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Effector and potential immunoregulatory roles of mast cells in IgE-associated acquired immune responses

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Mast cells are best known as critical effector cells in anaphylaxis and other examples of IgE-associated immediate hypersensitivity reactions. However, mast cells also can contribute to the development of the late-phase responses that occur in some sensitized subjects hours after initial exposure to specific antigen, and can promote many of the features of chronic allergic inflammation, including tissue remodeling and functional changes in the affected organs. In addition to such effector cell functions in IgE-associated immune responses, recent evidence indicates that mast cells can importantly influence the sensitization phase of at least some acquired immune responses, and can contribute to the pathology of autoimmune disorders and to the expression of peripheral tolerance.

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Introduction

Mast cells are important effector cells in anaphylaxis and in IgE-associated allergic diseases such as atopic asthma, allergic rhinitis (hayfever) and atopic dermatitis (eczema) [1–3]. In such subjects, mast cells bear on their surface, bound to high affinity receptors for IgE (i.e. FcεRI), IgE antibodies that have specificity for the antigen(s) to which the subject is sensitive [1–3]. In such antigen-sensitized individuals, subsequent exposure to bi- or multi-valent antigen that is recognized by the mast cell-bound IgE initiates crosslinking of FcεRI-bound IgE on the mast cell surface, aggregation of the FcεRI, and the subsequent activation of mast cells to secrete preformed mediators stored in the cells' granules (in a process called 'degranulation') and to synthesize *de novo* several cytokines,

chemokines and lipid mediators [1–3]. This IgE-dependent mast cell activation, in some settings together with similar antigen-, IgE- and FcεRI-dependent activation of basophilic granulocytes ('basophils', which also express FcεRI), in turn contributes to the acute manifestations of IgE-dependent reactions to antigen, including anaphylaxis, bronchoconstriction (in subjects with asthma), and sneezing and rhinitis (in subjects with allergic rhinitis) [1–3].

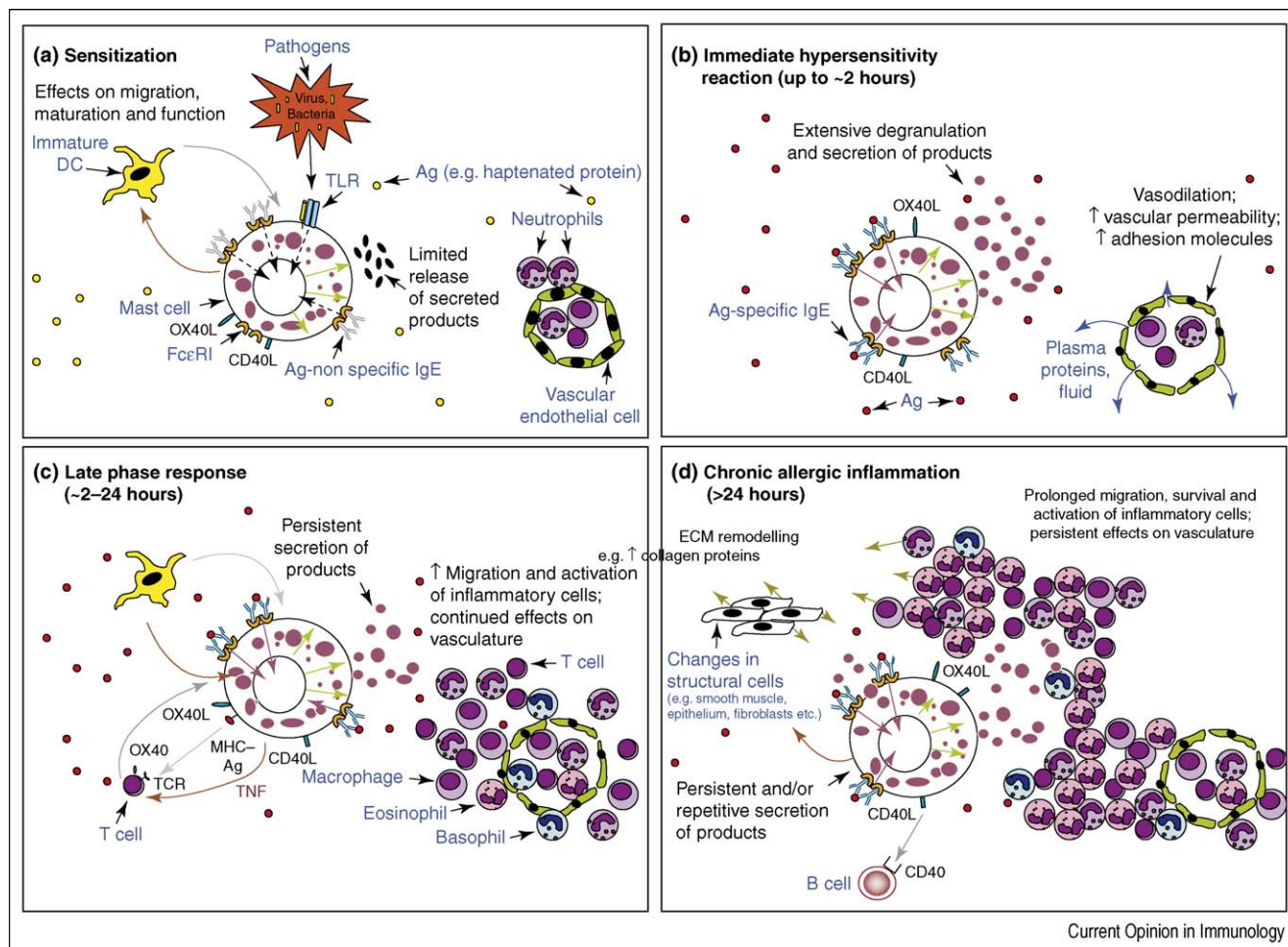
This review focuses especially on the roles of mast cells in: the sensitization phase of acquired immune responses, when the host first encounters antigen; the immediate 'mast cell autonomous' phase of those immediate hypersensitivity reactions that are initiated when challenge with specific antigen induces activation of tissue mast cells via the FcεRI-bound antigen-specific IgE of the cells; the IgE-associated late phase response (LPR) that is characterized by recruitment of inflammatory cells to the site of antigen challenge; and IgE-associated chronic allergic inflammation that is associated with structural and related functional changes in the underlying tissue (Figure 1). But, before addressing these topics, we will briefly review certain important aspects of mast cell biology, as well as some mouse models that are currently being used to assess mast cell function *in vivo*.

Basic biology of mast cells

In mammals and other vertebrates, mast cells reside in virtually all vascularized tissues and can be especially numerous in anatomical sites that are directly exposed to the environment, including the skin, airways and gastrointestinal tract [1–4]. It has long been known that mast cells arise from hematopoietic progenitor cells and that mature mast cells ordinarily do not circulate in the blood; instead, mast cells acquire their mature phenotype locally in the tissues in which they will ultimately reside [5]. Two reports recently attempted to clarify the hematopoietic developmental pathway that leads to the generation of committed mast cell progenitors in adult mice, but arrived at rather different conclusions [6,7]. Although it will be important to resolve the differences between the results presented in those two reports, several lines of evidence indicate that changes in mast cell numbers, as well as local changes in the tissue distribution and/or phenotypic characteristics of the cells, can be finely controlled by growth factors such

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Figure 1



Mechanisms by which mast cells (MCs) might **(a)** promote the transition from innate to acquired immune responses or contribute to the development of **(b)** immediate hypersensitivity reactions, **(c)** late phase responses and **(d)** chronic allergic inflammation. Some of the MC surface structures and secreted products that can influence various aspects of the biology of dendritic cells (DCs), T cells, B cells, granulocytes and other leukocytes, as well as vascular endothelial cells and other cells normally resident in the affected tissues such as smooth muscle cells, fibroblasts, epithelial cells, nerves, etc., are shown. (a) MCs can respond to local signals (e.g. certain haptenated non-microbial proteins or other antigens [Ags], or the products of pathogens). Such responses can include secretion of mediators or expression of other functions that can enhance the sensitization phase of acquired immune responses through effects on DC migration, maturation and/or function. For example, exposure to Ag-non specific IgE might 'prime' MCs to express higher levels of mRNA for some crucial mediators or cytokines (see main body of text for details). MC activation also can contribute to the development of the inflammation associated with certain innate immune responses. (b) In hosts sensitized to express an IgE-associated immune response, secondary exposure to bi- or multi-valent Ag initiates IgE + Ag-dependent MC activation. The clinical features of the ensuing 'immediate hypersensitivity' reactions primarily reflect the actions of cells normally resident at such sites (MCs, vascular endothelial cells and smooth muscle cells, nerves, etc.). (c) Sometimes, IgE-associated 'immediate' reactions are followed, hours later, by 'late phase responses' (LPRs). MCs can contribute to such reactions through effects of secreted mediators that promote the recruitment and/or functional activation of circulating leukocytes, as well as by persistent effects on cells resident at the site. IgE-dependent MC activation can also promote DC migration from sites of Ag challenge. Direct activation of effector T cells by Ag, and perhaps bi-directional interactions between MCs and T cells (see text), also can contribute to LPRs. (d) At sites of prolonged or repetitive exposure to specific Ag, MC activation can be prolonged and/or recurrent, MC numbers can increase, and MC phenotype and/or anatomical distribution can change. In such settings, MCs can contribute significantly to many of the features of chronic allergic inflammation, including functional changes in the affected organ (e.g. airway hyperresponsiveness to immunologically non-specific agonists of bronchoconstriction in the asthmatic lung). MCs also might have effects (including those mediated through interactions of MC CD40 ligand [CD40L] with B cell CD40 and/or effects of MC-derived histamine on T-cell polarization [see text]) that could promote local IgE production. However, in some circumstances (not shown), certain MC products or functions can serve to limit or to resolve aspects of these inflammatory responses. Arrows within MCs: black dashed arrow, signaling related to occupancy of FcεRI by IgE in the absence of known specific antigen; red arrow, strong FcεRI aggregation signal; green arrow, synthesis of newly formed mediators and products.

as stem cell factor — the main survival and developmental factor for mast cells — interleukin-3 (IL-3) and the T helper type 2 (Th2) cell-associated cytokines IL-4 and IL-9, as well as probably many other factors [1–5,8,9**].

Although the best-studied mechanism of mast cell activation is that induced by the aggregation of the high affinity receptor for IgE — FcεRI — for example, by IgE and specific antigen, many other stimuli can also elicit the secretion of mast cell mediators and/or influence the responsiveness of the cells to IgE and specific antigen or other stimuli of activation [1,2,8,10–12]. Several cell surface receptors or intracellular molecules can negatively regulate mast cell activation or signaling [1–4,8,10,11]; however, this important topic is beyond the scope of this review. Instead, we focus primarily on those stimuli and consequences of mast cell activation that appear to promote mast cell function in IgE-associated adaptive immune responses. We particularly emphasize findings that have been derived from *in vivo* studies of mast cell function, especially studies of mast cell-engrafted *c-kit* mutant mice.

C-kit mutant mast cell-deficient and ‘mast cell knock-in’ mice

In vitro studies using mouse bone marrow-derived cultured mast cells (BMCMCs) or human mast cell populations can be useful for investigating mechanisms by which mast cells might influence adaptive immune responses [13–15,16*,17,18**]. However, it is important to attempt to assess the *in vivo* relevance and biological

importance of such *in vitro* observations. *C-kit* mutant mice that virtually lack mast cell populations, but that can be successfully repaired of their mast cell deficiency by selective systemic or local engraftment of wild-type (WT) or genetically altered mast cells (i.e. ‘mast cell knock-in mice’), can be employed to assess the importance of mast cells in regulating the expression of biological responses *in vivo*.

The most commonly used model for such studies has been the (WB/ReJ x C57BL/6)F₁-*Kit*^{W/W^{-v}}, or WBB6F₁-*Kit*^{W/W^{-v}}, mouse [19,20]. However, C57BL/6-*Kit*^{W-sh/W-sh} mice are gaining popularity as an alternative model (see Table 1). Although each of these *c-kit* mutant mice is profoundly mast cell-deficient and virtually lacks melanocytes and interstitial cells of Cajal, the double-dose of *W-sh* mutations in C57BL/6-*Kit*^{W-sh/W-sh} mice results in fewer, or less severe, phenotypic abnormalities than those observed in *Kit*^{W/W^{-v}} mice (Table 1). Like WBB6F₁-*Kit*^{W/W^{-v}} mice, C57BL/6-*Kit*^{W-sh/W-sh} mice can be selectively engrafted with BMCMCs [21,22]. However, unlike WBB6F₁-*Kit*^{W/W^{-v}} mice, C57BL/6-*Kit*^{W-sh/W-sh} mast cell-deficient mice are fertile [23] and therefore can easily be crossed with mice that carry other defined genetic abnormalities of interest.

Transition from innate to acquired immune responses: the initial encounter with antigen

Mast cells can provide many signals that have the potential to enhance or to suppress aspects of the sensitization phase of adaptive immune responses [4,12] (Figure 1a). Bryce *et al.* [24] reported that mast cells and physiological

Table 1

Comparison of phenotypic characteristics of *c-kit* mutant C57BL/6-*Kit*^{W-sh/W-sh} and WBB6F₁-*Kit*^{W/W^{-v}} mice.

Phenotypic characteristics in naïve mice (at baseline)	C57BL/6- <i>Kit</i> ^{W-sh/W-sh} mice	WBB6F ₁ - <i>Kit</i> ^{W/W^{-v}} mice
Reduced KIT signaling	Yes	Yes
Sterile	No	Yes
Anemic	No	Yes
Virtually lack melanocytes	Yes	Yes
Lack interstitial cells of Cajal ^a	Yes	Yes
Virtually lack mast cells in all tissues ^a	Yes	Yes
Non-irradiated mice develop mast cell populations after adoptive transfer of congenic <i>Kit</i> ^{+/+} BMCMCs	Yes	Yes
Unfractionated bone marrow cells	No ^b	Yes
Normal levels of neutrophils and macrophages in bone marrow, spleen and peritoneal cavity ^a	Yes	Yes
Normal levels of basophils in bone marrow and spleen ^a	Yes	Yes
Normal levels of CD11c ⁺ DCs and NK cells in spleen ^a	Yes	Yes
Normal levels of CD19 ⁺ B cells in bone marrow and spleen ^a	Yes	Yes
Normal levels of CD8 ⁺ and CD4 ⁺ T cells in thymus and spleen ^a	Yes	Yes
Deficiency in number of TCRγδ T cells in the small intestine ^a	No	Yes
Exhibit bile reflux	Yes	Yes
Develop stomach papillomas and ulcers	No	Yes
Develop idiopathic dermatitis	No	Yes

^a In adult mice.

^b Mast cells develop in *Kit*^{W-sh/W-sh} mice that have received whole bone marrow cells intravenously after 950 rad irradiation; however, as in WBB6F₁-*Kit*^{W/W^{-v}} mice, such ‘mast cell engraftment’ of C57BL/6-*Kit*^{W-sh/W-sh} mice, is not selective for the mast cell lineage because multiple hematopoietic lineages of donor origin develop in these mice.

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concentrations of antigen-nonspecific IgE are both required for optimal sensitization in a model of contact hypersensitivity (CHS) to oxazolone (Ox) and can enhance the emigration of skin Langerhans cells from the epidermis of naïve mice in response to epicutaneous application of Ox in ethanol. The binding of IgE to FcεRI on dermal mast cells, even in the absence of antigen known to be recognized by that IgE, enhanced levels of mRNA for certain mast cell-associated products that were detected in the skin one hour after the first epicutaneous application of the hapten; moreover, several of the products, which might be secreted by such mast cells (e.g. IL-6, monocyte chemoattractant protein-1 and tumor necrosis factor [TNF]), are known to influence dendritic cell (DC) biology. These data represent the strongest evidence currently available that the effects of IgE on mast cells that can be detected in the absence of specific antigen known to be recognized by such IgE [8,25] can be important in modulating mast cell function *in vivo*.

In another model of CHS, mast cell-deficient C57BL/6-*Kit^{W-sh/W-sh}* mice exhibited significantly impaired CHS to fluorescein isothiocyanate (FITC) applied in a vehicle of acetone-dibutylphthalate (in a ratio of 1:1) [26]. The reduced expression of CHS observed at sites of hapten challenge in *Kit^{W-sh/W-sh}* mice was fully repaired by prior local transfer of WT BMCMCs to sites later challenged with hapten, but only partially repaired by transfer of TNF^{-/-} BMCMCs. Mast cell-derived TNF was required for optimal migration of FITC-bearing DCs to draining lymph nodes (LNs) in this model, as well as in a model of airway challenge with FITC-ovalbumin (OVA). However, the mast cell-associated defect in CHS to FITC in this setting appeared to be caused by impairment of the effector phase of the response, not of the sensitization phase. Evidence has also been reported that mast cell activation by way of Toll-like receptor 4 (TLR4) can enhance the sensitization phase of the immune response to OVA in mice that have been exposed to that antigen by way of the airways [27•].

Finally, there is evidence that, in some circumstances, mast cells might have effects that suppress the development of adaptive immune responses. For example, several mediators that can be secreted by mast cells can have actions that might interfere with antigen sensitization [28–35]. Moreover, Depinay *et al.* [36•] demonstrated recently that the bites of *Anopheles* mosquitoes can have effects that impair the development of antigen-specific T-cell responses in a model of delayed-type hypersensitivity (DTH) to OVA in mice, and that this phenomenon requires the presence of mast cells in the skin at the site of the bite.

The mechanism of mast cell-dependent immunomodulation in this setting, and the extent to which the crucial mast cell function(s) might be influenced by the effects of

antigen-nonspecific IgE on mast cells, remain to be determined. However, the authors speculate that mast cell-derived histamine might be one key mediator. Notably, mast cells and histamine had previously been shown to be required for the optimal expression of ultraviolet B-induced immune suppression of CHS responses to 2,4,6-trinitro-1-chlorobenzene in mice [37], and histamine was shown to influence T cell- and antibody-dependent responses through the actions on H1 and H2 receptors [38].

The 'immediate hypersensitivity' or 'mast cell/basophil autonomous' phase

The immediate phase of an IgE-associated allergic response generally occurs within the first two hours after antigen exposure (Figure 1b). In appropriately sensitized hosts, encounter with specific antigen by IgE on the mast cell surface rapidly induces aggregation of FcεRI receptors, initiating a signaling response that results, within minutes, in the secretion of diverse mediators; in mice, mast cells also can undergo activation by IgG₁- and FcγRIII-dependent mechanisms (e.g. in response to immune complexes of antigen and IgG₁ antibodies) [3,4,10,11,39]. Studies employing *c-kit* mutant mice have proven that such mast cell activation can contribute importantly to the pathology of IgE-associated acute allergic disorders, including anaphylaxis, in actively or passively sensitized animals [40–42]. Moreover, work in mast cell knock-in mice showed that mast cells are essential for virtually all of the augmented vascular permeability and tissue swelling associated with IgE-dependent passive cutaneous anaphylaxis reactions [3,43•,44].

At least one instance has been identified in which the presence of IgE can result in the development of a chronic inflammatory response in the skin in the absence of mast cells [43•], and one example has been reported in which genetically mast cell-deficient mice can exhibit an acute allergic response (i.e. anaphylaxis) that might be IgE-dependent but that is mast cell-independent [45]. However, mouse studies and clinical observations support the conclusion that mast cells are either fully sufficient for or importantly contribute to the development of the majority of (if not virtually all) IgE-dependent immediate hypersensitivity reactions [1–4,11,42]. Basophils might also contribute significantly to some acute reactions of this type, particularly those that have a prominent systemic component, such as anaphylaxis [1–4,11,42].

The IgE-associated 'late phase response': mast cells and the inflammatory cell influx

Many of the clinically significant consequences of IgE-associated antigen-dependent reactions in the respiratory tract, skin and other sites are now thought to depend crucially on the actions of leukocytes recruited to these sites during LPRs, rather than on the direct effects of the mediators released by mast cells at early intervals after

antigen challenge [46–48]. LPRs can be defined as the recurrence of signs and symptoms of inflammation at the site of antigen challenge at a few to several hours after initial antigen challenge in sensitized hosts. In many, but not all, cases, such LPRs are preceded by evidence of an acute allergic reaction at the same site [46,48]. It is difficult to define exactly when the ‘immediate’ phase of an IgE-associated response transitions into the LPR (Figure 1c). However, it seems reasonable to propose that the appearance of significant numbers of recruited leukocytes at the reaction site should represent at least one of the key criteria.

Several lines of evidence, drawn from human experiments and mouse studies (including work in mast cell knock-in mice), indicate that IgE-dependent activation of mast cells can contribute importantly to the development of LPRs [1–3,43^{••},46,49]. In humans, experimental LPRs also can be induced by challenge with allergen-derived peptides that can activate T cells but that are not able to induce IgE-dependent activation of mast cells or basophils [48]. Such work indicates that some clinically significant LPRs in naturally sensitized hosts might occur by T cell-dependent but mast cell-independent mechanisms.

Although each of a diverse set of mast cell-derived mediators has the potential to influence the leukocyte recruitment and other features of IgE-associated LPRs [1–3,46], the one mast cell-derived product that has been implicated in this setting based on work with mast cell knock-in mice is TNF [49,50]. However, it is likely that many other mast cell-derived products also importantly influence the features of certain IgE-associated LPRs.

In addition to contributing to the features of LPRs, the ongoing release of cytokines, chemokines and other mediators by mast cells that have been activated by IgE-dependent mechanisms at sites of antigen challenge can have additional effects. These include actions that have the potential to influence further the development of acquired immune responses in such settings. For example, histamine derived from IgE- and antigen-stimulated skin mast cells can promote the migration of Langerhans cells to draining LNs by way of actions on H2 receptors [51]. This finding raises the possibility that, in individuals who already have developed IgE specific for particular epitopes of an environmental antigen, subsequent challenge with that antigen (alone, or in the presence of additional antigens) might result in IgE- and mast cell-dependent effects on local DCs. This, in turn, might function to increase the spectrum of epitopes of the original antigen (or of the additional antigens encountered at the same time) against which that individual develops sensitivity. As proposed in Jawdat *et al.* [51], should this mechanism actually occur in naturally acquired allergic disorders, it would have the

potential to increase the severity of that individual’s chronic allergic disease.

Chronic allergic inflammation: persistence of inflammation and tissue remodeling

Mast cells can provide mediators and cellular functions that have the potential to influence multiple features of the pathology observed at sites of ‘chronic allergic inflammation’ — inflammation that can persist for long periods of time at sites of disease in subjects who have IgE-associated allergic disorders such as asthma, allergic rhinitis and atopic dermatitis [1–4,12,13,16[•],17,46]. At the affected sites, chronic allergic inflammation can be associated with dramatic changes in the extracellular matrix as well as with important alterations in the numbers, structure and function of cells that are normally resident there, including epithelial cells, vascular endothelial cells, vascular and airway smooth muscle cells, fibroblasts and nerves (Figure 1d).

In humans, it can be quite difficult to assess the relative importance of the contribution of mast cells to individual examples of chronic allergic inflammation, as opposed to that of the many other cell types that participate in these complex inflammatory disorders. By contrast, work in mice has shown that mast cells can contribute significantly to the development of many of the characteristic features of such disorders. Most studies of ‘asthma models’ in mice have employed relatively short-term protocols for antigen sensitization and challenge, which can replicate some but not all of the features of chronic asthma in humans; mast cells have been shown to contribute to several features of such models [52,53].

However, Yu *et al.* [54^{••}] reported recently that mice that had been sensitized to OVA without using an artificial adjuvant and were then exposed to long-term repetitive intra-nasal antigen challenge developed many features of chronic asthma. Furthermore, based on studies in mast cell-deficient (*Kit^{W-sh/W-sh}* or *Kit^{W/W^{-v}}*) mice engrafted with *FcRγ^{+/+}* (WT) or *FcRγ^{-/-}* mast cells, optimal expression of all of these features of the disorder were shown to be mast cell-dependent [54^{••}]. Notably, whereas many features of the response were markedly reduced in mice whose mast cells lacked *FcRγ*, and therefore could not be activated by IgE/*FcεRI*- or IgG₁/*FcγRIII*-dependent mechanisms, optimal development of other features of the response appeared to require mast cells but not *FcRγ*. Thus, mechanisms of eliciting mast cell function independently of *FcεRI*- or IgG₁/*FcγRIII*-dependent signaling must also contribute to the development of those features of this model. Whereas the alternative mechanisms of mast cell activation in this setting have not yet been identified, work in other models has implicated certain chemokines [55] or products of complement activation [56,57] as potentially important modulators of mast cell function in allergic inflammation.

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In addition to influencing certain features of chronic inflammation directly, for example through the effects of their secreted products on local resident cells such as vascular endothelial cells, epithelial cells, smooth muscle cells and fibroblasts, mast cells also have the potential to modulate certain features of these disorders by effects on the recruitment, phenotype and/or function of lymphocytes and other cells that importantly contribute to these responses [1–4,12,13,15,16*,17,18**,26]. TNF represents one, but not the only, mediator derived from mast cells stimulated via the FcεRI that has the potential to enhance the proliferation and cytokine production of multiple T-cell subsets *in vitro* and to enhance the expression of T cell-dependent inflammation *in vivo* [16*,17]. Certain co-stimulatory molecules expressed by mast cells, including OX40 ligand, also have the potential to enhance T-cell function in these settings [4,12,15,16*].

Finally, although pathological IgE-associated immune responses can account for significant human morbidity and mortality, it is thought that IgE-associated acquired immune responses can confer benefit in the context of infection with certain parasites [1–3,58–60].

Roles of mast cells in other examples of acquired immune responses

Based on the work of many different investigators, it is now clear that mast cells can substantially influence several features of acquired immune responses in which IgE antibodies were thought to have little or no importance. However, it remains to be determined whether in some of these responses, for example in certain models of CHS, mast cell function might depend, at least in part, on as yet poorly defined ‘priming’ effects of the occupancy of mast cell FcεRI by antigen-nonspecific IgE [24].

Work in mast cell knock-in mice, as well as evidence from human studies, indicates that mast cells can contribute to the pathology observed in some autoimmune disorders, including multiple sclerosis, bullous pemphigoid and rheumatoid arthritis in humans and models of experimental autoimmune encephalomyelitis [14,61], bullous pemphigoid [62] and (IgG₁ antibody-dependent) autoimmune arthritis [63] in mice [47,64,65]. Moreover, mast cells might express effector and/or immunoregulatory functions in such disorders (e.g. [14,18**,61]).

In addition, under certain (but not all) experimental conditions, mast cells can be required for optimal elicitation of models of hapten-induced CHS [24,26,66–68], including the elongation of cutaneous nerves that can accompany such responses [69], as well as hapten-induced non-atopic asthma [70] or inflammatory bowel disease [71*]. Mast cells have also been identified as being necessary for the optimal expression of peripheral tolerance to skin allografts [9**] — an observation that provides another, provocative, example of the ability of mast

cells to downregulate important aspects of at least some acquired immune responses. Elucidation of the mechanisms by which mast cells can either enhance or suppress features of the sensitization or elicitation phases of acquired immune responses, and identification of the signals that can elicit such distinct mast cell functions, represent important goals for future research.

Conclusions

Work in mouse model systems, and particularly in ‘mast cell knock-in mice’, has confirmed the widely held belief that mast cells can contribute significantly to the acute manifestations of IgE-dependent immune responses. These include the dramatic systemic features of anaphylaxis, as well as the more localized signs and symptoms that are elicited within minutes of antigen challenge in subjects who have atopic asthma and other IgE-associated allergic disorders.

However, it is becoming increasingly clear that the functions of mast cells in the biology of IgE-associated immune responses include contributions in addition to the role of the cell as a major effector element in the acute features of these responses. In mice, IgE-dependent mast cell activation can promote features of LPRs [43**,49], and FcR common γ chain-dependent mast cell activation (which, in the mouse, might reflect contributions of both antigen-, IgE- and FcεRI-dependent and IgG₁-antigen immune complex-dependent mast cell stimulation) can contribute significantly to the development of multiple features of chronic allergic inflammation of the airways, including the tissue remodeling and functional changes associated with this model of chronic asthma [54**]. It is likely that such acute, late-phase and chronic consequences of mast cell activation by IgE-dependent mechanisms can also contribute to host defense against certain parasites, including internal parasites such as nematodes [58,60] and ectoparasites such as ticks [59]; in some of these settings, basophils might have roles that complement or overlap with those of mast cells [60,72,73].

But the potential roles of mast cells in IgE-associated immune responses extend substantially beyond such ‘effector’ functions. Surprisingly, it appears that occupancy of the FcεRI by IgE alone, in the absence of known antigen recognized by that IgE, can have effects on mast cell survival, phenotype and function [8,25], including as yet poorly understood ‘priming’ effects that can enhance the mast cells’ ability to promote the sensitization phase of certain T cell-associated immune responses [24]. Whether immune responses in which the sensitization phase can be enhanced by mast cells include those with a significant IgE component remains to be determined. However, it already is clear that mast cells and their products can have a number of effects that have the potential to promote the transition from innate to

acquired immune responses [4,12]. A partial list of such potential functions (naming some for which there is evidence of *in vivo* relevance) includes effects of mast cell-derived histamine [51] or TNF [26] on DC migration and effects of histamine (although not proven to be of mast cell origin) on T-cell polarization [38]. Mast cells (or basophils) also might influence the local production of IgE *in vivo* through interactions of CD40 ligand (CD40L) expressed on their surface with CD40 on B cells [74–76]. However, the list of candidate mast cell-associated mediators or functions that could play a role in enhancing (or suppressing) the sensitization phase of acquired immune responses is quite long [4,12]. Working out the extent to which these potential mast cell functions actually can be important *in vivo* represents an interesting challenge.

Finally, even the best understood of the mast cells' roles in disease — functioning as a key effector cell in the acute manifestations of IgE-associated immune responses — retains some mysteries. It is well known that some subjects who develop anaphylaxis upon challenge with a small amount of the offending allergen can have relatively low levels of total or antigen-specific IgE and/or relatively weak skin test responses to the allergen [77,78]. By contrast, some patients who have severe allergic diseases have extremely high levels of total IgE, and patients with certain parasite infections can have even higher IgE levels [79]. The immunological specificity of antigen- and IgE-dependent mast cell activation in each of these settings of course depends on the recognition of antigen by antigen-specific IgE. However, high total IgE levels, by having effects that increase levels of FcεRI expressed on the mast cell surface, can make mast cells more potent effector cells [8]. Why are some of the individuals who develop IgE antibody-associated immune responses predisposed to anaphylaxis, whereas others are not (despite the suffering they endure as a result of the local signs and symptoms of their allergic disorders)?

The answer(s) to this question might be complex, involving genetic and/or epigenetic contributions [79,80], the nature of the antigen (although many more subjects develop IgE specific for components of honeybee venom than exhibit anaphylaxis upon being stung [78]), the extent of engagement of negative regulatory mechanisms that can diminish the responses of mast cells and other effector cells that are activated by IgE and antigen [8,10,12,39,81,82^{••},83^{••}], and many other potential factors. Accordingly, we are not proposing here that the key to understanding why some individuals develop anaphylactic reactivity to certain antigens necessarily is a particular feature of that subject's mast cells (and/or basophils). However, it would be interesting to know whether individual variation in aspects of the regulation of mast cell or basophil phenotype, signaling or function might represent one of the factors that can contribute to

the susceptibility of some individuals to develop this inappropriate immune response.

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