Commentary

Complexity and Redundancy in the Pathogenesis of Asthma: Reassessing the Roles of Mast Cells and T Cells

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Asthma affects millions of people worldwide, and its reported incidence is increasing dramatically in many developed nations; the human and economic costs of this disorder, in morbidity, health care expenses, lost productivity, and, most tragically, even mortality, are staggering (1, 2).

It is now generally thought that asthma is a syndrome, typically characterized by the three cardinal features of intermittent and reversible airway obstruction, airway hyperresponsiveness, and airway inflammation, that may arise as a result of interactions between multiple genetic and environmental factors (1–4). Nevertheless, most cases of the disorder (the so-called "atopic" or "allergic" asthma) occur in subjects whom also exhibit immediate hypersensitivity responses to defined environmental allergens, and challenge of the airways of these subjects with such allergens can produce reversible airway obstruction (1–5). It is also known that the overall incidence of asthma in several different populations exhibits a strong positive correlation with serum concentrations of IgE, which, in humans, is the main (if not the only) Ig isotype that can mediate immediate hypersensitivity responses (1, 5). Moreover, it has been demonstrated that mast cells, derivatives of hematopoietic precursor cells that undergo their terminal stages of differentiation/maturation in the peripheral tissues in which they reside (6, 7), express cell surface receptors (FcεRI) that permit them to bind the Fc portion of IgE with high affinity, and also that such IgE-sensitized mast cells, upon encounter with specific antigen that is recognized by their FcεRI-bound IgE, secrete a broad panel of bioactive mediators, including: (*a*) preformed mediators that are stored in the cell's cytoplasmic granules (e.g., histamine, heparin, and neutral proteases), (*b*) newly synthesized lipid products (e.g., prostaglandin D_2 and leukotriene C_4), and (*c*) diverse cytokines (4, 6, 8, 9). Finally, several lines of evidence indicate that many of these potentially mast cell–derived mediators can promote reversible airway obstruction, bronchial hyperreactivity, and/or airway inflammation (see reviews in references 2–4, 8, and 9).

In light of these findings, it was once widely believed that atopic or allergic asthma is a disease that primarily reflects the consequences of IgE- and allergen-dependent mast cell activation. Yet several observations have called into question the central role of mast cells in asthma. These include the demonstration that additional cell types, including eosinophils (10) and Th2 lymphocytes (11), both of which are well represented in the chronic inflammatory infiltrates in the airways of patients with asthma (2–4, 12, 13), also can produce cytokines or other mediators that may contribute to many of the features of the disease. Moreover, it has recently been shown that the FcεRI, which was once thought to be restricted to tissue mast cells and basophils (circulating granulocytes that can produce a panel of mediators that is similar, but not identical, to that of mast cells [6, 9]) can also be expressed on the surface of monocytes, circulating dendritic cells, Langerhans' cells, and eosinophils (see reviewes in references 14 and 15), thus identifying these cells as additional potential sources of mediators in various IgE-dependent inflammatory responses.

Given the large number of potential culprits, some of which can express similar or overlapping functions, how can one assess the relative importance of individual cell types in the pathogenesis of asthma? Although this represents an exceedingly difficult challenge in the setting of human asthma, some aspects of this issue are accessible by taking advantage of animal models of the disease. However, when considering the results of such animal studies, several points should be kept in mind. (*a*) These are models of human asthma, not asthma itself, and the extent to which the findings in these models actually elucidate the human condition(s) needs to be demonstrated by appropriate studies in human subjects. (*b*) Experimental animal species and humans can differ in significant details of immunological and inflammatory responses (e.g., in the mouse, antigen- and mast cell–dependent airway obstruction can be mediated by either IgE or IgG_1 [16], whereas it seems likely that only IgE is involved in the analogous human responses [1, 5]). (*c*) The procedures of allergen sensitization and challenge that are used in animal models of asthma are typically "optimized" to give strong responses for endpoint analysis, and this (as well as the increasing costs of animal experimentation, which discourages the use of large numbers of animals) may make it difficult to detect contributions of cell types that function to amplify the intensity or kinetics of such responses at relatively low levels of allergen challenge. (*d*) Finally, the models used by different investigators may differ in a number of factors, which can have potentially significant effects on the results, including the species (or strain) of experimental animal, the choice of antigen, the protocols for antigen sensitization and challenge, and the means of assessing and quantifying the individual characteristics of the responses.

In other words, the demonstration that a particular cell

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or mediator can produce a feature of asthma in an animal model neither proves that this element can have the same effect in human asthma nor excludes the possibility that other cells or mediators can have similar, and perhaps even more critical, functions, either in experimental animals or humans.

These reservations notwithstanding, how have the results of studies in experimental animals influenced our thinking about the pathogenesis of asthma, and in particular, the potential role of the mast cell in the expression of the three cardinal features of the disorder? The most definitive approach for characterizing the importance of a single potential effector cell or molecule in a biological response is to attempt to elicit the response in animals that differ solely in having or lacking the element of interest. With respect to mast cells, the best current approximation of this ideal is to investigate genetically mast cell–deficient (WB-*W*/+ × C57BL/6-W^v/+)F_1-*W*/W^v (WBB6F_1-*W*/W^v) mice (now more properly designated WBB6F_1-Kit^W/$Kit^{W\text{-}v}$ mice [17]) and the congenic normal (WBB6F_1-+/+) mice (6, 18, 19). Because of the effects of their mutations at c-*kit*, which encodes the receptor for a pleiotropic growth factor that represents a major mast cell survival/developmental factor, stem cell factor (also known as kit ligand or mast cell growth factor; 18), adult Kit^W/$Kit^{W\text{-}v}$ mice virtually lack tissue mast cells (<1.0% the +/+ number in the skin, essentially none in the airways and other sites), but they are also mildly anemic, lack melanocytes in the skin and interstitial cells of Cahal in the gastrointestinal tract, and are sterile due to a virtual absence of germ cells (18–22). However, these mice appear to have little or no abnormalities of B or T cell function, levels of granulocytes (including basophils) or platelets, or hemostasis, nor do they exhibit Ig deficiencies or impairments in their ability to generate IgE or IgG_1 antibody responses (18, 19). Finally, the mast cell deficiency of Kit^W/$Kit^{W\text{-}v}$ mice can be selectively repaired by the adoptive transfer of lineage-committed immature mast cells (BMCMCs, or bone marrow-derived cultured mast cells) which have been generated in vitro from the bone marrow cells of the congenic +/+ mice (6, 19, 21). Such "mast cell knock-in mice" can be used to test whether abnormalities in the expression of biological responses in Kit^W/$Kit^{W\text{-}v}$ mice, which theoretically could be due to any direct or indirect consequence of their c-*kit* mutations, specifically reflect the animals' mast cell deficiency (6, 18, 19, 21).

Studies in Kit^W/$Kit^{W\text{-}v}$ and congenic normal mice have clearly established that, in the mouse: (*a*) IgE-dependent acute reversible airway obstruction can occur by mechanisms that appear to be entirely mast cell dependent (16, 22, 23). (*b*) Although many manifestations of active anaphylactic reactions in the mouse, including changes in airway function and death, can occur by IgE- and mast cell–independent, but IgG_1-dependent, mechanisms, IgE and mast cells probably contribute importantly to the initial rapid and partially reversible phases of airway obstruction, and diminished pulmonary compliance, that are observed during certain models of active anaphylaxis (16). (*c*) The acute airway hyperresponsiveness to intravenous methacholine challenge that can be detected in immunologically naive mice 20 min after intravenous challenge with anti–mouse IgE antibodies is largely (if not entirely) mast cell dependent, and is expressed before the development of any histologically apparent leukocyte infiltration in the airways at sites of mast cell degranulation (23). Although the specific mediator(s) responsible for this example of mast cell–dependent airway hyperreactivity remain to be defined, the candidates include representatives of all three classes of mast cell–derived mediators (see reviews in references 4, 8, 9, and 23).

These findings show that, in WBB6F_1 mice, IgE-dependent mast cell degranulation can result in both reversible airway obstruction and airway hyperresponsiveness to cholinergic stimulation, in the absence of detectable infiltration of the airways with circulating leukocytes. On the other hand, it is now clear that eosinophil recruitment to the airways of mice can occur in response to aerosol challenge with antigen even in the virtual absence of mast cells, at least with some protocols of antigen sensitization and challenge. For example, in this issue, Takeda et al. (24) report that when Kit^W/$Kit^{W\text{-}v}$ and congenic +/+ mice were sensitized with OVA and then assessed 48 h after the last of 3 consecutive daily aerosol challenges with OVA, both the mast cell–deficient and the wild type mice exhibited similar numbers of eosinophils in bronchoalveolar lavage fluid and lung digests, as well as similar levels of airway hyperreactivity to methacholine challenge.

At least four previous studies (each using a different protocol of antigen sensitization and challenge, and, in some cases, a different antigen) also reported that mast cells are not essential for the development of antigen-induced infiltration of the airways with eosinophils (25–28). However, Kung et al. (27), using a protocol in which aerosol challenge with OVA was performed only twice on a single day, found that eosinophil infiltration of the airways in Kit^W/$Kit^{W\text{-}v}$ mice was ≤50% of that in the +/+ mice ($P < 0.05$) and was largely normalized after the selective repair of the animals' mast cell deficiency. Brusselle et al. (26), who performed daily OVA challenge for 7 d, also found that eosinophil influx into bronchoalveolar lavage fluid was reduced by ~50% in Kit^W/$Kit^{W\text{-}v}$ versus +/+ mice ($P = 0.06$).

Taken together, these five studies suggest that the relative contribution of mast cells to eosinophil infiltration of the airways may vary; mast cells may have no detectable role in experiments that use strong procedures of immunization and challenge, but may contribute significantly when protocols for sensitization and, especially, challenge have been selected to yield relatively attenuated responses. Moreover, in a model of peritoneal inflammation, the mast cell significantly enhanced the kinetics of leukocyte recruitment, even though it had no effect on the final magnitude of the response (29). The data of Kung et al. (27) indicate that mast cells can also enhance the kinetics of eosinophil responses to aerosol allergen challenge.

Takeda et al. (24) are the first to show that mast cell–deficient Kit^W/$Kit^{W\text{-}v}$ mice can express allergen-induced

airway hyperresponsiveness to cholinergic stimulation. This important observation provides yet more support for the now widespread view that there may be multiple routes to this defining characteristic of asthma. Indeed, it is thought that airway hyperresponsiveness, i.e., the development of bronchoconstriction in response to an immunologically nonspecific stimulus that would have no discernable effect in a normal individual, may reflect a consequence of any of a number of acute and/or chronic processes, including damage to the bronchial epithelium, submucosal edema, alterations of smooth muscle function (e.g., in response to mast cell mediators or other products present at sites of inflammation), and alterations in the production or degradation of neuroactive mediators (4, 8, 30). And although airway hyperresponsiveness and infiltration of the airways with eosinophils are often linked, both in animal models and in human asthma, airway hyperresponsiveness has been reported to occur in the absence of significant eosinophilia in certain settings such as in aerosol-challenged BALB/c mice that had been treated with an anti–IL-5 neutralizing antibody (31).

Depending on the model system, airway hyperresponsiveness also can occur either by IgE-dependent mechanisms (23, 32) or independently of IgE (33, 34) and/or IgG_1 (34). IL-5 derived from $CD4^+$ T cells has been implicated in the development of IL-4– and IgE/IgG_1–independent airway inflammation (34), adding to a large body of evidence that indicates that $CD4^+$ T cells can mediate airway hyperreactivity (35–37) as well as infiltration of the airways with eosinophils (25, 35–38). And although it has often been proposed that $CD4^+$ T cells promote the development of airway hyperreactivity indirectly through the recruitment of eosinophils and/or other leukocytes, the possibility that products derived from the T cells themselves can importantly contribute to airway hyperresponsiveness must also be considered (35).

Perhaps the simplest conclusions to draw from the various studies of mouse models of allergic asthma are that, in mice: (*a*) Airway hyperreactivity to cholinergic stimulation can occur by either mast cell–dependent mechanisms (which can be expressed even in the absence of leukocyte recruitment) or by $CD4^+$ T cell–dependent mechanisms (which typically occur in a setting that also includes eosinophil infiltration of the airways). (*b*) Mast cells are not necessary for the recruitment of Th2 cells or eosinophils to the airways after aerosol challenge with antigen, but can influence the kinetics or magnitude of the responses, especially at "suboptimal" levels of antigen exposure. (*c*) The extent to which eosinophils are necessary for the expression of T cell–dependent changes in airway hyperreactivity in different models remains to be fully defined. (*d*) In many experimental settings, particularly in various strains of normal mice, the expression of airway hyperresponsiveness (and other "asthma-like" features of these models) probably reflects the combined contributions of both mast cell– and T cell–dependent pathways.

But what about the role of the mast cell in "real" allergic asthma, in humans? It seems very likely that IgE-dependent mast cell activation importantly contributes to acute allergen-induced bronchoconstriction in human atopic asthma, and that mast cells can contribute to the airway inflammation associated with this disorder as well (2–4, 6, 8, 9). However, in humans, unlike in mice, the FcεRI can be expressed on several potential effector cells in addition to mast cells and basophils (14, 15). Also, the form of the FcεRI expressed on 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 (14). 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.

In addition, two newly recognized aspects of FcεRI function or expression provide strong support for the hypothesis that mast cells (and perhaps other $Fc\epsilon RI^+$ effector cells) may have a particularly important role in initiating and/or amplifying IgE-dependent inflammatory reactions, especially in response to low dose antigen challenge. First, Lin et al. (39) have identified the FcεRI β chain as an "amplifier" of signaling through this receptor, which can markedly upregulate the magnitude of the mediator release response to FcεRI aggregation; notably, it has been reported that certain mutations that result in amino acid substitutions in the human β chain may be linked to atopic disease (see reviews in reference 39). Second, studies in both mice (40, 41) and humans (42, 43) 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 upregulation of FcεRI expression both permits the cells to exhibit mediator release at lower concentrations of specific antigen (40, 42, 43), and also primes such cells to produce strikingly higher levels of certain mediators, including IL-4 and other cytokines (40, 43), under optimal conditions of antigen challenge.

These findings thus identify two FcεRI-dependent mechanisms (β chain "amplifier" function, IgE-dependent upregulation of FcεRI surface expression) for enhancing the sensitivity and intensity of the effector phase of IgE-dependent reactions. They also suggest a potential positive feedback mechanism ($\uparrow$IgE$\rightarrow\uparrow$FcεRI$\rightarrow\uparrow$antigen-, IgE-, and FcεRI-dependent release of IL-4 [40] and/or IL-13 [44]$\rightarrow\uparrow$IgE) by which mast cells (and possibly basophils) may enhance the further evolution, and persistence, of Th2-biased, IgE-associated immune responses. And studies in mice have identified yet another IgE-dependent, but apparently mast cell– and FcεRI-independent, mechanism to augment Th2 responses and associated eosinophil infiltration in the airways: IgE- and CD23-facilitated antigen presentation to T cells (28). Finally, mast cells and basophils may enhance IgE production via expression of the CD40 ligand (44, 45).

The clinical significance 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 $Fc\epsilon RI^+$ 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 testing (42), not only may reduce CD23-dependent antigen presentation (28) and FcεRI$^+$ cell effector function (40–43), but also may diminish FcεRI$^+$ cell immunoregulatory function by reducing both mast cell (or basophil) IL-4/IL-13 production (40, 44) and FcεRI$^+$-dependent antigen presentation (14). 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 (see reviews in references 9, and 46), raise the possibility that the clinical benefits of such agents in asthma 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.

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