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IgE and mast cells in allergic disease

Stephen J Galli[1,2] & Mindy Tsai[1]

Immunoglobulin E (IgE) antibodies and mast cells have been so convincingly linked to the pathophysiology of anaphylaxis and other acute allergic reactions that it can be difficult to think of them in other contexts. However, a large body of evidence now suggests that both IgE and mast cells are also key drivers of the long-term pathophysiological changes and tissue remodeling associated with chronic allergic inflammation in asthma and other settings. Such potential roles include IgE-dependent regulation of mast-cell functions, actions of IgE that are largely independent of mast cells and roles of mast cells that do not directly involve IgE. In this review, we discuss findings supporting the conclusion that IgE and mast cells can have both interdependent and independent roles in the complex immune responses that manifest clinically as asthma and other allergic disorders.

People with allergic disorders such as atopic dermatitis (eczema), allergic rhinitis (hay fever), food allergy and allergic (or atopic) asthma can experience acute signs and symptoms of disease within minutes of exposure to the associated allergens. However, such individuals also typically develop long-term changes in the affected tissues, often called tissue remodeling, after repeated exposure to these allergens over periods of weeks to years. There is consensus that antigen-specific IgE antibodies, together with one of the major effector cells of allergy, the mast cell (**Box 1**), can be crucial for the development of the acute manifestations of these allergic disorders. But there is less agreement about the role of IgE and mast cells in the chronic, long-term tissue changes that account for much of the morbidity of these increasingly prevalent diseases.

IgE[1–3] and mast cells[4–7] have each been the topic of recent reviews. We focus here on aspects of the biology of IgE and mast cells that we think are most relevant to their proven or potential roles in allergic disorders, especially asthma. We discuss evidence indicating that IgE and mast cells, acting either individually or in concert, can have both nonredundant and partially redundant roles in the pathogenesis of chronic and acute manifestations of asthma. We also describe some approaches that are being taken to exploit our understanding of the biology of IgE and mast cells to craft better ways to manage and treat people with allergic diseases.

Allergen sensitization and antigen-specific IgE production

The discovery and characterization of the antibody class now called IgE[8], culminating in the independent descriptions of this class of antibodies by the Ishizakas[9] and Johansson and Bennich[10], arguably represents the most crucial advance in our understanding of the immunological basis of allergic disorders. Production of antigen-specific IgE requires that such antigens are taken up by dendritic cells, B cells or other antigen-presenting cells, which, in the presence of interleukin-4 (IL-4) or IL-13 provided early in the process by one or more cell types, present the processed antigens to cognate naive T cells that then acquire a T helper type 2 (T_H2) cell phenotype[11] (**Fig. 1**, left). T_H2 cells both engage cognate B cells through B cell major histocompatibility complex (MHC) class II and co-stimulatory molecules and secrete IL-4 and IL-13, inducing B cells to undergo class-switch recombination (CSR), resulting in the variable, diverse and joining (VDJ) segments that were initially linked to another constant (C) region in the immunoglobulin heavy chain locus (for example, Cμ or Cγ) to instead be linked to the Cε region (**Fig. 1**, right). CSR also can be induced by IL-4 and/or IL-13 that is derived from cells other than T_H2 cells, which may include mast cells and basophils[11–13].

Antigen sensitization was previously thought to occur primarily in lymphoid germinal centers, but IgE-producing B cells that undergo clonal selection and affinity maturation also can be generated in the respiratory mucosa[14] (**Fig. 1**, left). CSR resulting in production of IgE (in addition to IgA) also can occur in the gastrointestinal tract[15], and patients with food allergy have higher concentrations of IgE in the gastrointestinal tract than healthy individuals[15]. Such evidence supports the conclusion that IgE can be produced locally by B cells in the gut- or airway-associated lymphoid tissue, as well as in the lymph nodes, of individuals with food allergy[15], seasonal or perennial allergic rhinitis[16] or atopic or nonatopic asthma[14].

These observations suggest that much of the IgE responsible for 'organ-specific' allergic disorders may be produced locally in the affected anatomical sites, which also may be a survival niche for long-lived IgE-antibody–secreting plasma cells, and that IgE measured in the peripheral circulation may be primarily antibody that has escaped from the site of disease[15]. Indeed, concentrations of IgE in the peripheral blood are typically much lower than those of any other immunoglobulin isotype[1]. These findings also suggest that locally produced IgE may be pathogenic in at least some cases of so-called

[1]Department of Pathology, Stanford University School of Medicine, Stanford, California, USA. [2]Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California, USA. Correspondence should be addressed to S.J.G. (sgalli@stanford.edu).

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BOX 1 The basics of IgE antibodies and mast cells in allergy

Antigen-dependent activation of tissue mast cells that have specific IgE bound to their surface is the central event in acute allergic reactions. IgE, the immunoglobulin isotype with by far the lowest concentration in the circulation, is unable to fix complement and has little ability to cross the placenta. Its plasma concentrations can be markedly elevated in some individuals with allergic diseases or parasite infections[1]. IgE is thought to mediate biological functions primarily by binding to FcεRI, CD23 and other receptors that are expressed on mast cells and other hematopoietic cells[1,2]. The binding of antigen-specific IgE to FcεRI sensitizes mast cells and other effector cells to release mediators in response to subsequent encounters with that specific antigen or with crossreactive antigens[1–3]. Binding of antigen-IgE immune complexes to CD23 or FcεRI can serve to amplify IgE-associated immune responses by facilitating antigen presentation through CD23 on B cells or by 'antigen focusing' through FcεRI on dendritic cells or other antigen-presenting cells, leading to the production of IgE to additional epitopes of the antigens that are contained in such immune complexes[1,2].

However, it is thought that the most crucial function of IgE in allergic diseases is its ability to sensitize mast cells to release biologically active mediators in an antigen-specific manner. Mast cells are distributed throughout virtually all vascularized tissues in vertebrates, with relatively high numbers occurring near body surfaces, including the airway epithelium[63,97]. Along with dendritic cells, mast cells are one of the first immune cells to interact with allergens and other environmentally derived substances. Unlike granulocytes, mature mast cells do not ordinarily circulate in the blood; instead, hematopoietic stem cell–derived circulating mast cell precursors migrate to the peripheral tissues, where they complete their differentiation and maturation and take up residence[79]. Mast cells are potentially long-lived cells, and their number, distribution, phenotype and function can be regulated by many factors whose local concentrations can change at the sites of innate or adaptive immune responses[78]. In response to activation by specific antigens and IgE through FcεRI or by many other endogenous or exogenous substances, mast cells can produce diverse mediators that can promote or downregulate inflammation and influence tissue remodeling and function.

nonatopic asthma (that is, asthma in which IgE-dependent allergic mechanisms are not thought to have a key role) under circumstances in which it may be difficult to detect the crucial IgE antibodies systemically and in individuals in which no triggering antigen has been identified[14].

Amplification of the IgE response to allergens through CD23

Once an individual has developed IgE antibodies to certain antigen epitopes, multiple mechanisms can lead to a more robust and diverse IgE responses to both the original as well as other antigens. Some of these mechanisms are mediated by CD23 (ref. 1), which can be expressed on cells such as epithelial cells, B cells and myeloid cells (**Fig. 1**). CD23 is a C-type lectin that can exist in a membrane-bound form that has three lectin domain 'heads' separated from the membrane by a triple α-helical coiled-coil stalk, as well as in various soluble forms whose functions depend on whether these soluble forms are monomeric or trimeric[1,17] (**Table 1**). The CD23 sheddase, ADAM metallopeptidase domain 10 (ADAM10), is the main protease that releases soluble CD23 from the membrane-associated form[3,18]. CD23 is sometimes called a low-affinity receptor for IgE, but when the three lectin head domains of CD23 interact with a single IgE molecule, the resulting affinity constant (K_a) (~10^8–10^9 M^{-1}) approaches that of the high-affinity receptor for IgE, Fcε receptor I (FcεRI) (~10^{10} M^{-1})[1,17].

CD23 is thought to contribute to both positive and negative regulation of IgE production (**Table 1**), but the mechanisms responsible for this, and the role of CD23 in the pathology of allergic diseases, are not fully understood[1]. Moreover, some effects of CD23 on IgE production may be influenced by other CD23 binding partners, including CD21, which can permit CD23 to participate simultaneously in biological networks involving either the complement system or IgE, and various integrins[1]. However, certain functions of CD23 clearly have the potential to influence the biology of IgE-associated allergic disorders.

For example, CD23 on epithelial cells might amplify IgE responses by moving IgE and antigen-IgE complexes present in the lumens of the gut or respiratory tract across the intestinal[19] or respiratory[20] epithelium by transcytosis ('1' in **Fig. 1**, right), where such antigen-IgE complexes can bind to and activate FcεRI on mast cells, basophils, macrophages and dendritic cells, thereby promoting allergic inflammation, and, by inducing the secretion of IL-4 and/or IL-13 by mast cells or basophils, contribute to local IgE production ('2' in **Fig. 1**, right). IgE- and antigen-activated mast cells also release mediators such as histamine, tumor necrosis factor (TNF) and prostaglandin D_2 (PGD_2) that can, in turn, promote the maturation, functional activation and migration of dendritic cells, favoring the development of sensitization to additional antigens ('3' in **Fig. 1**, right).

IL-4 and IL-13 also can increase CD23 expression on B cells and myeloid cells[21], thereby enhancing facilitated antigen presentation (FAP). In FAP, antigen-IgE complexes bound to the CD23 that is expressed on antigen-activated B cells can favor the presentation of such antigens to cognate T cells ('4' in **Fig. 1**, right and **Table 1**). The presentation of antigen-derived epitopes initiated by the recognition of an antigen by membrane-associated B cell receptors is by definition effected only by interactions of cognate B cells with T_H cells (**Fig. 1**, left). By contrast, FAP of antigens bound to secreted IgE can permit any antigen-activated, CD23-expressing B cells, regardless of the specificity of the cells' B cell receptors, to present diverse epitopes (from related or unrelated antigens) to cognate T cells (**Fig. 1**, right). Thus, FAP is an efficient mechanism for so-called epitope spreading, in which the presence of an antibody response to one epitope can ultimately result in the production of antibodies to other epitopes on the same or unrelated antigens[1].

Epitope spreading is thought to contribute to the progressive development of allergies to multiple antigens in individuals with allergy. Epitope spreading may also contribute to the 'atopic march', wherein individuals who first present in early childhood with atopic dermatitis later develop allergic rhinitis and then atopic asthma[22], and may help explain how genetic abnormalities affecting one epithelium (for example, the epidermis) can predispose to allergic disorders affecting other epithelia. Notably, a large fraction of Europeans and Asians with atopic dermatitis have loss-of-function mutations in the gene encoding filaggrin, which results in impaired barrier function of the skin[23]. Filaggrin is expressed in the epidermis of the skin and in other squamous epithelia but not in the airway or gastrointestinal mucosae[24], however, individuals with filaggrin mutations that are associated with the development of atopic dermatitis are also at increased risk for the later development of atopic asthma[25].

Additional functions of CD23 include the clearance of antigen-IgE complexes, the killing of pathogens by IgE-bearing monocytes and eosinophils[26], involvement in IgE-independent[27] and IgE-dependent[28] monocyte-mediated toxicity against target cells and, through CD23 expressed on intestinal epithelial cells, the transportation of IgE and antigen-IgE complexes directly across the intestinal epithelium[19,29], which may account for delivery of maternal IgE to the fetus by swallowed amniotic fluid[30] (**Table 1**). By moving IgE in the

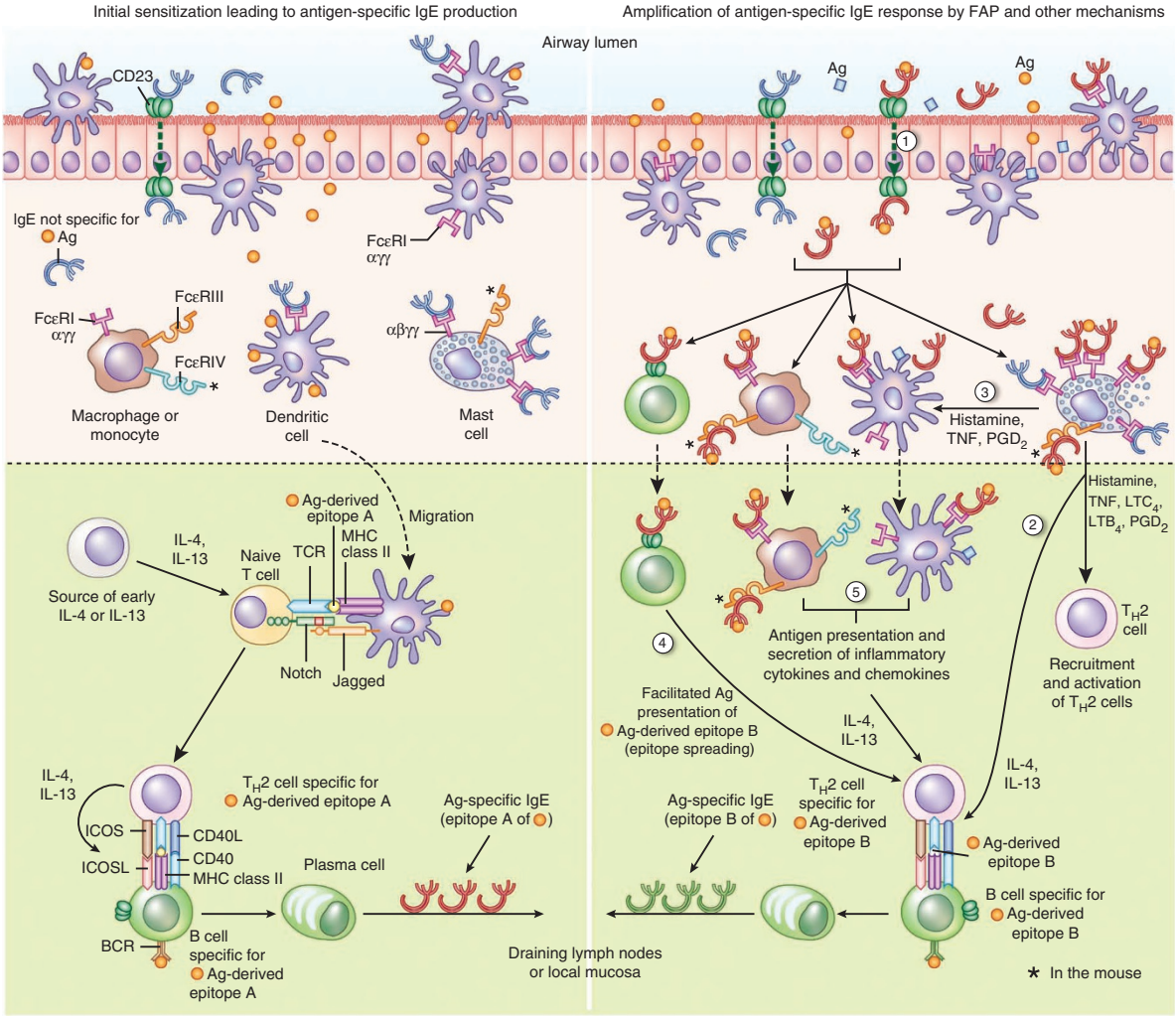

Figure 1 Allergen sensitization and IgE production. Initial allergen sensitization results in antigen-specific IgE production (left). In individuals not yet exposed to a new environmental allergen (designated here as an antigen (Ag)), the only IgE present (blue) does not have specificity for the new antigen(s). Such IgE can be bound to the αβγγ form of FcεRI on mast cells or to the αγγ form of FcεRI on the surface of macrophages, monocytes or dendritic cells or to CD23 on airway epithelial cells or other cells (not shown here). The new antigens (orange circles) are captured by dendritic cells or macrophages in the airway lumen or in the epithelium of the airway mucosa or gain access to submucosal dendritic cells through disrupted epithelium or, for some antigens with intrinsic protease activity, by disrupting epithelial cell tight junctions. Antigen-activated dendritic cells mature and migrate to regional lymph nodes or to sites in the local mucosa, where they present processed antigen epitopes to cognate T cells; in the presence of IL-4 or IL-13, which may be derived from a variety of potential cellular sources, this induces such T cells to become differentiated and activated T_H2 cells. IL-4 and IL-13, which may be derived from T_H2 cells (shown here), basophils, mast cells and/or other sources, also activate immunoglobulin heavy chain gene CSR for antigen-specific IgE production, designated here antigen-specific IgE (epitope A), in B cells. The antigen-specific IgE response is amplified by FAP and other mechanisms (right). Antigen-specific IgE can bind to multiple cell types through various IgE receptors. Antigen-induced aggregation of IgE bound to FcεRI stimulates mast cell degranulation and the release of mediators such as histamine, PGD_2 and TNF, which promote recruitment of T_H2 cells, the migration, maturation and activation dendritic cells and antigen presentation. IgE and antigen-IgE complexes can cross the epithelium by transcytosis mediated by CD23 on airway epithelial cells (1), allowing them to bind to and activate FcεRI on mast cells and dendritic cells. This process contributes to the perpetuation of allergic inflammation and, potentially, through promotion of IL-4 and/or IL-13 secretion by mast cells (2) and effects of activated mast cells on dendritic cells (3), to additional local IgE CSR and IgE production in B cells, either to additional epitopes of the original antigen (shown here) or to new antigens bound by dendritic cells (square blue symbols). Antigen presentation mediated by binding of antigen-IgE complexes to CD23 on B cells, followed by antigen presentation by these B cells to cognate T cells (not shown here), is called FAP (4), a process that can result in epitope spreading, with production of IgE recognizing new epitopes of the original antigen (for example, epitope B, shown here) or to epitopes of new antigens, if some IgE antibodies to that antigen already exist (not shown), and the subsequent exacerbation of allergic disorders. FcεRI αγγ trimers on other antigen-presenting cells (for example, dendritic cells, monocytes and macrophages) permit these cells to bind and internalize IgE that is bound to complex antigens; epitopes derived from such antigens, including those comprising epitopes for which there is not yet a specific IgE response, are then presented to cognate T cells, which, in the presence of IL-4 and/or IL-13, can become T_H2 cells that in turn promote the production of IgE against these new epitopes by B cells (5). ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; BCR, B cell receptor.

Table 1 Expression and major functions of IgE-binding receptors or molecules

Receptors or molecules	Cell types[a]	Major functions
FcεRI (αβγγ or αγγ)	**Mast cells**[38], **basophils**[38], Langerhans cells[38], **dendritic cells**[38,41], monocytes[38], **eosinophils**[38,40], **neutrophils**[39,40], platelets[138,139], bronchial epithelial cells of asthmatics[45] and airway smooth-muscle cells[44,140]. In mice: dendritic cells after Sendai virus infection[41], neutrophils and eosinophils during *Plasmodium* infection[40] and superior cervical ganglion and myenteric plexus neurons[43]; in rats: pinealocytes[141].	αβγγ: immediate hypersensitivity[2], parasite immunity[2], enhanced cytokine production and survival in mast cells[59] and MCp recruitment in the airway[142]. αγγ: antigen presentation[1,38].
FcεRII (CD23)	**B cells**[143], T cells, NK cells, monocytes, macrophages, **follicular dendritic cells**[143], Langerhans cells, bone marrow stromal cells, neutrophils, eosinophils, platelets[1,3,17] and airway[20] and **intestinal**[144,145] epithelial cells.	Regulation of IgE production[1], killing of intracellular pathogens (*Leishmania major*[146] and *Toxoplasma gondii*[26]) or tumor cells[28], facilitated antigen presentation[1] and transport of IgE and antigens across the epithelium[19,144].
FcγRII and FcγIII (in mice[b])	Mast cells[147] and macrophages[147].	Cell activation[147].
FcγRIV (only in mice)	Monocytes, neutrophils and macrophages[148,149].	Phagocytosis, cytokine production and antigen presentation in macrophages[148,149].
Gelactin-3	**Mast cells**[150,151], basophils[150], neutrophils[152], **monocytes** and **macrophages**[153–156], eosinophils[157], **Langerhans cells**[158,159], T cells[160], B cells[161] and dendritic cells[162].	Potentiate FcεRI activation[151].

[a]The cell types listed in bold express that receptor in both humans and mice. [b]Human FcγRIII has no affinity for IgE. However, human mast cells and basophils express the immunoreceptor tyrosine-based inhibitory motif–containing receptor, FcγRIIB, which can reduce activation of these effector cells through the FcεRI when it is co-ligated with the FcεRI[127].

opposite direction across the intestinal[31,32] or respiratory[20] epithelium, CD23 can favor the formation of antigen-IgE complexes in the lumen that can then be transported by CD23 back across the epithelium, resulting in the activation of local mast cells (or other FcεRI-bearing effector cells), a process that may both exacerbate allergic inflammation and impair mucosal epithelial function at the affected sites.

It has been reported that local IgE synthesis and expression of CD23 can occur concurrently in the fetus[30,33] and that a parental history of atopy and high titers of IgE in the cord blood are predictive of early atopy[34]. Moreover, *CD23* gene polymorphisms have been associated with effects on the development of atopy in mice and humans[35]. It is thus tempting to attribute to CD23 at least some role in the development and, through epitope spreading and other mechanisms, the exacerbation of allergic disorders.

Amplification of the IgE response to allergens through FcεRI

IgE does not fix complement and has only limited ability to cross the placenta[36], and it is thought that IgE's main biological roles reflect its ability to bind to receptors on mast cells, basophils and a variety of other cell types. The high-affinity receptor for IgE, FcεRI, as expressed by mast cells and basophils, consists of an IgE-binding α chain, in which the two extracellular domains bind IgE, a β chain, which spans the plasma membrane four times and functions as a signal amplifier[37], and two identical and largely intracellular γ chains[38]. The signaling motifs of this αβγγ form of FcεRI consist of immunoreceptor tyrosine-based activation motifs, one in the β chain and one in each of the γ chains[38]. An αγγ form of the receptor can be expressed on a variety of other cell types, including macrophages, dendritic cells, eosinophils, platelets and neutrophils[38–40] (**Table 1** and **Fig. 1**).

Although it was once thought that such widespread expression of the αγγ form of FcεRI among hematopoietic cells was more characteristic of humans than of mice, it is now known that mouse dendritic cells[41,42], eosinophils[40] and neutrophils[40] can upregulate expression of this receptor during certain immune responses. Moreover, expression of the αβγγ form of FcεRI has been detected in mouse superior cervical ganglion and myenteric plexus neurons[43] and in human airway smooth muscle cells[44]; FcεRI has also been reported on bronchial epithelial cells of asthmatic but not healthy individuals[45] (**Table 1**). Although the *in vivo* importance of such non-hematopoietic expression of FcεRI has not yet been determined, these observations suggest that IgE and FcεRI may be able to induce functional changes in such structural cells directly rather than only indirectly through IgE-driven functions of FcεRI-bearing myeloid cells.

Interactions of IgE with FcεRI-bearing myeloid cells can have multiple effects with the potential to augment production of antigen-specific IgE. Antigens can be captured (or 'focused') by IgE bound to the αγγ form of FcεRI on the surface of cutaneous Langerhans cells and other dendritic cells, which then can migrate to regional lymph nodes or perhaps to local sites in the submucosa where they can present the processed antigens to cognate naive T cells, generating T_H2 cells[46] ('5' in **Fig. 1**, right). Although such Langerhans and dendritic cell functions can be expressed in the absence of mast cells, data from mast-cell–deficient mice[47–50] and mast-cell–knockin mice (genetically mast-cell–deficient mice that have been engrafted with mast cells)[47,48] indicate that mast cells have the potential to enhance these processes by promoting Langerhans and dendritic cell migration and, perhaps, by effects on the maturation and function of these two types of cells ('3' in **Fig. 1**, right).

In addition to immunologically 'arming' mast cells and basophils to undergo antigen- and IgE-mediated activation for mediator release, IgE binding to FcεRI also stabilizes the receptor's expression on the surface of the cells[51], thereby increasing the numbers of FcεRI on the cell surface[52–54]. This may largely account for observations showing that humans and mice with high circulating concentrations of IgE have large numbers of FcεRI on the surface of their basophils[55,56] and mast cells[54,57]. IgE-dependent upregulation of mast-cell FcεRI surface expression allows the cells to bind more IgE, which can enable the cells to respond to a larger number of different antigens, to release mediators at lower concentrations of antigens and, perhaps, to secrete certain mediators that may not be detectably released by cells with lower numbers of surface FcεRI[54,58,59]. For example, when the cells were incubated for 4 d with IgE at 5 μg ml^{-1}, the numbers of FcεRI on mouse mast cells derived from bone marrow[54] or human mast cells derived from umbilical cord blood[58] increased approximately 30-fold or doubled, respectively. In the human mast cells, the increase in surface expression of FcεRI was associated with increases of 73% and 156% in the amount of histamine and leukotriene C4 (LTC_4), respectively, secreted by the cells after challenge with antibodies to IgE[58]. Thus, IgE-dependent upregulation of mast-cell FcεRI surface

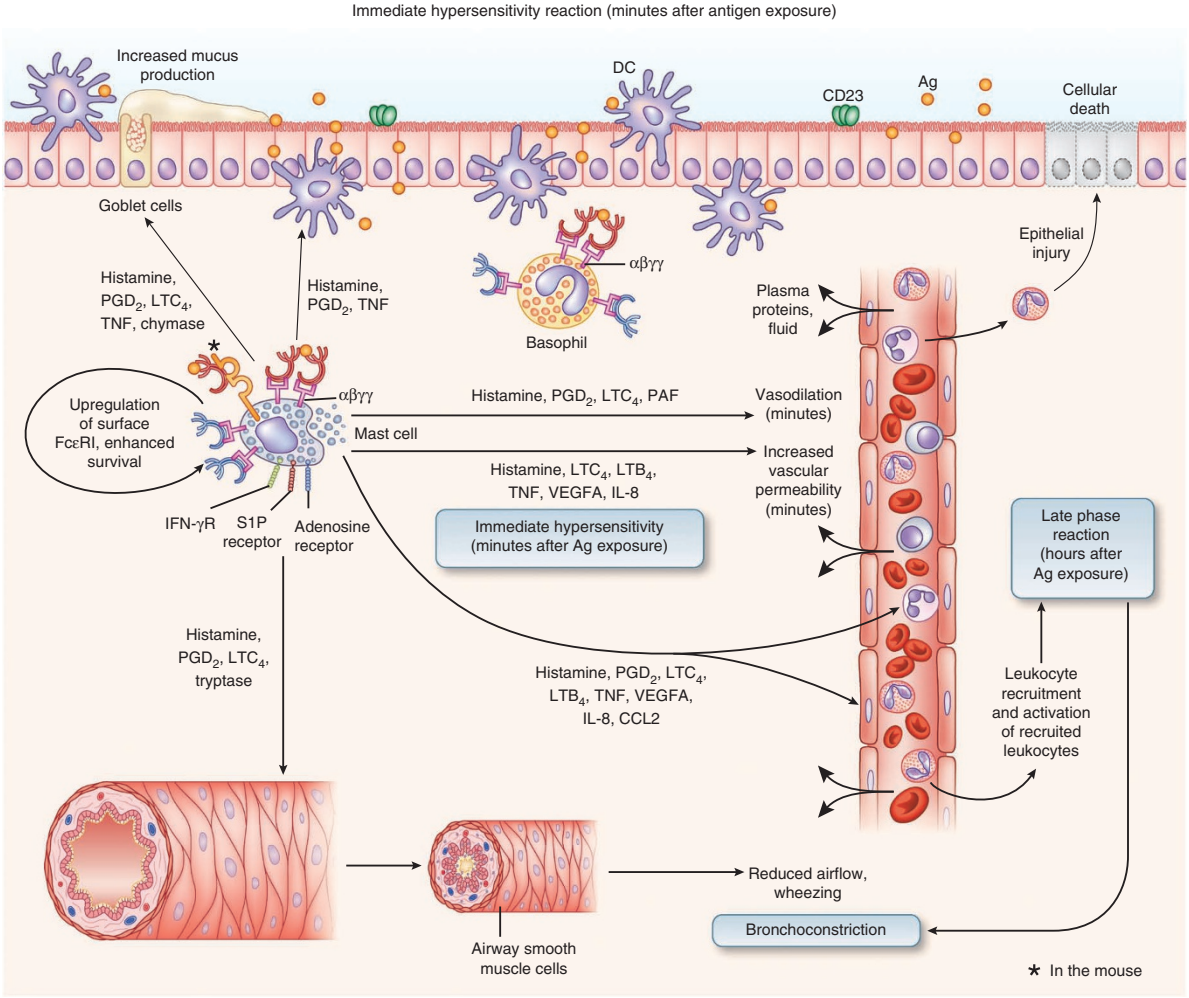

Figure 2 The early, immediate hypersensitivity, phase of antigen-induced airway inflammation. The individual IgE molecules that are bound to FcεRI molecules on a single mast cell can be specific for different antigens (red and blue IgE symbols). Binding of IgE to FcεRI αβγγ on mast cells, which are normally located in airway tissues, and basophils, if they have been recruited from the blood to airway tissues, upregulates FcεRI surface expression and sensitizes these cells to respond when later exposed to specific antigens, and, in mast cells, some IgE molecules can enhance cytokine production and survival. The recognition of a particular bivalent or multivalent antigen by at least two IgE molecules bound to adjacent FcεRI molecules induces FcεRI aggregation, activating mast cells (and basophils, if they are present in airway tissues) to initiate an immediate hypersensitivity response by secreting preformed mediators and lipid mediators within minutes of antigen exposure. These mast cells also upregulate the production of many cytokines, chemokines and growth factors. Within minutes of exposure, the rapidly secreted mediators lead to bronchoconstriction, vasodilation, increased vascular permeability and increased mucus production. Mast cell mediators produced rapidly after antigen challenge can also promote dendritic cell migration, maturation and function and can contribute to the transition to the late phase reaction by promoting an influx of circulating leukocytes, both by upregulating adhesion molecules on vascular endothelial cells (for example, through TNF) and by secreting chemotactic mediators (such as LTB_4 and PGD_2) and chemokines (such as IL-8 and CC-chemokine ligand 2 (CCL2)). These recruited leukocytes can induce further inflammation and bronchoconstriction during the late phase reaction. PAF, platelet activating factor; IFN-γR, IFN-γ receptor; VEGFA, vascular endothelial growth factor A.

expression is a potentially important positive amplification loop of allergic disease in individuals who develop increased concentrations of circulating or tissue IgE.

IgE and mast cells mediate an immediate hypersensitivity response

In an allergic person, whose tissue mast cells and other cell types already have antigen-specific IgE bound to FcεRI, re-exposure to the original or a crossreactive bivalent or multivalent antigen results in the crosslinking of adjacent FcεRI-bound IgE and the consequent aggregation of surface FcεRI. When the FcεRI aggregation is of sufficient strength and duration, it triggers mast cells and basophils to initiate complex signaling events that ultimately result in the secretion of a diverse group of biologically active products[2,4,6,38,60–63]. Some products, such as those stored preformed in the cells' cytoplasmic granules, for example, histamine, serotonin (in rodents to a much greater extent than in humans), proteases such as tryptase, chymase and/or carboxypeptidase A3 and proteoglycans (heparin and/or chondroitin sulfates), as well as newly formed lipid-derived mediators, for example, PGD_2, LTB_4, LTC_4, LTD_4 and LTE_4 and certain cytokines, are released by mast cells within minutes of antigen exposure. Others, including a diverse spectrum of cytokines, chemokines and growth factors, are produced in mast cells from new transcripts and are therefore secreted over a period of hours after the initial mast cell activation. Studies in mice suggest that, in addition to IgE, immunoglobulin light chains can also mediate antigen-specific mast cell activation, although the receptor responsible for this effect has been elusive[64].

BOX 2 Late phase reactions and chronic antigen exposure lead to persistent allergic inflammation and tissue remodeling

Mast cells previously activated during the early phase reaction secrete mediators that can orchestrate the recruitment, tissue infiltration and functional activation of circulating leukocytes, including granulocytes such as eosinophils, basophils and neutrophils, as well as monocytes and T cells[66,80,163] (**Fig. 2**), which substantially increases the diversity of the cellular drivers of inflammation at the site of antigen challenge. Mast cells may therefore be a crucial source of mediators contributing to the initiation of late phase reactions[164,165]. Other sources include antigen-specific T cells, as well as myeloid cells activated by antigen-containing immune complexes if these cells are present at the site of antigen challenge, such as in individuals with ongoing airway inflammation[163]. Indeed, low levels of ongoing inflammation in the airways, as can be observed in individuals with asthma even during treatment, together with exposure to antigen peptides that are recognized by effector T cells—but not IgE antibodies—may account for the development of late phase responses in individuals without previous detectable early phase reactions[163,166].

As people afflicted with allergic asthma are usually exposed repeatedly to the antigens that elicit their allergic reactions, and this may occur over periods of years, their airways have experienced many antigen-induced early and late phase reactions. However, in addition to developing inflammation, the airways of individuals with asthma also show structural changes, called airway remodeling, which include increased numbers of mucus-producing goblet cells in the epithelium, evidence of repair responses at sites of epithelial injury, thickening of the smooth muscle layer and changes in connective tissues, blood and lymphatic vessels, mucus glands and nerves[66,167]. Persistent airway inflammation, a key feature of both allergic and non-allergic forms of asthma, probably contributes in a crucial way to tissue remodeling in asthma[167,168]. Evidence suggests that IgE and mast cells can substantially contribute to chronic airway inflammation and tissue remodeling in asthma by functioning both in a single pathway—interdependently through antigen- and IgE-dependent mast cell activation—and independently (**Fig. 3**).

In aggregate, mediators released shortly after antigen- and IgE-induced mast cell degranulation induce a response termed an immediate hypersensitivity (or 'early phase') reaction within minutes of their release. If localized to the airways, this response is characterized by increased vascular permeability, contraction of the airway smooth muscle and enhanced secretion of mucus (**Fig. 2**), resulting in acutely reduced airflow and wheezing. If the response is systemic, it can result in anaphylaxis, a catastrophic immune response that can rapidly result in death if not properly treated[65]. The inflammation and functional changes associated with early phase responses to antigens typically resolve within a few hours. However, in some individuals, a second phase of inflammation, called the late phase reaction, develops at the site of antigen challenge, typically beginning a few hours after antigen exposure.

The IgE–mast-cell axis in chronic allergic inflammation

Mast cells activated by IgE and specific antigens produce mediators that drive early phase reactions (**Fig. 2**) and contribute to late phase reactions (**Box 2**), but these mast cells also secrete diverse cytokines, chemokines and growth factors that have the potential to influence airway remodeling[4–7,63,66] (**Fig. 3**). Compared to wild-type mice, mice lacking the FcεRI α chain showed diminished airway inflammation, as reflected in decreased numbers of eosinophils in the bronchoalveolar lavage fluid, in an asthma model[67]. Studies in wild-type, genetically mast-cell–deficient and mast-cell–knockin mice indicated that activation of mast cells through the FcR γ chain (which in mice is required for mast cell activation by antigen-IgG1 immune complexes through FcγRIII, as well as for signaling through FcεRI) is required for the full development of many features of allergic inflammation and tissue remodeling in a model of chronic asthma[68,69]. However, many other effector cells also have the potential to contribute to these features of asthma, including antigen-specific effector T cells[70], and the relative roles of mast cells compared to other effector cells in some of these settings is not fully resolved, particularly in human subjects.

In addition to possible redundancy in the roles of mast cells and other cell types in the chronic changes associated with asthma, there is evidence that many factors can modify mast cell function in this setting. For example, *in vitro*[58,71–76] and *in vivo*[69,76,77] evidence indicates that the extent of antigen- and IgE-dependent mast cell activation may be influenced substantially (or 'tuned') by microenvironmental factors that affect the expression or function of surface receptors or signaling molecules that contribute to the positive or negative regulation of such responses[4,6,7,78,79]. Tuning factors that can be present locally at the sites of allergic inflammation, such as in the airways and other anatomical sites, include adenosine[75], sphingosine-1 phosphate (S1P)[76], certain chemokines[77] and a variety of cytokines, such as IL-4 (refs. 58,71), IL-33 (refs. 72–74) and interferon γ (IFN-γ)[69]. Tuning also can be accomplished by cell-cell interactions. For example, interactions of mast cells and T cells can be bidirectional and complex[79,80] and include the ability of IgE-activated mast cells to enhance proliferation and cytokine production in multiple T cell subsets[81,82] and the ability of $CD4^+CD25^+$ regulatory T (T_{reg}) cells to suppress IgE-dependent mast cell activation through interactions between tumor necrosis factor receptor superfamily, member 4 (OX40), either as expressed by T_{reg} cells[83] or in a soluble form[84], and the OX40 ligand (OX40L) expressed on mast cells (**Fig. 3**).

In addition to stabilizing expression of FcεRI on the mast cell surface and sensitizing mast cells to respond to specific antigens, IgE antibodies can have effects on mast cell survival or function[59,85] that seem to be independent of the presence of the antigen for which the IgE has specificity. Such findings suggest that certain IgE antibodies might favor the expansion of mast cell numbers or have effects on mast cell function *in vivo*, including increasing their secretion of cytokines and chemokines, even in the absence of a specific antigen. In addition to binding to FcεRI or CD23, IgE, and FcεRI itself, can be bound by β-galactose–containing olilgosaccharide chains of galectin-3, permitting galectin-3 to activate mast cells and basophils through carbohydrate interactions that crosslink receptor-bound IgE, FcεRI or both[86] (**Table 1**). Studies in mice lacking galectin-3 support the notion that galectin-3 can amplify the pathology that is observed in models of asthma[87] or atopic dermatitis[88].

Independent roles of IgE and mast cells in allergic inflammation

By contrast, some potentially key effects of IgE or mast cells in allergic disease seem not to require direct interactions between these two effector elements. For example, IgE-dependent antigen focusing on dendritic cells and IgE-dependent FAP are thought to occur independently of mast cells (**Fig. 1**, right). Antigen- and IgE-dependent activation of other effector or immunoregulatory cells, including basophils, that can

produce a spectrum of mediators partially overlapping with those of mast cells[89,90], does not require mast cells, except perhaps for helping to recruit such cells to sites of disease, and mast cells are not required for the actions of IgE that are mediated through CD23 on other cell types.

Mast-cell–mediator secretion can be directly activated by diverse stimuli independently of IgE and specific antigens, and many of these factors are known to be present locally at sites of allergic inflammation (**Fig. 3**). Different mast cell populations show different patterns of expression of receptors for pathogen-associated molecular patterns, including Toll-like receptors (TLRs)[4–7], and activation of mast cells through different TLRs can induce these cells to secrete distinct patterns of cytokines or chemokines[4–7]. Many additional stimuli can directly activate mast cells and, in some cases, also enhance IgE-dependent mast cell activation, including adenosine[75], S1P[76], thymic stromal lymphopoietin (TSLP)[91], IL-33 (refs. 72–74) and many other cytokines, as well as proteases,

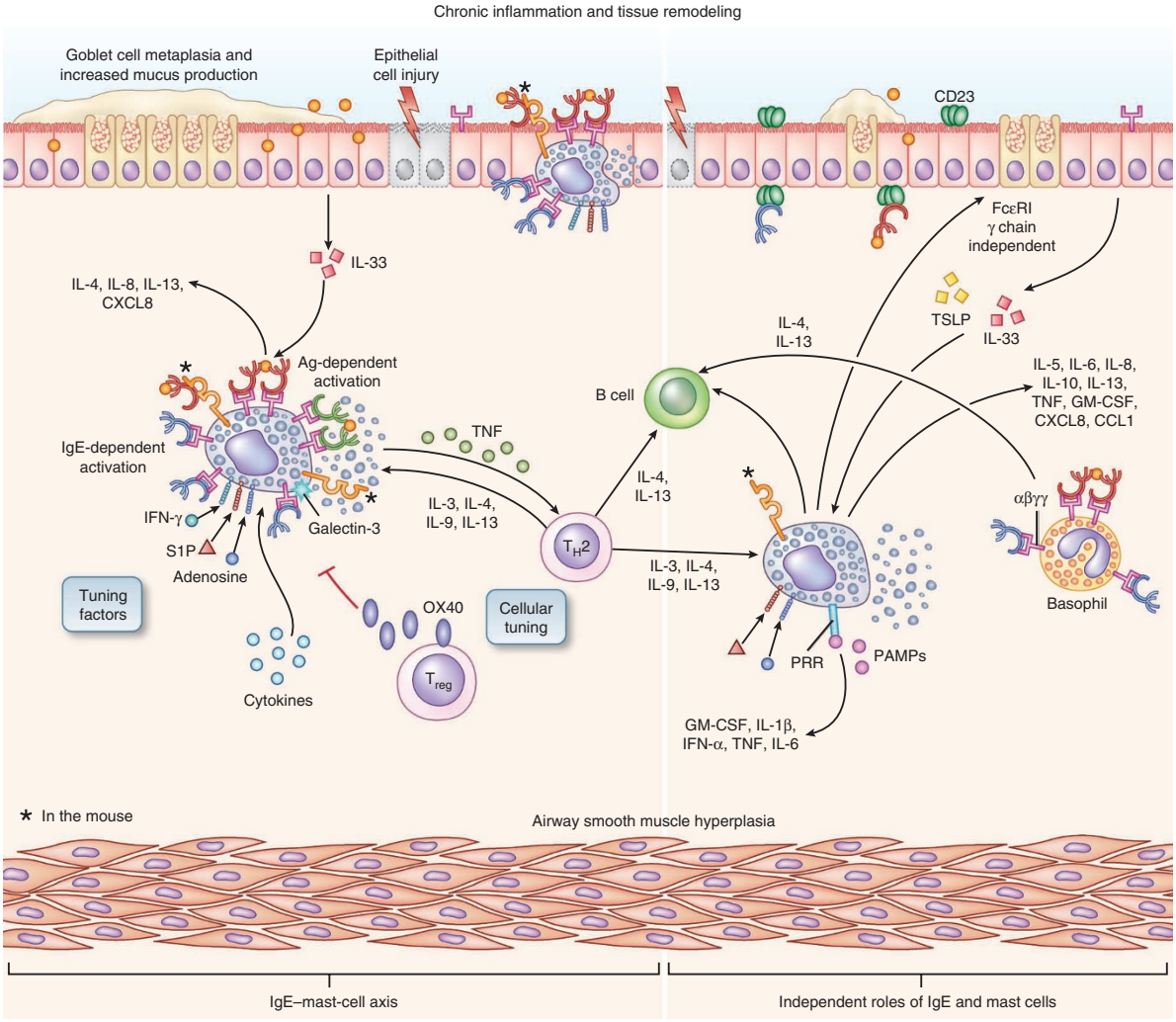

Figure 3 Roles of IgE and mast cells in chronic airway inflammation and tissue remodeling. In chronic allergic inflammation, repetitive or persistent exposure to allergens can result in both the production of IgE against multiple antigen epitopes of several different antigens (**Fig. 1**, right) and the development of long-term changes in the involved tissues (**Box 2**), including changes in mast cell number, tissue distribution (with mast cells in the epithelium and the smooth muscle layer, not shown here) and phenotype. Moreover, repetitive epithelial injury caused by chronic allergic inflammation can be exacerbated by exposure to environmental factors or pathogens such as viruses or bacteria, and the consequent repair response results in epithelial and mesenchymal changes that are thought to sustain T_H2 cell–associated inflammation, promote sensitization to additional allergens or allergen epitopes (for example, epithelial-cell–derived TSLP can upregulate the expression of co-stimulatory molecules such as OX40, CD40 and CD80 by dendritic cells, not shown here) and regulate the airway remodeling process. These processes in turn result in many functionally relevant changes in the structure of the affected tissue. There is evidence that many of these changes can be influenced by IgE and mast cells, either acting in concert through the IgE–mast-cell axis or independently. For example, both soluble factors, such as IFN-γ, S1P, adenosine and IL-33, and cells present at the site, such as T_H2 cells and T_{reg} cells (which can interact with OX40L on mast cells) can modulate, or tune, IgE-dependent mast cell activation, and some pathogen-associated molecular patterns (PAMPs) and cytokines, including TSLP and IL-33, can activate mast cells independently of IgE to produce different spectra of cytokines or chemokines. Studies in mast-cell–knockin mice have indicated that some actions of mast cells, such as increasing the number of epithelial goblet cells, can occur in a model of chronic asthma by mast-cell–dependent mechanisms that do not require mast cell signaling through the FcεRI γ chain, whereas mast cells must express both the FcεRI γ chain and the IFN γ receptor 1 (IFN-γR1) to mediate increases in lung eosinophils, neutrophils and collagen (not shown here). Amplification of the IgE response by IgE, for example, by FAP (**Fig. 1**, right) and IgE- and antigen-dependent activation of basophils after their recruitment to the airways can occur independently of mast cells. PRR, pattern recognition receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

inflammatory mediators, products of complement activation and exogenous agents, including bacterial toxins[4–7]. Thus, diverse mechanisms, not just stimulation with IgE and specific antigens, can elicit mast cell activation and mediator release in individuals with asthma and other allergic disorders, and the interactions among these various activation pathways in the setting of allergic disease may be quite complex.

For example, evidence from mast-cell–knockin mice suggests that the marked increase in the number of airway goblet cells observed in a model of chronic asthma can occur by mechanisms that are mast-cell–dependent but that do not require that the mast cells express the FcεRI γ chain[68,69] (**Fig. 3**). Although the relevance of these findings to human asthma has not been determined, gene set enrichment analyses have indicated that the changes in gene expression in the lung that are associated with this model of chronic asthma in mice[69], in which many of the key features seem to require mast cells for full expression[68,69], are similar to the mRNA changes observed in bronchial biopsy specimens obtained from a small group of patients with mild asthma[92].

In a different model of asthma, evidence obtained using mice lacking the mast-cell–associated chymase, mast cell protease 4 (MCPT4), indicates that the local secretion of this protease by mast cells, presumably in response to their activation by IgE and specific antigens and/or other mechanisms, can diminish the airway hyperreactivity, airway inflammation and airway smooth muscle thickening that is associated with this model[93]. These provocative findings suggest that at least some mast-cell–derived mediators may have functions that can curtail the extent of pathology at the sites of chronic allergic disease.

However, defining the roles of mast cells in asthma and other disorders could well be characterized as a moving target. For example, analyses of airway epithelial brushings or endobronchial biopsies[94–96], or lungs obtained at autopsy[97,98], from different groups of patients have documented changes in the number, distribution and/or phenotype of mast cells in asthmatic airways (**Fig. 3**). Such changes include increased numbers of mast cells in the airway smooth muscle of some individuals with clinically mild asthma[63,94], a significant trend to higher numbers of chymase-positive mast cells in the proximal airway epithelium of individuals with more severe asthma (such chymase-positive intraepithelial mast cells were rarely seen in healthy individuals)[96] and a significant trend toward lower levels of submucosal mast cells in the proximal airways, but a significantly higher ratio of chymase-positive mast cells to total mast cells, with increasing severity of asthma[96]. In a group of individuals with mild to moderate asthma, those with high expression of IL-13–responsive genes in their epithelial brushings ('T_H2-high asthmatics') had significantly higher numbers of intraepithelial mast cells than healthy controls or those individuals in the 'T_H2-low' group, and these mast cells were positive by immunohistochemistry for tryptase and carboxypeptidase A3 (CPA3) but not chymase[95]. Morphological studies of autopsy specimens revealed evidence for higher levels of degranulation of mast cells in the airway smooth muscle of individuals with fatal asthma than in individuals without asthma or those with non-fatal asthma[97], as well as increased numbers of neutrophils and degranulated mast cells in submucosal glands[98]. By altering the proximity of airway mast cell populations to key airway structural cells that are targets of mast-cell–derived mediators, and possibly by changing the reactivity of mast cells to various stimuli of mast cell activation, such perturbations of airway mast cell populations may influence the extent to which mast cells contribute to airway functional and structural changes in asthma[63,94–98] (**Fig. 3**).

Why do such changes in mast cell populations occur in asthma? Many growth factors, cytokines and chemokines, some of which can be derived from mast cells, as well as other sources, can positively or negatively influence the number, phenotype and tissue distribution of mast cells, including the main survival and developmental factor for human and mouse mast cells, the c-KIT ligand stem-cell factor; many of these factors have been identified at sites of allergic inflammation in asthma and other allergic disorders[4,6,7,62,63,79,99]. However, which of these factors are most crucial in altering mast cell populations in the airways of patients with asthma *in vivo* has not yet been determined.

Therapeutic approaches targeting IgE or mast cells

Therapeutic approaches in allergic diseases have for many years included attempts to target particular mediators that can be derived from mast cells and, in many cases, also from other cells types[100]. In addition, corticosteroids, whose effects can suppress many proinflammatory pathways[101], including some that may depend on mast cell functions such as cytokine production[102–104], can ameliorate disease in many individuals with asthma and other allergic disorders[101]. However, although such approaches have been useful in many patients, there are major unmet therapeutic needs, particularly in asthma[100].

Accordingly, given their role as key drivers of the pathology in allergic disorders, efforts are underway to target IgE and mast cells. Years of clinical experience with omalizumab, a humanized monoclonal antibody to IgE, have shown that it can provide benefit in some patients with moderate to severe asthma[105,106], as well as in some individuals with intermittent (seasonal) and persistent (perennial) allergic rhinitis[105], food allergy[107] or atopic dermatitis[108]. Omalizumab also has been reported to provide clinical benefit in a small group of patients with chronic autoimmune urticaria (a disorder characterized by recurrent episodes of hives that are resistant to antihistamine treatment and in which many patients have autoantibodies to the FcεRI α chain or to IgE itself)[109], in one patient with a severe case of apparently idiopathic cold-induced urticaria[110] and in a multicenter, randomized, double-blind, placebo-controlled study of patients with chronic urticaria who had IgE autoantibodies against thyroperoxidase[111]. These findings strongly implicate IgE and/or activation of the mast cell FcεRI in these disorders.

Much of the benefit of omalizumab treatment is thought to reflect its ability to reduce the concentration of free IgE in the blood, which can in turn lower the expression of FcεRI on mast cells and basophils and perhaps other cell types[56,57,112]. Other effects, such as downregulation of IgE-committed B cells, may also contribute to the efficacy of the drug[113]. However, not all patients with asthma are helped by such treatment, whether because of difficulty in lowering IgE concentrations sufficiently at the sites of disease or for other reasons[114], and such treatment is expensive; both of these factors limit the utility of omalizumab. Nevertheless, clinical experience with this agent supports the conclusion that IgE can have a key role in the pathology that is associated with asthma in some patients, fueling efforts to devise more effective and less costly ways to target IgE in allergic disease, including attempting to reduce or eliminate IgE using a synthetic IgE peptide vaccine[115,116].

Efforts also are underway to interfere with the binding of IgE to FcεRI. Such work includes the design of small peptides that can block this binding[117–120]. Other blocking peptides have been identified using a combinatorial chemistry approach[121], phage display[122–124] or modifications of known IgE receptor agonists[125,126]. Some of these

IgE-blocking peptides can inhibit mast cell activation *in vitro*[120,121,126] and IgE-dependent passive cutaneous anaphylaxis reactions *in vivo*[121]. In addition, there is preclinical evidence that it may be possible to achieve therapeutic benefit in IgE-associated disorders by enhancing the negative regulation of signaling through the FcεRI, for example, through the use of fusion proteins that co-ligate the FcεRI with the immunoreceptor tyrosine-based inhibitory motif–containing receptor, FcγRIIB, that is expressed on both mast cells and basophils[127].

Agents that target tyrosine kinases associated with mast cells, as well as with other cell types, are also being investigated, including those with activity against c-KIT[128–131] or spleen tyrosine kinase (SYK)[132,133]. Among the questions that need to be answered in future work targeting mast cells with these or other, perhaps more specific, agents are: can mast cells be targeted with high specificity and/or perhaps locally at sites of disease, can mast cells be eliminated without activating the cells to release clinically relevant amounts of mediators[134], and is there sufficient redundancy of the effector mechanisms in the beneficial innate and adaptive immune responses to which mast cells contribute such that mast cell numbers or functions can be safely ablated or reduced? As with any new therapeutic approach, careful studies will be required to assess whether the benefits of mast-cell–targeted treatments in selected patients outweigh any potential risks of adverse effects.

Conclusions

Despite many years of intense study, the roles of IgE and mast cells in asthma and other allergic diseases are not fully understood. This is particularly true regarding possible beneficial roles of certain mast cell products in these disorders. However, there is strong evidence that antigen-, IgE- and FcεRI-dependent activation of mast-cell–mediator secretion can influence the pathology of allergic disorders and that the consequences of this process can either directly affect structural cells residing in the affected tissues or influence the pathology indirectly through effects of mast cells on dendritic cells, T cells, B cells and other hematopoietic cell types. Other potentially key roles of IgE and mast cells in allergic disorders may reflect the actions of each of these two effectors that can be performed largely independently of the other, such as IgE-facilitated antigen presentation and epitope spreading and the effects of mast cells on certain aspects of tissue remodeling. However, IgE and mast cells are not the only contributors to pathology in allergic disease, and both clinical studies and analyses of animal models have indicated that there can be considerable redundancy in the innate and adaptive immune mechanisms that are at work in this setting.

We suggest that an appreciation of the complexity of allergic disorders, including the potential redundancy of the effector mechanisms that drive their pathology, has clear implications for efforts to prevent or treat such diseases. To the extent that it is possible to identify factors that can favor or suppress the development of allergic disorders, efforts should be made to avoid or reduce the effects of the former and exploit the latter to help genetically susceptible persons avoid becoming sensitized to allergens in the first place. For those individuals in whom these disorders have already developed, it would be useful to have reliable, objective criteria that have been independently confirmed in large cohorts of subjects and that can be used to subcategorize patients according to the most dominant pathways driving their disease, with particular attention being paid to those that are amenable to therapeutic manipulation. Such efforts to identify subsets of patients who may respond well to individualized pathway-targeted treatment are already underway for asthma[135–137].

It seems to us that although efforts to define therapeutically relevant subsets of patients with allergic diseases are important and should continue to be pursued, it is probable that such work will confirm that IgE and mast cells contribute substantially to disease development, progression and organ-localized pathology in many people afflicted with asthma and other allergic disorders. In such individuals, we propose that targeting only IgE or mast cells may not produce as much benefit as effectively and judiciously targeting both. Such combination approaches would have the advantage of encompassing the pathological roles of IgE that do not involve mast cells and vice versa, as well as targeting the antigen-IgE-FcεRI–mast-cell axis that long has been considered a major driver of the pathology of allergic disease.

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