-8 and stimulates the selective release of IL-8 from human umbilical vein endothelial cells. *J Immunol* 1998;161:1939-46.
37. Rumsaeng V, Vliagoftis H, Oh C, Metcalfe DD. Lymphoactin gene expression in mast cells following Fc ϵ RI aggregation: modulation by TGF- β , IL-4, dexamethasone, and cyclosporin A. *J Immunol* 1997;158:1353-60.
38. Rumsaeng V, Cruikshank WW, Foster B, Prussin C, Kirshenbaum AS, David TA, et al. Human mast cells produce the CD4⁺ T lymphocyte chemoattractant factor, IL-16. *J Immunol* 1997;159:2904-10.
39. Laberge S, Cruikshank WW, Kornfeld H, Center DM. Histamine-induced secretion of lymphocyte chemoattractant factor from CD8⁺ T cells is independent of transcription and translation: evidence for constitutive protein synthesis and storage. *J Immunol* 1995;155:2902-10.
40. Bellini A, Yoshimura H, Vittori E, Marini M, Mattoli S. Bronchial epithelial cells of patients with asthma release chemoattractant factors for T lymphocytes. *J Allergy Clin Immunol* 1993;92:412-24.
41. Cruikshank WW, Long A, Tarpy RE, Kornfeld H, Carrol MP, Teran L, et al. Early identification of interleukin-16 (lymphocyte chemoattractant factor) and macrophage inflammatory protein 1 alpha (MIP1 alpha) in bronchoalveolar lavage fluid of antigen-challenged asthmatics. *Am J Respir Cell Mol Biol* 1996;13:738-47.
42. Hershkovitz R, Lider O, Baram D, Reshef T, Miron S, Mekori YA. Inhibition of T cell adhesion to extracellular matrix glycoproteins by histamine: a role for mast cell degranulation products. *J Leukoc Biol* 1994;56:495-501.
43. Taub D, Dasty J, Inamura N, Upton J, Kelvin D, Metcalfe D, et al. Bone marrow-derived murine mast cells migrate, but do not degranulate, in response to chemokines. *J Immunol* 1995;154:2393-402.
44. Nilsson G, Johnell M, Hammer CH, Tiffany HL, Nilsson K, Metcalfe DD, et al. C3a and C5a are chemotaxins for human mast cells and act through distinct receptors via a pertussis toxin-sensitive signal transduction pathway. *J Immunol* 1996;157:1693-8.
45. Gruber BL, Marchese MJ, Kew R. Angiogenic factors stimulate mast-cell migration. *Blood* 1995;86:2488-93.
46. Matsura N, Zetter BR. Stimulation of mast cell chemotaxis by interleukin 3. *J Exp Med* 1989;170:1421-6.
47. Gruber BL, Marchese MJ, Kew RR. Transforming growth factor- β 1 mediates mast cell chemotaxis. *J Immunol* 1994;152:5860-7.
48. Nilsson G, Butterfield JH, Nilsson K, Siegbahn A. Stem cell factor is a chemotactic factor for human mast cells. *J Immunol* 1994;153:3717-23.
49. Galli SJ, Gordon JR, Wershil BK. Cytokine production by mast cells and eosinophils. *Curr Opin Immunol* 1991;3:865-70.
50. Malaviya R, Tweten NJ, Ross EA, Abraham SN, Pfeifer JD. Mast cells process bacterial Ags through a phagocytic route for Class I MHC presentation to T cells. *J Immunol* 1996;156:1490-6.
51. Frandji P, Oskeritzian C, Cacaraci F, Lapeyre J, Peronet R, David B, et al. Antigen-dependent stimulation by bone marrow-derived mast cells of MHC class II restricted T cell hybridoma. *J Immunol* 1993;151:6318-28.
52. Fox CC, Jewel SD, Whitacre CC. Rat peritoneal mast cells present antigen to a PPD-Specific T cell line. *Cell Immunol* 1994;158:253-64.
53. Love KS, Lakshmanan RR, Butterfield JH, Fox CC. IFN- γ -stimulated

- enhancement of MHC Class II antigen expression by the human mast cell line HMC-1. *Cell Immunol* 1996;170:85-90.
54. Frandji P, Tkaczyk C, Oskeritzian C, David B, Desaymard C, Mecheri S. Exogenous and endogenous antigens are differentially presented by mast cells to CD4⁺ T lymphocytes. *Eur J Immunol* 1996;26:2517-28.
55. Pfeifer JD, McKenzie DT, Swain SL, Dutton RW. B cell stimulatory factor (interleukin-4) is sufficient for the proliferation and differentiation of lectin-stimulated cytolytic T lymphocyte precursors. *J Exp Med* 1987;166:1464-70.
56. Petersen LJ, Brasso K, Pryds M, Skov PS. Histamine release in intact human skin by monocyte chemoattractant factor-1, RANTES macrophage inflammatory protein-1 α , stem cell factor, anti-IgE, and codeine as determined by an ex vivo skin microdialysis technique. *J Allergy Clin Immunol* 1996;89:790-6.
57. Levi Schaffer F, Segal V, Shalit M. Effects of interleukins on connective tissue type mast cells co-cultured with fibroblasts. *Immunology* 1991;72:174-80.
58. Inamura N, Mekori YA, Bhattacharyya SP, Bianchini PJ, Metcalfe DD. Induction and enhancement of Fc ϵ RI-dependent mast cell degranulation following coculture with activated T cells: dependency on ICAM-1-and leukocyte function-associated antigen (LFA)-1-mediated heterotypic aggregation. *J Immunol* 1998;160:4026-33.
59. Bhattacharyya SP, Drucker I, Reshef T, Kirshenbaum AS, Metcalfe DD, Mekori YA. Activated T lymphocytes induce degranulation and cytokine production by human mast cells following cell-to-cell contact. *J Leukoc Biol* 1998;63:337-41.
60. Oh CK, Metcalfe DD. Activated lymphocytes induce promoter activity of TCA-3 gene in mast cells following cell-to-cell contact. *Biochem Biophys Res Commun* 1996;221:510-4.
61. Kirshnasawamy G, Lakshman T, Miller AR, Srikanth S, Hall K, Huang S-K, et al. Multifunctional cytokine expression by human mast cells: regulation by T cell membrane contact and glucocorticoids. *J Interferon Cytokine Res* 1997;17:167-76.
62. Frandji P, Mourad W, Tkaczyk C, Singer M, David B, Colle J-H, et al. IL-4 mRNA transcription is induced in mouse bone marrow-derived mast cells through an MHC class II-dependent signaling pathway. *Eur J Immunol* 1998;28:844-54.
63. van Seventer GA, Bonvini E, Yamada H, Conti A, Stringfellow S, June CH, et al. Costimulation of T cell receptor/CD3-mediated activation of resting human CD4⁺ T cells by leukocyte function-associated antigen-1 ligand intercellular cell adhesion molecule-1 involves prolonged inositol phospholipid hydrolysis and sustained increase of intracellular Ca²⁺ levels. *J Immunol* 1992;149:3872-80.
64. Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc ϵ RI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;99:1492-9.
65. Romagnani S. The Th₁/Th₂ paradigm. *Immunol Today* 1997;18:263-6.
66. Huels C, Germann T, Goedert S, Hoehn P, Koelsch S, Hultner L, et al. Co-activation of naive CD4⁺ T cells and bone marrow-derived mast cells results in the development of Th₂ cells. *Int Immunol* 1995;7:525-32.
67. Bradding P, Feather IH, Wilson S, Bardin PG, Heusser CH, Holgate ST, et al. Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. *J Immunol* 1993;151:3853-65.