

New millennium: The conquest of allergy

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The diverse potential effector and immunoregulatory roles of mast cells in allergic disease

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Mast cells are of hematopoietic origin but typically complete their maturation in peripheral connective tissues, especially those near epithelial surfaces. Mast cells express receptors that bind IgE antibodies with high affinity (FcεRI), and aggregation of these FcεRI by the reaction of cell-bound IgE with specific antigens induces mast cells to secrete a broad spectrum of biologically active preformed or lipid mediators, as well as many cytokines. Mast cells are widely thought to be essential for the expression of acute allergic reactions, but the importance of mast cells in late-phase reactions and chronic allergic inflammation has remained controversial. Although it is clear that many cell types may be involved in the expression of late-phase reactions and chronic allergic inflammation, studies in genetically mast cell-deficient and congenic normal mice indicate that mast cells may be critical for the full expression of certain features of late-phase reactions and may also contribute importantly to clinically relevant aspects of chronic allergic inflammation. Moreover, the pattern of cytokines that can be produced by mast cell populations, and the enhancement of such cytokine production in mast cells that have undergone IgE-dependent up-regulation of their surface expression of FcεRI, suggests that mast cells may contribute to allergic diseases (and host defense) by acting as immunoregulatory cells, as well as by providing effector cell function. (*J Allergy Clin Immunol* 2000;105:847-59.)

Key words: Allergic inflammation, allergy, atopy, asthma, basophils, chemokines, eosinophils, growth factors, IgE, mast cells, stem cell factor, T_H2 cells

There is considerable debate about the importance of mast cells in the pathogenesis of allergic inflammation. Although most allergists and immunologists believe that mast cells are critical for the expression of many acute allergic reactions, such as anaphylaxis or the acute wheezing provoked by allergen challenge in subjects

Abbreviations used

bFGF:	Basic fibroblast growth factor
BMCMC:	Bone marrow-derived cultured mast cell
CsA:	Cyclosporin A
FcεRI:	High-affinity receptor for IgE
FcγRIII:	Receptor for IgG ₁
IHC:	Immunohistochemistry
LT:	Leukotriene
MCP:	Monocyte chemoattractant protein
MIP:	Macrophage inflammatory protein
MMP:	Matrix metalloproteinase
mRNA:	Messenger RNA
NGF:	Nerve growth factor
PAF:	Platelet-activating factor
PCA:	Passive cutaneous anaphylaxis
SCF:	Stem cell factor
TGF:	Transforming growth factor
T _H 2:	Type 2 T helper
VPF/VEGF:	Vascular permeability factor/vascular endothelial cell growth factor

with atopic asthma, there is much less agreement about the roles of mast cells in late-phase reactions or chronic allergic inflammation. In this review we will discuss the characteristics of the mast cell that enable it to act as both an effector cell and as a potential immunoregulatory cell in allergic diseases and will present evidence, much of it derived from *in vivo* studies in mice, indicating that mast cells can indeed contribute importantly to the expression of both IgE-dependent late-phase reactions and certain features of chronic allergic inflammation. We will also consider 2 important issues that contribute to the controversy about the relevance of the findings obtained in murine model systems to our understanding of allergic disease in humans: the redundancy and complexity of effector and immunoregulatory mechanisms in IgE-associated immune responses and certain differences in these processes in mice and humans.

MAST CELL DEVELOPMENT, DISTRIBUTION, AND HETEROGENEITY

Mast cells are derived from CD34⁺ hematopoietic progenitor cells and, except for the small numbers of mast

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cells that reside in the bone marrow, maturation typically occurs in the peripheral tissues.¹⁻⁵ Several lines of evidence indicate that interactions between the tyrosine kinase receptor c-kit, which is expressed on the surface of mast cells and their precursors, and the c-kit ligand, stem cell factor (SCF), are essential for mast cell development and survival both in mice and rats and in humans.¹⁻⁵

Mast cells are ideally positioned anatomically to participate in allergic reactions at cutaneous or mucosal surfaces. Unlike mature basophils, mature mast cells do not normally circulate in the blood but are widely distributed throughout normal connective tissues, where they often lie adjacent to blood and lymphatic vessels, near or within nerves, and beneath epithelial surfaces that are exposed to the external environment, such as those of the respiratory and gastrointestinal systems and skin.²⁻⁹ Mast cell numbers in healthy tissues exhibit considerable variation according to anatomic site, and these "baseline" numbers of mast cells can change strikingly in association with certain inflammatory or immunologic reactions.¹⁻⁸ For example, a marked expansion of mast cell populations occurs in mice at sites of infection with some parasites that induce a strong T helper type 2 (T_H2) response, and this process is dependent on both the c-kit ligand, SCF, and IL-3.¹⁰ Increased numbers of mast cells also have been reported in tissues affected by chronic allergic inflammation in humans.¹¹⁻¹³

In addition to being able to undergo changes in their numbers and anatomic distribution, studies in both humans and experimental animals have indicated that mast cell populations can vary in many aspects of their phenotype, including morphologic characteristics, mediator content, histochemistry, and response to drugs and stimuli of activation.²⁻⁸ Consequently, to understand the relevance of mast cells to a particular biologic response, ideally those mast cells that actually participate in that response in vivo should be studied. This is not as simple as it may seem because mast cells in a specific anatomic location can undergo alterations in phenotype during the course of immunologic or inflammatory responses and some of these changes may be reversible.^{1-8,14,15}

"MAST CELL KNOCK-IN MICE": A MODEL FOR ANALYZING MAST CELL DEVELOPMENT AND FUNCTION IN VIVO

IgE-associated immune responses and other inflammatory processes typically involve the coordinated and potentially redundant activities of several cell types; under these circumstances, characterizing the specific contributions of a single cell can be difficult. In the case of the mast cell, this problem can be addressed by use of genetically mast cell-deficient *Kit^W/Kit^{W-v}* mice.^{1,14,16} These mice are anemic and virtually lack tissue mast cells, germ cells, melanocytes, and interstitial cells of Cajal.^{1,3,16,17} These defects reflect consequences of the animals' mutations affecting both copies of c-kit, which result in a marked reduction in the c-kit-dependent signaling in the affected lineages; thus such cells respond

poorly or not at all to stimulation with the kit ligand SCF.^{1,17} However, mast cell activity can be selectively reconstituted in *Kit^W/Kit^{W-v}* mice to compare the expression of biologic responses in tissues that differ solely in containing, or virtually lacking, mast cells.^{1,14-16,18,19} Selective repair of the mast cell deficiency of *Kit^W/Kit^{W-v}* mice may be achieved by the adoptive transfer of bone marrow-derived cultured mast cells (BMCMCs) of wild-type origin; alternatively, other mast cell populations that express genetically determined abnormalities in products that potentially affect the cells' development, survival, or function may be substituted.^{1,18,20-22} (Fig 1).

Notably, when *Kit^W/Kit^{W-v}* mice were injected intradermally, intraperitoneally, or intravenously with phenotypically "immature" mast cells (BMCMCs) that had been generated in vitro, the recipient "mast cell knock-in mice" developed tissue mast cell populations of donor origin whose anatomic distribution and histochemical characteristics were similar to those of the corresponding mast cell populations in the tissues of normal mice.¹⁸

As described below, we have used this system to characterize and quantify the specific contributions of mast cells to the expression of various features of IgE-dependent reactions and other biologic responses in vivo. But before reviewing these data, we will first briefly discuss certain characteristics of mast cells that enable them to express their function during allergic inflammation.

MAST CELL MEDIATORS

Mast cells contain, or elaborate on appropriate stimulation, a diverse array of potent biologically active mediators that can have many different potential effects in inflammation, tissue remodeling, and organ function at sites of mast cell activation (Fig 2).^{4-8,15,23-29} Some of these products are stored preformed in the cells' cytoplasmic granules, whereas others are synthesized on appropriate cell activation. Cytokines are the most recently identified group of mast cell mediators; it appears that at least 2 of these, TNF- α and VPF/VEGF, can be released by activated mast cells from both preformed and newly synthesized pools.³⁰⁻³⁴

Preformed mediators

Mediators stored preformed in the cytoplasmic granules of mouse or human mast cells include histamine (mouse and rat, but not human, mast cells also contain serotonin), proteoglycans, serine proteases, carboxypeptidase A, and small amounts of sulfatases and exoglycosidases.^{4,7,8,15,23,25} Studies in genetically mast cell-deficient and congenic normal mice indicate that mast cells account for nearly all the histamine stored in normal tissues, with the exception of the glandular stomach and the central nervous system.³⁵ Mouse and human mast cell populations contain variable mixtures of heparin and chondroitin sulfate proteoglycans.^{4,8,23,27} Mast cell proteoglycans probably have several biologic functions both within and outside the cells. By ionic interactions, they bind histamine, neutral proteases, and carboxypeptidase,

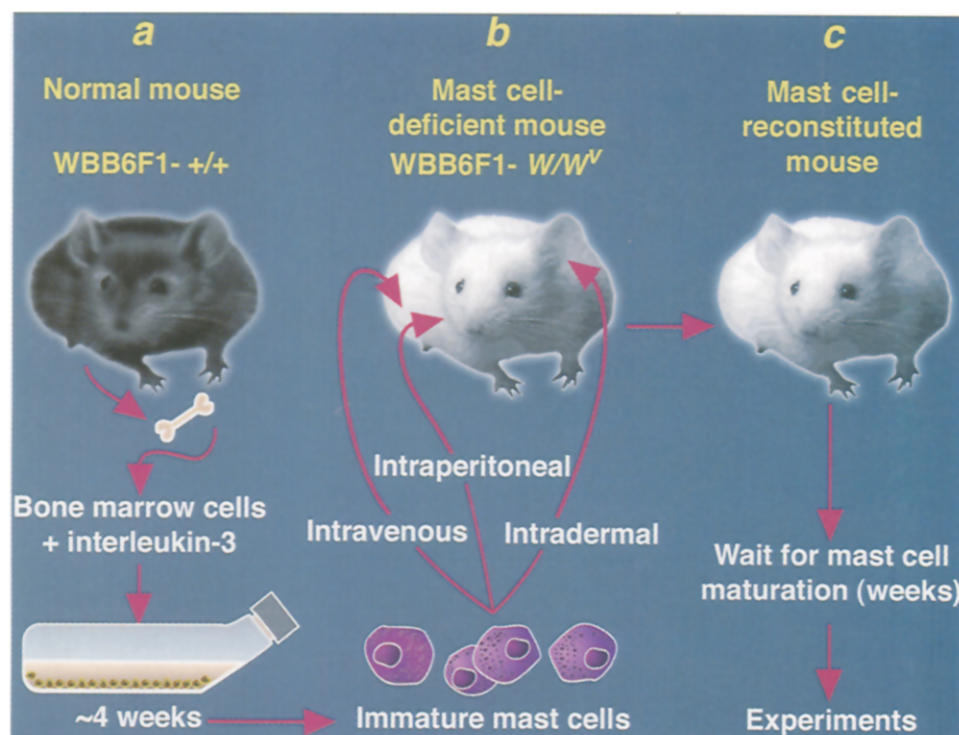


FIG 1. Making "mast cell knock-in mice": selective reconstitution of mast cells in *Kit^W/Kit^{W-v}* mast cell-deficient mice. **a**, Generate lineage-committed immature mast cells in vitro from bone marrow cells derived from normal mice that are congenic to WBB6F1-*Kit^W/Kit^{W-v}* mast cell-deficient mice (or for certain mechanistic studies, from bone marrow cells of mice with defined mutations that affect mast cell development, mediator content, or function; mast cells that express genetic alterations of interest may also be derived from embryonic stem cells in vitro). **b**, Transfer in vitro-derived immature mast cells intravenously, intraperitoneally, or into specific tissues (for instance, the skin or gastrointestinal tract) of genetically mast cell-deficient *Kit^W/Kit^{W-v}* mice. **c**, Wait several weeks before performing experiments to allow mast cells to mature and acquire phenotypic characteristics that are appropriate for the sites of transfer. (Reproduced with permission from Galli SJ, Wershil BK. The two faces of the mast cell. *Nature* 1996;381:21-2.)

and they contribute to the packaging and storage of these molecules within the secretory granules.³⁶⁻³⁸ When the granule matrices are exposed to physiologic conditions of pH and ionic strength during degranulation, the various mediators associated with the proteoglycans dissociate at different rates—histamine very rapidly but tryptase and chymase much more slowly.⁸ In addition to regulating the kinetics of release of mediators from the granule matrices, proteoglycans can also regulate the activity of some of the associated mediators.

Neutral proteases are the major protein component of mast cell secretory granules. By weight, tryptase is the major enzyme stored in the cytoplasmic granules of human mast cells, and this neutral protease occurs in most, if not all, human mast cell populations.⁸ Human mast cell tryptase is a serine endopeptidase that exists in the granule in active form as a tetramer of 134-kd-containing subunits of 31 to 35 kd, each of which contains an active site. Tryptase has also been identified in human basophils and may be increased in the basophils of subjects with allergic disorders.³⁹⁻⁴¹ Recent evidence indicates that there may be multiple forms of human tryptase derived from distinct transcripts and genes; the biologic significance of these findings is not yet clear.⁴²⁻⁴⁴ Mast

cell chymase is also a serine protease that is stored in the active form, as a monomer with a molecular weight of 30 kd in the granules of some, but not all, human mast cells.⁸ A discussion of the diverse potential biologic functions of the many mouse and rat mast cell proteases that have been identified, or of the human mast cell proteases, is beyond the scope of this review. However, in the case of the mouse system transgenic mice that lack expression of specific proteases will be very valuable resources for defining the specific roles of these mediators in vivo.^{15,45}

Newly synthesized lipid mediators

The most important mast cell-derived lipid mediators are the cyclo-oxygenase and lipoxygenase metabolites of arachidonic acid, which have potent inflammatory activities and which may also play a role in modulating the release process itself.^{27,29} The major cyclo-oxygenase product of mast cells is PGD₂, and the major lipoxygenase products derived from mast cells are the sulfidopeptide LTs: LTC₄ and its peptidolytic derivatives, LTD₄ and LTE₄. Human mast cells can produce LTB₄, although in much smaller quantities than PGD₂ or LTC₄,^{27,29} and some mast cell populations represent a potential source of PAF.⁴⁶

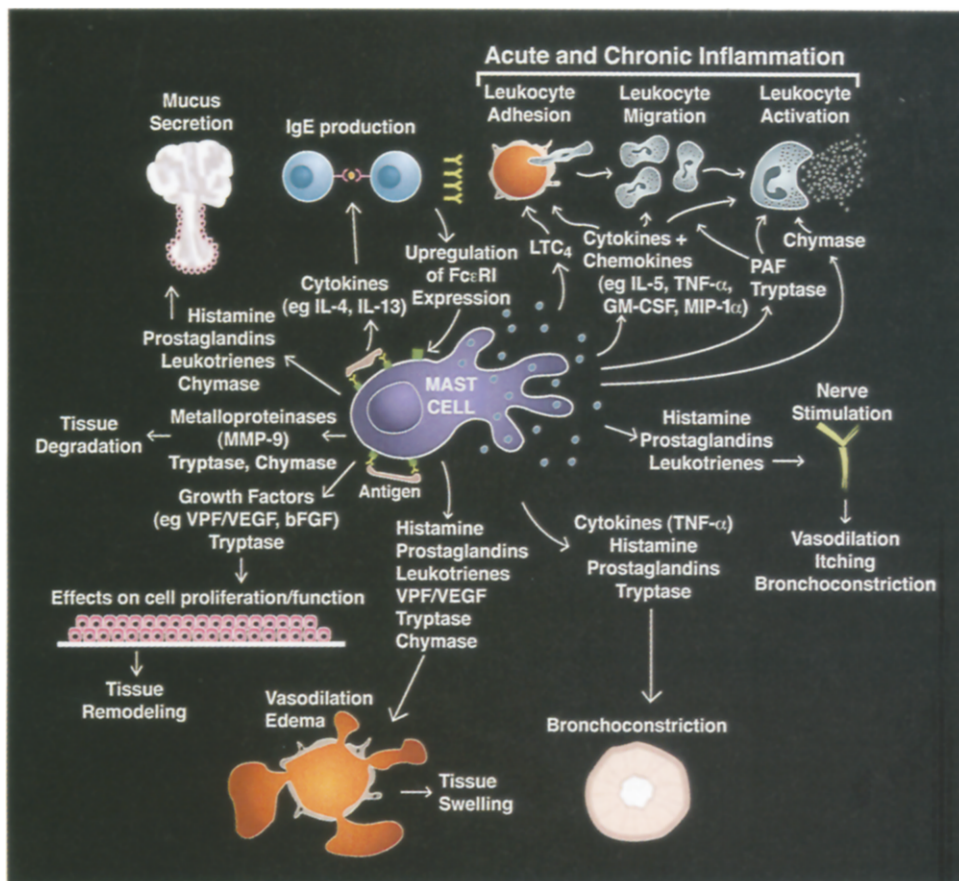


FIG 2. Diagrammatic representation of some of the major mediators, cytokines, and growth factors that are produced on IgE- and antigen-dependent activation of mast cells and the potential contributions of these products to various features of the acute, late-phase, and chronic inflammation that is associated with allergic diseases. Disclaimers: 1, different individual mast cells may vary in their ability to express certain products, especially individual proteases (tryptases, chymases), cytokines, chemokines, and growth factors; 2, the fact that a particular mediator can exert a particular effect (in vitro or after administration in vivo) does not prove that such an effect is critical to the expression of allergic inflammation during actual disease processes in vivo; 3, other effector cell types that participate in allergic inflammation can produce some of the same mediators as mast cells. *bFGF*, Basic fibroblast growth factor; *Fc ϵ RI*, high-affinity receptor for IgE; *LT*, leukotriene; *MIP*, macrophage inflammatory protein; *MMP*, matrix metalloproteinase; *PAF*, platelet-activating factor; *VPF/VEGF*, vascular permeability factor/vascular endothelial cell growth factor.

Cytokines

Several lines of evidence indicate that certain mature, "resting" (unactivated) mouse³⁰⁻³² or human⁴⁷⁻⁴⁹ mast cells contain preformed stores of TNF- α available for immediate release on appropriate stimulation of the cells. Certain mast cell populations may also have preformed stores of VPF/VEGF.^{33,34} Many other cytokines have been identified in various mast cell populations by immunohistochemical (IHC) or immunocytochemical methods; these may represent additional cytokines that can be released in part from "stored" pools.⁴⁸ Thus, in IgE-dependent reactions, mast cells are likely to represent an important initial source of TNF- α and perhaps other cytokines.

Mast cells represent a potential source of many cytokines and growth factors that might influence IgE-

associated allergic inflammation, and the synthesis and release of many of these products can be induced by IgE-dependent mechanisms. For example, certain mouse mast cells activated by Fc ϵ RI contain increased levels of messenger RNA (mRNA) for many cytokines, including IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-13, GM-CSF, transforming growth factor- β (TGF- β), TNF- α , VPF/VEGF, IFN- γ , and the chemokines MIP-1 α , MIP-1 β , MCAF (monocyte chemoattractant protein [MCP]-1), MARC, and I-309, or secrete substances with the corresponding bioactivities, including IL-1, IL-3, IL-4, IL-6, IL-9, IL-13, GM-CSF, and TNF- α .^{26,30-34,50-54} The list of cytokines/growth factors associated with various populations of purified or in vitro-derived human mast cells (or detected in human mast cells in situ) includes IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, TNF- α , VPF/VEGF, GM-CSF, SCF, bFGF, and MIP-1 α .^{33,34,47-50,55-72}

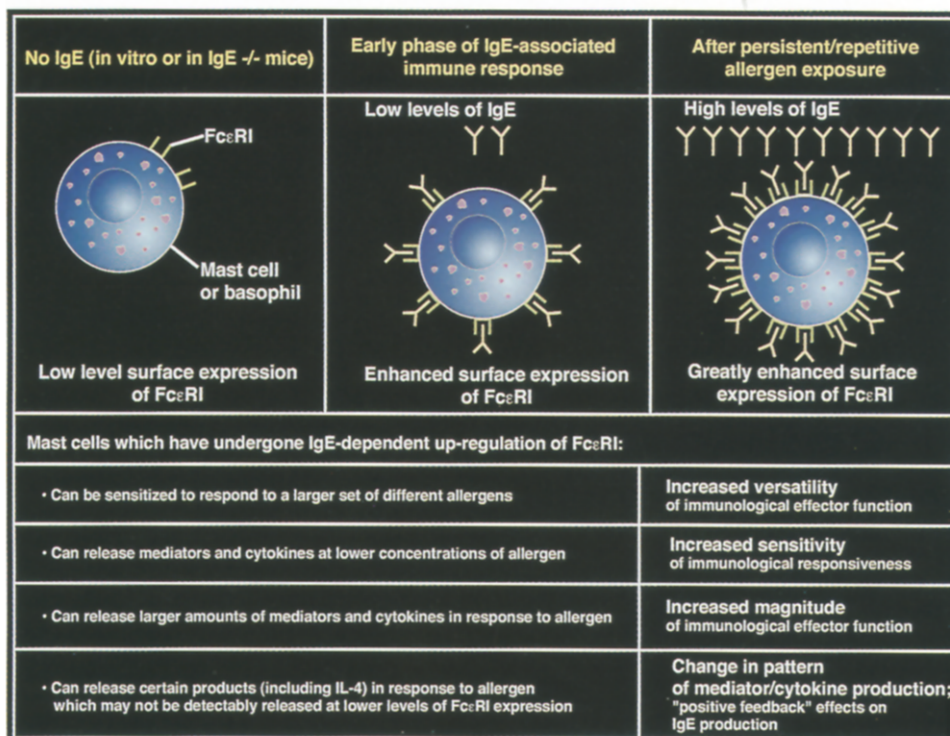


FIG 3. Potential consequences, for mast cell effector and possible immunoregulatory functions, of IgE-dependent up-regulation of surface expression of FcεRI. (Reproduced with permission from Galli SJ, Lantz CS. Allergy. In: Paul WE, editor. Fundamental immunology. 4th ed. Philadelphia: Lippincott-Raven; 1999. p 1127-74.)

FCεRI

In humans, mast cells are thought to express immunologically specific effector function in allergic disorders primarily as a result of their ability to bind IgE antibodies to FcεRI, the high-affinity receptor for IgE; aggregation of the FcεRI on binding of allergen to multiple cell-bound IgE antibodies activates mast cells to release all classes of mediators.^{73,74} The expression of FcεRI on the surface of mouse mast cells appears to occur early in their differentiation or maturation,⁷⁵⁻⁷⁸ and mature mouse mast cells can express FcεRI in excess of 10⁵ per cell.⁷⁹ In normal mice FcεRI are detectable only on mast cells and basophils.⁷⁴ Human mast cells and basophils also express large numbers of FcεRI on their cell surface; however, at least under some circumstances many other potential effector cells in humans, including Langerhans cells, blood monocytes and macrophages, circulating dendritic cells, and eosinophils also may express at least small numbers of this receptor.⁷⁴ Thus many cells in addition to mast cells and basophils may contribute to the expression of IgE-associated immune reactions in humans.

On the other hand, mouse mast cells express the receptor for IgG₁ (FcγRIII), which uses the same β- and γ-chains as FcεRI, as do mouse monocytes and macrophages, neutrophils, and natural killer cells.⁷⁴ FcγRIII can bind IgG₁ antibodies, which typically are produced along with IgE antibodies during T_H2 responses in mice.^{23,74,80}

The widespread distribution of FcγRIII on various mouse effector cells permits these cells, in addition to mast cells and basophils, to participate in the expression of IgE- (and IgG₁-) associated immune responses in mice.

Studies in both mice and humans have revealed that levels of FcεRI surface expression on mast cells and basophils can be regulated by levels of IgE.^{58,61,81-84} For example, genetically IgE-deficient mice exhibit a dramatic (greater than 80%) reduction, relative to wild-type mice, in mast cell and basophil FcεRI expression, and this abnormality can be corrected by administration of monomeric IgE in vivo.^{81,82} Such IgE-dependent up-regulation of FcεRI expression permits mouse or human mast cells to exhibit IgE-dependent mediator release on challenge with lower concentrations of specific antigen or anti-IgE or to secrete increased amounts of preformed and lipid mediators at a given level of challenge, as well as to produce strikingly higher levels of certain cytokines and growth factors.^{33,58,61,82}

This work thus identifies a potentially important mechanism for enhancing the expression of effector-cell function in IgE-dependent allergic reactions or immunologic responses to parasites (Fig 3). Because this process also can increase the ability of mast cells to produce IL-4,⁸² IL-13,⁵⁸ and MIP-1α,⁶¹ all of which can promote IgE production,^{58,61,82} IgE-dependent up-regulation of FcεRI expression may also be part of a positive-feedback

mechanism for inducing further production of IgE and thereby promoting a persistent "T_H2 bias" of the immune system in subjects with parasite infections or allergic diseases associated with high levels of IgE. Although the mechanism(s) by which monomeric IgE regulates FcεRI expression are not yet fully understood (at least in part, the phenomenon reflects the ability of IgE binding to stabilize the expression of FcεRI on the cell surface^{74,82}), research in this area may suggest novel therapeutic approaches for the management of allergic disease.

MAST CELLS AND IgE-ASSOCIATED IMMUNE RESPONSES

It is useful to think of the effector phases of IgE-associated immune responses as occurring in 3 temporal patterns: (1) acute reactions, which develop within seconds or minutes of allergen exposure, (2) late-phase reactions, which develop within hours of allergen exposure, often after at least some of the effects of the acute reaction have partially diminished, and (3) chronic allergic inflammation, which can persist for days to years.

Acute allergic reactions

Passive cutaneous anaphylaxis (PCA) represents one of the simplest experimental models of an acute allergic reaction. In this model IgE (and/or, in mice, IgG₁) antibodies of defined allergenic specificity are injected into the skin, and, at a suitable interval thereafter (for IgE-dependent PCA reactions, typically 24 to 48 hours), the specific allergen is administered intravenously.^{85,86} The ensuing FcεRI aggregation induced in cutaneous mast cells at the site where IgE was injected results in the secretion of all classes of mast cell-derived mediators. These products in turn produce multiple local effects, including enhanced local vascular permeability (leading to leakage of plasma proteins, including fibrinogen, resulting in local deposition of cross-linked fibrin and tissue swelling), increased cutaneous blood flow, with intravascular trapping of red blood cells (because of arteriolar dilation and increased loss of intravascular fluid from postcapillary venules, producing erythema), and other effects, such as itching, resulting from the stimulation of cutaneous sensory nerves by histamine.^{27,85,86}

We have shown that mast cell-deficient *Kit^W/Kit^{W-ν}* mice are not able to express detectable PCA reactions.⁸⁶⁻⁸⁸ By contrast, IgE-dependent PCA reactions can be readily expressed in *Kit^W/Kit^{W-ν}* mice at cutaneous sites that have been selectively repaired of their mast cell deficiency.^{86,87} Similar approaches have been used to show that essentially all the assessed acute consequences of IgE-dependent reactions elicited in the respiratory tract⁸⁹ or stomach⁹⁰ of mice are also mast cell dependent. Studies in mast cell-deficient mice indicate that mast cells are also essential for the cardiopulmonary changes and death associated with IgE-dependent passive systemic anaphylaxis responses.⁹¹ On the basis of this evidence, it appears very likely that mast cells are essential for the expression of at least the major features of IgE-dependent acute allergic reactions in mice.

Mast cell-leukocyte cytokine cascades: A mechanism by which mast cells can contribute to late-phase reactions and chronic allergic inflammation

Several groups have shown that various features of late-phase reactions or chronic allergic inflammation can be expressed in mice that lack IgE, B cells, or mast cells.⁹²⁻¹⁰⁰ In part because of such work, interest has focused increasingly on eosinophils and T_H2 lymphocytes as key effector cells of these phases of allergic inflammation.¹⁰¹⁻¹¹⁵ Both eosinophils and T_H2 cells are well represented in the chronic inflammatory infiltrates in the airways of patients with asthma and they are known to produce cytokines and other mediators that may contribute to the expression of late-phase reactions and chronic allergic inflammation, in asthma as well as in other settings.¹⁰¹⁻¹¹⁵

Although this remains an important area of research, we feel that the key question is not whether IgE and mast cells, as opposed to eosinophils or T cells, are mainly responsible for the pathologic features associated with chronic allergic diseases (because in different settings it is likely that each type of effector cell may be important) but to identify the extent to which particular clinically significant characteristics of these disorders reflect the specific contributions of distinct potential effector cell types.

Our group has formulated the hypothesis that a "mast cell-leukocyte cytokine cascade" can critically contribute to the initiation, amplification, and perpetuation of IgE-associated allergic inflammation in the airways and other sites.^{7,14,23,26,28,31} Although classic studies of late-phase reactions proposed that IgE and mast cells may contribute to the expression of these responses,¹¹⁶ this work was performed long before it was clear that mast cells, basophils, and eosinophils represented potential sources of cytokines. Our hypothesis thus extends the earlier work by emphasizing the potential roles of cytokines, derived from mast cells and other cell types, in the acute, late-phase, and chronic manifestations of allergic inflammation. Specifically, we propose that the activation of mast cells through the FcεRI can initiate both the acute and late-phase components of the response, the latter orchestrated in part through the release of TNF-α and other cytokines that can influence the recruitment and function of additional effector cells. These recruited cells then promote the further progression of the inflammatory response by providing additional sources of certain cytokines that may also be produced by mast cells stimulated by continuing exposure to allergen, as well as new sources of cytokines and other mediators that may not be produced by mast cells. Certain mast cell cytokines, such as TNF-α, VPF/VEGF, and TGF-β, may also contribute to chronic allergic inflammation through effects on fibroblasts, vascular endothelial cells, and other cells resident at the sites of these reactions.^{33,34,53,54} Finally, mast cell activation may directly or indirectly promote the release of cytokines from certain other cells resident in the tissues (eg, in the respiratory tract; such cells would include alveolar macrophages, eosinophils, bronchial epithelial cells,

vascular endothelial cells, fibroblasts, epithelial cells, and nerves); together, the diverse cytokines that are released in these responses then contribute to the vascular and epithelial changes and to the tissue remodeling, angiogenesis, and fibrosis that can be so prominent in IgE-associated chronic allergic inflammation and many other disorders associated with mast cell activation and leukocyte infiltration.^{14,28,117,118} At certain points in the natural history of these complex processes, cytokines and other mediators derived from mast cells, or from eosinophils or other recruited cells, may also contribute to the down-regulation of the response. As described below, certain aspects of this hypothesis have already been confirmed by studies in “mast cell knock-in mice” and also are supported by more indirect lines of evidence, including data derived from studies in human subjects.

Mast cell–derived TNF- α importantly contributes to IgE-dependent cutaneous late-phase reactions in mice

Our studies in “mast-cell knock-in mice” showed that mast cells were required for essentially all the leukocyte infiltration observed in the skin after challenge with IgE and specific antigen and that ~50% of such IgE- and mast cell–dependent leukocyte infiltration was inhibitable with a neutralizing antibody to recombinant mouse TNF- α .⁸⁷ Other mast cell–derived mediators, including histamine and serotonin, probably also contribute to mast cell–associated leukocyte infiltration in this setting. Granulocyte recruitment in this system was affected minimally, if at all, in mice that lacked either P-selectin or E-selectin but was essentially eliminated in mice that lacked both these selectins.¹¹⁹ Finally, we showed that either dexamethasone or cyclosporin A (CsA) can substantially suppress (1) the IgE-dependent secretion of TNF- α by mouse mast cells in vitro, (2) the leukocyte recruitment induced by the injection of recombinant mouse TNF- α into mouse skin in vivo, and (3) the mast cell-, IgE-, and TNF- α –dependent leukocyte infiltration observed at cutaneous reaction sites in mice in vivo.¹²⁰

Taken together, these findings demonstrate the importance of mast cells and TNF- α , as well as P- and E-selectin, in the leukocyte recruitment associated with IgE-dependent allergic cutaneous inflammation in mice. Our findings are also consistent with the hypothesis that at least some of the therapeutic benefit of drugs such as corticosteroids and CsA, both in asthma and in other inflammatory disorders,^{121,122} may reflect the ability of these agents to interfere with multiple steps in the pathogenesis of mast cell–leukocyte cytokine cascades, including the mast cell–dependent production of TNF- α and other cytokines.¹²⁰

TNF- α and asthma

TNF- α can induce bronchial hyperresponsiveness in rats.¹²³ Moreover, several groups have provided evidence that TNF- α may contribute to the initiation and perpetuation of the inflammation associated with allergic asthma

and that the mast cell may represent an important source of TNF- α in this setting. Bradding et al⁴⁸ reported that TNF- α expression is up-regulated in the airway mucosa of subjects with allergic asthma and that this expression of TNF- α occurs predominantly in mast cells and monocytes/macrophages; no TNF- α immunoreactivity was localized in either T cells or eosinophils. On the other hand, Walsh et al⁴⁷ found that human skin mast cell immunoreactivity for TNF- α decreased in association with mast cell activation (probably reflecting release of stored TNF- α), and Finotto et al¹²⁴ reported that eosinophils infiltrating nasal polyps, as well as eosinophils secreting TNF- α in vitro, exhibited little or no TNF- α by IHC although most of these cells were strongly positive for TNF- α mRNA by in situ hybridization. Moreover, Ohkawara et al¹²⁵ found that three resident cell populations in human lung fragments expressed TNF- α by IHC 4 hours after anti-IgE challenge in vitro: mast cells, tissue and alveolar macrophages, and bronchial epithelial cells, whereas no cells exhibited TNF- α immunoreactivity in specimens incubated with medium alone. Taken together, this work suggests that “normal” human lung mast cells might exhibit low levels of stored TNF- α but that expression of the cytokine can be up-regulated in mast cells challenged via the Fc ϵ RI.

Mast cells and chronic tissue eosinophilia

Are mast cells important in orchestrating eosinophil infiltration into the airways, a hallmark of human asthma? Many studies of “asthma models” in mice have suggested that the answer to this question is no. For example, at least 4 studies with mast cell–deficient *Kit^W/Kit^{W-v}* mice reported that mast cells were not essential for the development of antigen-induced infiltration of the airways with eosinophils.^{92-94,99} However, in each of these studies the investigators used strong procedures of sensitization and challenge, often in conjunction with an adjuvant such as alum, approaches that favor the production of strong nonspecific antibody responses.

These studies prove that mast cells are not essential for antigen-induced eosinophil infiltration, at least under the conditions of antigen sensitization and challenge tested. However, human subjects with asthma often express dramatic pathophysiologic responses after sensitization and challenge with very low doses of specific antigen.^{126,127} In settings such as this (ie, in “naturally” sensitized subjects exposed to low doses of antigen), mast cells may serve as critical “amplifiers” of IgE-associated inflammation, including eosinophil infiltration.¹²⁸ In accord with this hypothesis, Kung et al,¹²⁹ employing a protocol in which aerosol challenge with ovalbumin was performed only twice in a single day, found that eosinophil infiltration of the airways in *Kit^W/Kit^{W-v}* mice was $\leq 50\%$ of that in the $+/+$ mice. Subsequently, using “mast cell knock-in mice,” we showed that mast cells can importantly contribute to the recruitment of eosinophils to the airways, especially in a model of asthma that does not use alum as an adjuvant during sensitization.¹³⁰ On the basis of these findings, we hypothesize that mast cells

can indeed be critical in regulating eosinophil infiltration during allergic inflammation in mice, but that this role may be undetectable or dispensable in models that induce strong immunologically nonspecific responses in addition to specific immunity, such as when alum or other adjuvants are used for sensitization or when challenge is performed with large doses of antigen.

The specific mechanisms by which mast cells might regulate eosinophil recruitment or activation remain to be determined, but it seems reasonable to suggest that chemokines, particularly eotaxin, may be involved. Thus Das et al¹³¹ have provided evidence that mast cells can contribute to eotaxin-induced eosinophil accumulation in vivo, Harris et al¹³² showed that mast cell-deficient *Kit^W/Kit^{W-v}* mice exhibited a delayed peak of eosinophil influx, as well as reduced numbers of peritoneal eosinophils, after intraperitoneal injection of eotaxin, and Hogaboam et al¹³³ reported that mast cell fibroblast coculture promotes enhanced production of eotaxin by the mast cells and that this process can be enhanced further by TNF- α . Other groups have shown that human lung mast cells can produce IL-5 and GM-CSF,^{48,63,67} both of which can enhance eosinophil recruitment or activation.

Mast cells and tissue remodeling

Persistent chronic allergic inflammation can result in remodeling of the affected tissues, and these structural changes are often associated with functional alterations. For instance, some patients with asthma have irreversible changes in lung function despite apparently appropriate and aggressive anti-inflammatory therapy,¹³⁴ and many subjects with asthma exhibit a decline in lung function over time.^{135,136} Moreover, airway tissues from patients with asthma can exhibit structural abnormalities such as smooth muscle hypertrophy, mucus gland hyperplasia, blood vessel proliferation, and collagen deposition beneath the epithelial basement membrane.¹³⁷⁻¹⁴⁰

We feel that it is too soon to conclude whether, and to what extent, mast cells contribute to the tissue remodeling associated with chronic allergic inflammation. However, several lines of evidence suggest that mast cells may indeed participate in this process. As summarized in Fig 2, mast cell-derived proteases, cytokines, growth factors, and other mediators have been shown to have a number of in vitro or in vivo effects that are consistent with the hypothesis that mast cells can promote tissue remodeling. For example, Kanbe et al¹⁴¹ recently showed that human skin, lung, and synovial mast cells are strongly positive for MMP-9 by IHC. Because they can promote the degradation of extracellular matrix, MMPs are believed to play a role in the pathogenesis of certain disorders associated with tissue remodeling.¹⁴² Various populations of mast cells also have been identified as sources of several growth-promoting peptide mediators, including TNF- α , VPF/VEGF, FGF-2 (also known as bFGF), platelet-derived growth factor, TGF- β , and nerve growth factor (NGF)^{31-34,47-49,53,71,143}; in aggregate, these products might contribute to the neovascularization, connective tissue remodeling, or re-epithelialization associated

with chronic tissue remodeling, in the context of allergic disease and in other settings.

However, there are very few studies that assess the actual importance of mast cells as sources of such growth factors or as effectors of tissue remodeling in vivo. By using the "mast cell knock-in mouse" model, we showed that the increased expression of type I collagen mRNA observed at sites of IgE-dependent PCA reactions in vivo was entirely mast cell dependent⁵³; parallel in vitro studies indicated that mast cell-dependent enhancement of skin fibroblast collagen mRNA expression was markedly diminished by absorption of mast cell supernatants with antibodies against TGF- β 1 or TNF- α and was essentially eliminated by absorption of the supernatants with antibodies against both cytokines.^{53,54} Miller et al¹⁴⁴ recently showed that TGF- β 1 can also markedly up-regulate the ability of mouse bone marrow-derived mast cells to produce and store the mucosal mast cell β -chymase, mouse mast cell protease-1. On the other hand, Fang et al¹⁴⁵ have shown that mast cell expression of gelatinase B (MMP-9) by dog mast cells can be induced by SCF but down-regulated by TGF- β . Finally, recent evidence indicates that human mast cells can themselves represent a potential source of SCF,^{69,146,147} which can be cleaved by human mast cell-derived chymase to release soluble biologically active SCF from the cell membrane-associated form of the molecule.^{146,148} Taken together with evidence that SCF itself can induce mast cell activation and release of VPF/VEGF and other mediators,^{1,33} these findings suggest that mast cells can participate in intricate paracrine and autocrine networks that may both contribute to tissue remodeling and influence mast cell numbers and function.

CONCLUSIONS

Data derived from "mast cell knock-in mice" support the notion that mast cells not only represent the key effector cells of acute IgE-dependent reactions but also can contribute significantly to certain features of IgE-associated late-phase reactions and chronic allergic inflammation (Table I). However, even in the mouse, the mechanisms that regulate allergic inflammation are complex and can exhibit significant redundancy, and this is especially true of the late-phase and chronic aspects of allergic inflammatory responses. Thus, given the right experimental conditions (often involving antigen sensitization with adjuvants and challenge with high doses of antigen), certain important features of allergic inflammation, such as eosinophil infiltration or airway hyperreactivity to cholinergic stimulation, can occur in mice by mechanisms that are entirely mast cell independent.^{92-94,99,128}

There is no reason to believe that the effector mechanisms of allergic inflammation in humans are any less complex or redundant than those in mice. And in humans, unlike in mice, one generally does not have the opportunity to analyze the expression of these reactions in subjects with defined mutations that affect various potential components of immunological or inflammatory responses. Nevertheless, we believe that the available data from humans,

TABLE I. Key concepts of mast cell biology

Mast cells are derived from hematopoietic precursors but typically complete their maturation and reside in peripheral connective tissues (by contrast, basophils generally mature in the bone marrow, circulate in mature form, and must be recruited to sites of inflammation).
In humans, FcεRI is expressed in large numbers (as the αβγ ₂ form) on mast cells and basophils and, in smaller numbers (as the αγ ₂ form), on monocytes, macrophages, dendritic and Langerhans cells, and eosinophils.
In normal mice, FcεRI are only expressed on mast cells and basophils, but mouse mast cells can be activated by IgG ₁ , as well as by IgE.
Mast cells produce preformed mediators (including histamine and proteases) and newly synthesized lipid mediators (eg, LTC ₄ and PGD ₂) that can promote inflammation, bronchial and gastrointestinal smooth muscle contraction, nerve stimulation, mucus secretion, and tissue remodeling.
Mast cells also can produce many cytokines (including those that promote T _H 2-type responses, promote inflammation, and regulate tissue remodeling).
Exposure to monomeric IgE can induce increased surface expression of FcεRI on mast cells and basophils, which in turn can permit such cells to express enhanced effector and potential immunoregulatory functions.
Mast cells are critical for the expression of acute allergic reactions and, through cytokine production and other mechanisms, can contribute to the expression of late-phase reactions and chronic allergic inflammation.
"Mast cell knock-in mice" (genetically mast cell-deficient <i>Ki^W/Ki^{W-v}</i> mice that have been selectively reconstituted with wild-type or genetically altered mast cells) permit analyses of the roles of mast cells and their products in the expression of IgE-dependent and other biologic responses in vivo.

when taken together with the findings from murine systems, support the following hypotheses (most of which can much more readily be tested in mice than in humans).

It seems very likely that IgE-dependent mast cell activation importantly contributes to the expression of many acute allergic reactions, including acute allergen-induced bronchoconstriction in human atopic asthma, and that mast cells can contribute to the leukocyte infiltration associated with allergic inflammation as well.^{14,27,28,149-151} Notably, 2 newly recognized aspects of FcεRI function or expression provide strong support for the hypothesis that mast cells (and perhaps other FcεRI⁺ effector cells, such as basophils) may have a particularly important role in initiating or amplifying IgE-dependent inflammatory reactions, especially in response to low-dose antigen challenge. First, it is now clear that the FcεRI β-chain functions as an "amplifier" of signaling through this receptor, which can markedly up-regulate the magnitude of the mediator release response to FcεRI aggregation.^{152,153} Moreover, it has been reported that certain mutations that result in amino acid substitutions in the human β-chain may be linked to atopic disease.^{74,152,153} Second, studies in both mice^{81,82,154} and humans^{58,61,83} indicate that the level of expression of FcεRI on the surface of mast cells and basophils can be regulated by ambient concentrations of IgE and that this IgE-dependent up-regulation of FcεRI expression both permits the cells to exhibit mediator release at lower concentrations of specific antigen or anti-IgE^{58,61,82,83} and also primes such cells to produce strikingly higher levels of certain mediators, including IL-4 and other cytokines,^{33,58,61,82} under optimal conditions of antigen challenge.

These findings thus identify 2 FcεRI-dependent mechanisms (β-chain "amplifier" function, IgE-dependent up-regulation of FcεRI surface expression) for enhancing the sensitivity and intensity of the effector phase of IgE-dependent reactions. Both of these mechanisms could promote enhanced IgE-dependent mast cell effector function not only in acute allergic reactions but also in late-phase reactions and chronic allergic inflammation.

In addition to their function as effector cells in allergic

inflammation, there are at least 3 mechanisms by which mast cells might contribute to the development or persistence of T_H2 responses: antigen processing/presentation, antigen transport, and the production of immunoregulatory cytokines. Work in mice¹⁵⁵⁻¹⁵⁷ and rats^{158,159} indicates that mast cells may participate in antigen processing or antigen transport through epithelial barriers. However, the extent to which such function is important in the development of T_H2 responses in mice or rats in vivo remains to be determined, and there is little information about the ability of normal human mast cells to process antigen or to promote its transport. On the other hand, in humans, unlike in mice, the FcεRI can be expressed on several cell types in addition to mast cells and basophils.^{74,160} Moreover, the form of the FcεRI expressed on human monocytes and dendritic cells (which lacks the β chain) can function to enhance the processing/presentation of antigens attached to proteins that are recognized by the cells' surface-bound IgE.^{160,161} Thus, in humans, IgE may not only serve to arm mast cells and other effectors of the efferent limb of acquired immune responses but may also contribute, by promoting antigen processing/presentation, to the evolution of such responses.

Mast cells may also express immunoregulatory function through the production of certain cytokines. For example, both mouse and human mast cells can produce IL-4 and IL-13 and other cytokines that can enhance IgE production. This fact, taken together with the new findings about IgE-dependent regulation of FcεRI surface expression, suggest a potential positive feedback mechanism (↑IgE → ↑FcεRI → ↑antigen-, IgE-, and FcεRI-dependent release of IL-4⁸² or IL-13⁵⁷ → ↑IgE) by which mast cells (and possibly basophils) may enhance the further evolution and persistence of T_H2-biased, IgE-associated immune responses. Finally, mast cells and basophils may enhance IgE production by expression of the CD40 ligand.^{57,162}

The clinical significance of many of these new findings largely remains to be established. However, this work clearly supports a complex, but more unified, view of the

pathogenesis of allergic diseases, which proposes that both T cells and mast cells (and other FcεRI⁺ cells) can have both effector cell and immunoregulatory roles in these disorders. This hypothesis has a number of interesting implications with respect to existing, and proposed, therapeutic approaches for asthma and other allergic diseases. For example, anti-IgE-based strategies, which are already in clinical testing⁸³ not only may reduce CD23-dependent antigen presentation¹⁶³ and FcεRI⁺ cell effector function⁸¹⁻⁸³ but also may diminish FcεRI⁺ cell immunoregulatory function by reducing both mast cell (or basophil) IL-4/IL-13 production^{57,82} and FcεRI-dependent antigen presentation.¹⁶⁰ Conversely, the findings that corticosteroids and other "immunosuppressive" drugs can diminish mast cell cytokine production, as well as reduce IgE- and mast cell-dependent inflammation and leukocyte recruitment in mice *in vivo*,¹²⁰ raise the possibility that the clinical benefits of such agents in allergic inflammation may reflect, at least in part, actions on mast cells, as well as on the T cells, eosinophils, and other effector and target cells that participate in these complex disorders.

Finally, no discussion of allergic inflammation would be complete without a brief consideration of the possibility that some of the cells and mediators that participate in these processes may help to down-regulate the responses. Even cytokines that mediate certain "proinflammatory" effects may have other actions that are "anti-inflammatory" in nature. For example, studies of TGF-β1-null mice indicate that the anti-inflammatory effects of TGF-β may be quite important *in vivo*,¹⁶⁴ and both mast cells^{53,54} and eosinophils,^{164,165} which are recruited in large numbers to sites of allergic inflammation, represent potential sources of this cytokine; eosinophils also represent a potential source of TGF-α.¹⁶⁶ It is thus possible that certain "effectors" of allergic inflammation, including the mast cell and the eosinophil, can express some cytokine-dependent actions that help to limit the duration or intensity of the reactions. If major cellular "effectors" of allergic inflammatory responses can indeed also express functions that are "anti-inflammatory" or "reparative," then the identification of factors that can instruct these cells to abandon their proinflammatory and "destructive" tendencies in favor of more protective actions would be of considerable interest.

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