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The development of allergic inflammation

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Abstract

Allergic disorders, such as anaphylaxis, hay fever, eczema and asthma, now afflict roughly 25% of people in the developed world. In allergic subjects, persistent or repetitive exposure to allergens, which typically are intrinsically innocuous substances common in the environment, results in chronic allergic inflammation. This in turn produces long-term changes in the structure of the affected organs and substantial abnormalities in their function. It is therefore important to understand the characteristics and consequences of acute and chronic allergic inflammation, and in particular to explore how mast cells can contribute to several features of this maladaptive pattern of immunological reactivity.

> The conception that antibodies, which should protect against disease, are also responsible for disease, sounds at first absurd.
>
> Clemens von Pirquet (1906)

The term ‘allergy’ was coined by Clemens von Pirquet in 1906 to call attention to the unusual propensity of some individuals to develop signs and symptoms of reactivity, or ‘hypersensitivity reactions’, when exposed to certain substances[1] (Box 1). Although the statement quoted above pertained to the cause of serum sickness[2], allergic disorders (also known as atopic disorders, from the Greek *atopos*, meaning out of place) are also associated with the production of allergen-specific IgE and with the expansion of allergen-specific T-cell populations, both of which are reactive with what typically are otherwise harmless environmental substances. These disorders are increasingly prevalent in the developed world and include allergic rhinitis (also known as hay fever), atopic dermatitis (also known as eczema), allergic (or atopic) asthma and some food allergies[3–5]. Some people develop a potentially fatal systemic allergic reaction, termed anaphylaxis, within seconds or minutes of exposure to allergens[6].

Box 1

Defining allergy, allergens and allergic inflammation

The term allergy can be used to refer to abnormal adaptive immune responses that either involve or do not involve allergen-specific IgE. This Review focuses on the former: that

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is, on the development, characteristics and consequences of the allergic inflammation that occurs in disorders in which IgE is thought to participate.

Allergy

An abnormal adaptive immune response directed against non-infectious environmental substances (allergens), including non-infectious components of certain infectious organisms. In allergic disorders, such as anaphylaxis, allergic rhinitis (hay fever), some food allergies and allergic asthma, these responses are characterized by the involvement of allergen-specific IgE and T helper 2 (T_H2) cells that recognize allergen-derived antigens. In other kinds of allergy, such as allergic contact dermatitis, IgE is thought not to be important.

Allergen

There are two main types of allergen.

The first type encompasses any non-infectious environmental substance that can induce IgE production (thereby 'sensitizing' the subject) so that later re-exposure to that substance induces an allergic reaction. Common sources of allergens include grass and tree pollens, animal dander (sheddings from skin and fur), house-dust-mite faecal particles, certain foods (notably peanuts, tree nuts, fish, shellfish, milk and eggs), latex, some medicines and insect venoms. In some instances, allergen-specific IgE directed against foreign antigens can also recognize crossreactive host antigens, but the clinical significance of this is unclear.

The second type is a non-infectious environmental substance that can induce an adaptive immune response associated with local inflammation but is thought to occur independently of IgE (for example, allergic contact dermatitis to poison ivy or nickel).

Allergic inflammation

The inflammation produced in sensitized subjects after exposure to a specific allergen(s). A single allergen exposure produces an acute reaction, which is known as an early-phase reaction or a type I immediate hypersensitivity reaction. In many subjects, this is followed by a late-phase reaction. With persistent or repetitive exposure to allergen, chronic allergic inflammation develops, with associated tissue alterations.

Early-phase reaction

An IgE-mediated type I immediate hypersensitivity reaction that can occur within minutes of allergen exposure. Reactions can be localized (for example, acute rhinoconjunctivitis in allergic rhinitis, acute asthma attacks, urticaria (hives) and gastrointestinal reactions in food allergies) or systemic (anaphylaxis). In such reactions, IgE bound to FcεRI on mast cells and basophils is crosslinked by allergen, resulting in the release of the cells' diverse preformed and newly synthesized mediators. These events cause vasodilation, increased vascular permeability with oedema, and acute functional changes in affected organs (such as bronchoconstriction, airway mucus secretion, urticaria, vomiting and diarrhoea). Some of the released mediators also promote the local recruitment and activation of leukocytes, contributing to the development of late-phase reactions.

Late-phase reaction

A reaction that typically develops after 2–6 h and peaks 6–9 h after allergen exposure. It is usually preceded by a clinically evident early-phase reaction and fully resolves in 1–2 days. Skin late-phase reactions involve oedema, pain, warmth and erythema (redness). In the lungs, these reactions are characterized by airway narrowing and mucus hypersecretion. They reflect the local recruitment and activation of T_H2 cells,

eosinophils, basophils and other leukocytes, and persistent mediator production by resident cells (such as mast cells). Mediators that initiate late-phase reactions are thought to be derived from resident mast cells activated by IgE and allergen or from T cells that recognize allergen-derived peptides (such T cells may be either resident at, or recruited to, sites of allergen challenge).

Chronic allergic inflammation

Persistent inflammation induced by prolonged or repetitive exposure to specific allergens, typically characterized not only by the presence of large numbers of innate and adaptive immune cells (in the form of leukocytes) at the affected site but also by substantial changes in the extracellular matrix and alterations in the number, phenotype and function of structural cells in the affected tissues.

In recent years, it has become clear that much of the pathology, and therefore the burden of disease, associated with allergic disorders reflects the long-term consequences of chronic allergic inflammation at sites of persistent or repetitive exposure to allergens[3,4] (Box 1). This realization has led to renewed efforts to define additional therapeutic targets in allergic disease[7–9], to devise improved strategies to induce immunological tolerance to the offending allergens[10,11], and even to manipulate the immune response to prevent the initial development of allergic disorders[12].

Here we outline some of the factors that can contribute to the development of IgE-associated allergic disorders and describe the features of allergic inflammation. We focus on the effects of short-term and long-term allergic inflammation on the structure and function of the affected tissues, particularly in asthma, and on the evidence that mast cells can contribute to multiple features of chronic, as well as acute, allergic inflammation. Finally, we briefly consider some of the approaches that are being used or contemplated to manage disorders associated with allergic inflammation. Some other disorders can also be considered allergic, such as allergic contact dermatitis and hypersensitivity pneumonitis, but these do not develop by the same immunological mechanisms — that is, they do not involve IgE- and T helper 2 (T_H2)-cell mediated responses[4] — and therefore are not discussed here.

Allergy and gene–environment interactions

Many features of allergic inflammation resemble those of the inflammation that results from immune responses to infection with enteric helminths[13] or from cutaneous responses to the bites of ectoparasites such as ticks[14]. Similarities to aspects of immune responses to parasites or environmental allergens have also been identified, notably that both involve T_H2 cells and are associated with antigen-specific IgE. These similarities have led to the idea that in allergic disorders the immune system is ‘tricked’ into reacting to otherwise inconsequential allergens in the same way as it does to signals derived from enteric helminths or ectoparasites.

In addition to the benefits conferred on the host by T_H2-cell responses to parasites, such as the development and enhancement of effector mechanisms that contribute to parasite clearance, chronic infection with certain parasites often also turns on immunological mechanisms that downregulate the inflammation and tissue damage that is associated with that infection[13,15]. Such mechanisms include the development of regulatory T cells that secrete interleukin 10 (IL-10), which has many immunosuppressive and anti-inflammatory effects[13,15,16]. In allergic disorders, it is thought that such downregulatory mechanisms do not fully develop, are lost or might be overwhelmed by inflammatory factors[13,15,16]. Indeed, observations of this type support the ‘hygiene hypothesis’[5,13,15,16]. This hypothesis is based on the observation that, as living standards advance, there is reduced exposure to parasitic

infections and to other pathogenic and non-pathogenic microorganisms (and their products). Such infections usually promote the normal development of immune responses (with a bias towards T_H1 cells rather than T_H2 cells) and favour the development of appropriate control of potentially harmful immune responses by various populations of regulatory T cells. However, as exposure to infections is reduced, and exposure to certain otherwise harmless environmental allergens is increased, there is a propensity for genetically predisposed individuals to develop T_H2-cell-type responses to a variety of common environmental allergens[5,13,15,16].

The molecular mechanisms underlying the hygiene hypothesis continue to be explored[13,15–17], but there can be no doubt that the recent marked increase in allergic disorders reflects recent changes in the interactions between the external environment and those individuals who are genetically predisposed to develop allergic diseases. Accordingly, many researchers are attempting to understand the gene–environment interactions that promote the development, increase the severity or limit the resolution of allergic inflammation[18,19]. There is already evidence that exposure to the same microbial products can have the opposite effect on an individual's propensity to develop allergic disorders, depending on an individual's genotype[19].

Allergen sensitization and epithelial barriers

Sensitization to an allergen reflects the allergen's ability to elicit a T_H2-cell response, in which IL-4 and IL-13 drive IgE production by promoting immunoglobulin class-switch recombination in B cells[4,10,11,20,21] (Fig. 1).

Many factors affect the likelihood of developing clinically significant sensitization[18,19]: host genotype, type of allergen, allergen concentration in the environment and whether exposure occurs together with agents that can enhance the sensitization process. These agents include certain ligands of Toll-like receptors, including endotoxin, which can promote T_H1-cell responses (as proposed in the hygiene hypothesis) and in certain circumstances (such as when encountered in appropriate concentrations together with an allergen) might be able to enhance the development of T_H2-cell responses[22]. Other agents that can enhance allergic sensitization are chitin, which is found in many organisms (including some that are important sources of allergens[23]), and environmental pollutants[24]. Another important factor is the pattern of contact of the immune system with allergens: for example, the amount, frequency and/or route of allergen exposure; and the type (myeloid and/or plasmacytoid) and phenotypic characteristics of the dendritic-cell subpopulations that participate in the responses[25]. The pattern of contact may affect whether there is a strong T_H2-cell response (and therefore clinical allergy), a T_H2-cell response that is kept in check by IL-10-secreting, and perhaps other, regulatory T cells[10,11,16], a modified T_H2-cell response that results in high concentrations of allergen-specific IgG_4 (ref. 26) or another form of immunological tolerance[25].

Genetic or environmental factors that influence the epithelium, including its permeability to allergens, can favour the subsequent development of a T_H2-cell response[18,27,28]. For example, loss-of-function mutations in *FLG*, which encodes filaggrin (a protein that promotes the organization of intermediate filaments of squamous cells into bundles for later crosslinking by transglutaminases), diminish the barrier function of the skin and result in ichthyosis vulgaris, a skin disease that is inherited in a semidominant pattern with incomplete penetrance[27]. Many patients with ichthyosis vulgaris also develop atopic dermatitis, and inheriting a single copy of certain loss-of-function alleles of *FLG* is associated with a markedly increased risk of developing atopic dermatitis[27]. Such *FLG*

mutations have been identified in approximately 10% of subjects of European ancestry and may occur in as many as 50% of patients who develop atopic dermatitis[27].

Patients with *FLG* mutations and atopic dermatitis are at greatly increased risk of developing asthma, even though filaggrin protein expression has so far not been detected in the lungs[29]. This finding strongly suggests that a defect in epithelial barrier function that increases the likelihood of sensitization to allergens encountered in the skin and upper airway, for example, can contribute to the development of systemic immune responses that result in allergic disease at other sites exposed to that allergen, such as the lungs. Genome-wide screens of individuals with atopic dermatitis and/or asthma have identified many other candidate genes that are expressed in the relevant epithelial-cell populations at the affected site, suggesting that mutations or polymorphisms that alter the normal barrier (and other) functions of epithelia may contribute to the development of allergies and allergic inflammation[18,27].

Most allergens are proteins (some are lipids or carbohydrates), and many, including the major house-dust-mite allergen, Der p 1, are proteases[25]. Some of these proteases can directly reduce epithelial barrier function[30] or hydrolyse substrates that participate in the development of T_H2-cell responses, including CD23, CD25, CD40 and DC-SIGN (dendritic-cell-specific ICAM3-grabbing non-integrin)[25]. Proteases are also used by parasites to invade tissues[31], and recent work suggests that basophils activated by exogenous proteases are one potential source of both thymic stromal lymphopoietin (TSLP), which can promote allergic inflammation, and the ‘early IL-4’ that can initiate sensitization for the development of T_H2-cell- and IgE-mediated immune responses to allergens or parasites[32,33].

Features of allergic inflammation

Allergic inflammation often is classified into three temporal phases. Early-phase reactions are induced within seconds to minutes of allergen challenge, and late-phase reactions occur within several hours. By contrast, chronic allergic inflammation is a persistent inflammation that occurs at sites of repeated allergen exposure[4,9] (Box 1).

Early-phase reactions

Early-phase reactions (or type I immediate hypersensitivity reactions[4]) occur within minutes of allergen exposure and mainly reflect the secretion of mediators by mast cells at the affected site. In sensitized individuals, these mast cells already have allergen-specific IgE bound to their surface high-affinity IgE receptors (FcεRI). When crosslinking of adjacent IgE molecules by bivalent or multivalent allergen occurs, aggregation of FcεRI triggers a complex intracellular signalling process that results in the secretion of three classes of biologically active product: those stored in the cytoplasmic granules, lipid-derived mediators, and newly synthesized cytokines, chemokines and growth factors, as well as other products[8,34–37] (Fig. 2).

The secretion of preformed mediators occurs when the membrane of the mast cells’ cytoplasmic granules fuses with the plasma membrane in a process called degranulation (or compound exocytosis)[38], exposing the granule contents to the external environment. The released mediators include biogenic amines (histamine and little or no serotonin in humans, but both histamine and serotonin in mice and rats[35,36]), serglycin proteoglycans (such as heparin and chondroitin sulphate), serine proteases (such as tryptases, chymases and carboxypeptidases) [39–41], and various other enzymes and certain cytokines and growth factors that can be associated with the granules (such as tumour-necrosis factor-α (TNF-α) and vascular endothelial growth factor A (VEGFA))[35,36,42,43]. Mast cells activated by the aggregation of FcεRI also release lipid-derived mediators. They metabolize arachidonic acid

through the cyclooxygenase and lipoxygenase pathways, resulting in the release of prostaglandins (particularly prostaglandin D_2 (PGD_2)), leukotriene B_4 (LTB_4) and cysteinyl leukotrienes (cys-LTs, particularly LTC_4)[44]. Some activated mast cells can also release platelet-activating factor (PAF)[45]. Both the phenotypic characteristics of mast cells (such as their mediator content and their susceptibility to activation by various stimuli) can vary considerably between mast-cell populations at different anatomical sites or as a result of exposure to cytokines or other microenvironmental factors at sites of immune responses[34,35,38–44].

The release of preformed and lipid-derived mediators contributes to the acute signs and symptoms associated with early-phase reactions[4,35,46] (Fig. 3). These signs and symptoms vary according to the site of the reaction but can include vasodilation (in part reflecting the action of mediators on local nerves, and producing erythema (reddening) of the skin or conjunctiva), markedly increased vascular permeability (leading to tissue swelling and, in the eyes, tear formation), contraction of bronchial smooth muscle (producing airflow obstruction and wheezing), and increased secretion of mucus (exacerbating airflow obstruction in the lower airways and producing a runny nose). Such mediators can also stimulate nociceptors of sensory nerves (both C-fibre-type unmyelinated nerves and thinly myelinated Aδ nerves) of the nose[47], skin[48] and airway[49], resulting in sneezing, itching or coughing.

When such mediators are released locally, an early-phase reaction ensues. By contrast, the rapid and systemic release of such mediators, from mast cells and basophils (which also express FcεRI and can release a panel of mediators similar, but not identical, to those of mast cells[35,50,51]), accounts for much of the pathology associated with anaphylaxis[6].

Late-phase reactions

Mast cells responding to IgE and allergen also release a broad range of newly synthesized cytokines, chemokines and growth factors[8,35–37], but these are released more slowly than the preformed mediators. Some mast-cell populations also can rapidly secrete some of these products, including TNF-α, from preformed stores[35]. Some mast-cell products have the potential to recruit other immune cells either directly or indirectly (for example, TNF-α, LTB_4, IL-8 (also known as CXCL8), CC-chemokine ligand 2 (CCL2) and many other chemokines), to activate innate immune cells (for example, TNF-α and IL-5), and to affect many aspects of the biology of dendritic cells, T cells and B cells (for example, IL-10, TNF-α, transforming growth factor-β (TGF-β) and histamine)[35,52]. However, some products secreted by activated mast cells (such as IL-10 and TGF-β) can have anti-inflammatory or immuno-suppressive functions[52,53]. Certain mast-cell-derived products can also influence the biology of structural cells, including vascular endothelial cells, epithelial cells, fibroblasts, smooth muscle cells and nerve cells[28,39–41,44,54,55]. Other products that contribute to late-phase reactions can be derived from T cells that recognize allergen-derived peptides; such T cells may be either resident at or recruited to early-phase reactions at sites of allergen challenge[4,9,56].

Late-phase reactions (Fig. 4) are thought to be coordinated in part by certain long-term consequences of the mediators released by activated mast cells during early-phase reactions, and in part by antigen-stimulated T cells. The clinical features of late-phase reactions reflect the activities of both resident cells and circulating leukocytes that are recruited to the site[4,9,35]. For example, calcitonin-gene-related peptide (CGRP), which is produced by epithelial cells, T cells, monocyte–macrophage lineage cells and possibly other sources, may contribute to the vasodilation that is associated with late-phase reactions[57].

Late-phase reactions typically develop 2–6 h after allergen exposure, and often peak after 6–9 h. It is not understood why they do not develop in all sensitized subjects, and in other patients there may be no clear clinical demarcation between the end of the early phase and the onset of the late phase[4]. In human skin, leukocytes recruited in late-phase reactions consist of T cells (T_H2 cells at early stages of the response, and T_H1 cells at late stages), which can contribute to changes in the cytokine environment at such sites), granulocytes (eosinophils and smaller numbers of neutrophils and basophils) and monocytes[58]. A similar set of cells has been found to participate in late-phase reactions that are elicited in the lower airways of patients with asthma, as determined by analysing bronchoalveolar lavage fluid[4,50,51]. Experimentally induced late-phase reactions typically resolve fully without treatment, but the mechanisms responsible largely remain to be defined.

Chronic allergic inflammation

When allergen exposure is continuous or repetitive, inflammation persists, and many innate and adaptive immune cells derived from the blood can be found in the tissues at sites of allergen challenge. This persistent inflammation is associated with changes in the structural cells at the affected sites, and in many cases with markedly altered function of the affected organs. Whereas early-phase reactions and late-phase reactions can easily be studied experimentally in human volunteers, most investigations of chronic allergic inflammation involve either experimental animal models of allergic disorders, none of which can be considered identical to the human diseases, or biopsy studies of human patients afflicted with these disorders. It is therefore not surprising that there is no clear understanding of how, after persistent and/or multiple exposures to allergen, local tissue inflammation changes from a series of early-phase and late-phase reactions to chronic allergic inflammation.

It is known that inflammation in patients with chronic asthma can involve all of the layers of the airway wall and typically is associated with: changes in the epithelium, including an increased number of goblet cells (which produce mucus); increased production of cytokines and chemo-kines by epithelial cells, as well as areas of epithelial injury and repair; substantial inflammation of the submucosa, including the development of increased deposition of extracellular-matrix molecules in the lamina reticularis (beneath the epithelial basement membrane); changes in fibroblasts, increased development of myofibroblasts and increased vascularity; and increased thickness of the muscular layer of the airways, with increased size, number and function of smooth muscle cells[28,59–61] (Figs 5 and 6).

Some studies[62], but not others[63], have reported increases in the number and length of tachykinin-containing nerves in the airways of patients with asthma. However, production of tachykinins by immune cells may also contribute to ‘neurogenic inflammation’ in asthma[64]. Patients with asthma show a marked bronchial hypersensitivity to both cholinergic and non-adrenergic, non-cholinergic (NANC) agonists of bronchoconstriction, as well as decreased sensitivity to adrenergic and NANC bronchodilators[65].

The complex interactions between affected airway epithelial cells and the underlying mesenchymal cells, which together are known as the ‘epithelial–mesenchymal trophic unit’ and are thought to regulate the tissue remodelling characteristic of chronic allergic inflammation of the airways, have been likened to those at a persistent wound[60]. In patients with asthma, mast cells can appear in increased numbers in the smooth muscle of the airway (Figs 5 and 6), placing this potent source of mediators that can influence smooth muscle function in intimate proximity to this crucial target-cell population[54,66]. This may contribute to the development of ‘non-specific airway hyperreactivity’ to agonists such as histamine, cys-LTs and methacholine, which is a hallmark of asthma[46,67].

In individuals with asthma, infections with common respiratory viruses such as rhinoviruses, influenza viruses and respiratory syncytial virus can produce a marked exacerbation of the signs and symptoms of asthma[68]. Although the mechanisms that underlie this exacerbation are not fully understood, one factor may be the way in which the viruses affect the function of bronchial epithelial cells[68]. Mast cells appear in the airway epithelium in asthma[54] and can be activated by viral products through Toll-like receptors[34]. However, the role (if any) of mast cells in viral exacerbations of asthma remains to be determined.

In atopic dermatitis[69] and allergic rhinitis[70], as well as in asthma, chronic allergic inflammation is associated with tissue remodelling. This remodelling can involve long-term changes to the structural elements of the affected sites (such as increased vascularity) and substantial alterations in the barrier function of the affected epithelia. In many patients with allergic rhinitis, structural changes include the development of nasal polyps[70]. In atopic dermatitis, impaired function of the skin barrier is associated with a markedly increased risk of both cutaneous infections and the colonization of the affected skin with the bacterium *Staphylococcus aureus*[69]. In allergic rhinitis, impaired barrier function of the upper airway[71] may contribute to an increased susceptibility of patients to chronic sinus infections[70].

IgE and the exacerbation of allergic disorders

Many patients who initially have a single allergic disorder, such as atopic dermatitis, eventually develop others, such as allergic rhinitis and allergic asthma (this is called the allergic march or atopic march)[72]. This process may be driven in part by a vicious circle in which allergic inflammation diminishes the function of the epithelial barrier. This increases the immune system's exposure to the original allergens and additional allergens, and existing allergen-specific IgE contributes to sensitiz ation to new allergens[21]. In this scheme, antigen-presenting cells (APCs) that express surface FceRI and/or the low-affinity IgE receptor CD23 (including FceRI-bearing Langerhans cells and other dendritic cells, as well as CD23-bearing B cells) capture allergens by means of their surface-bound allergen-specific IgE. By processing these IgE-bound antigens, APCs can promote the development of T_H2-cell responses to other epitopes of the allergen for which sensitization already exists or to other allergens that are being processed in parallel by the same APCs[21]. This proposed mechanism may result in epitope spreading (the production of IgE specific for multiple epitopes on single allergens and IgE specific for new allergens)[21].

In this model, the acquisition of IgE-dependent immunological reactivity to more and more allergens would occur in parallel with the clonal expansion of populations of effector T cells that can respond to any of a group of allergen-derived peptides[21]. However, a diverse range of genetic and environmental factors can influence the extent to which the pathology in individual allergic subjects depends on allergen, allergen-specific IgE, FceRI, mast cells and basophils, as opposed to allergen-derived peptides and effector T cells (either T_H2 cells or T_H17 cells[21,73]).

The increased levels of IgE observed in many allergic subjects can drive another amplification mechanism in allergic disorders. As local or circulating concentrations of IgE increase, mast cells and basophils display more FcεRI on their surface and have enhanced IgE-dependent effector function[8,35,74]. In addition, certain IgE molecules seem to be able to undergo antigen-independent aggregation after binding to FcεRI, thus provoking some mediator secretion by mast cells even in the absence of specific antigen[35,74]. Should this mechanism occur *in vivo*, it might contribute to the persistence of symptoms in some patients even in the absence of ongoing exposure to specific antigen.

There is strong evidence that immunoglobulin class-switch recombination can occur locally in tissues affected by allergic inflammation[21], resulting in the production of IgE. This

finding can help to explain why mast cells at these sites display FcεRI molecules that remain fully saturated with IgE even when circulating IgE concentrations are relatively low[21]. It also suggests that IgE-dependent mechanisms of effector-cell activation might contribute to the development of inflammation (and related organ dysfunction) that is indistinguishable from that observed in allergic asthma, even in subjects who have low levels of IgE and in which a specific allergen has not yet been identified[21].

In addition, several effector mechanisms that are independent of IgE may also contribute to the pathology of allergic inflammation. In a mouse model of chronic asthma, mast cells can substantially influence features of chronic allergic inflammation and tissue remodelling (including expansion of the number of goblet cells), independently of mast-cell signalling through either IgE–FcεRI or antigen–IgG_1–FcγRIII[75]. Thus mast cells have the potential to drive important features of allergic inflammation independently of IgE.

Moreover, in mouse models, allergic inflammation of the airways can be induced in mice that lack mast cells or B cells[75]. This underscores the important point that the coordination of chronic allergic inflammation may reflect complex and partly redundant pathways involving interactions between mast cells[35,51,52,55,75], T cells[4,9,56], eosinophils[76], basophils[50,51], neutrophils[73], monocyte–macrophage lineage cells[77], platelets[78] and natural killer T cells[79,80], as well as a large and growing list of cytokines (including IL-4, IL-5, IL-12, IL-13, IL-15, IL-25 and IL-33). However, the relative importance of each of these potential effector or regulatory elements may vary in different disorders or between patients, and many of these interactions may not be markedly affected by IgE. This possibility may explain, at least in part, why the humanized IgE-specific monoclonal antibody known as omalizumab (Xolair) has shown variable clinical effectiveness in patients with moderate-to-severe asthma[81]. Indeed, the results of attempts to target IgE-dependent mechanisms of inflammation in various allergic disorders support many other lines of evidence indicating that IgE has an important pathological role in some subjects with moderate-to-severe asthma[81], allergic rhinitis[81,82] or certain food allergies[83], whereas T-cell-dependent effector mechanisms are more important in most patients with atopic dermatitis and perhaps in some with asthma as well[4,58,69].

Suppression and resolution of allergic inflammation

Apart from the cessation of allergen-specific stimulation of effector cells, as occurs at the end of the pollen season in pollen-sensitive individuals, the factors that regulate the resolution of allergic inflammation are poorly understood. Some effector cells may undergo apoptosis as concentrations of cytokines that promote the survival of such cells locally diminish[84]; others (such as mast cells) may decrease the extent to which they differentiate, mature or proliferate locally[85]; and others may emigrate from the affected site[86].

In some models of allergic contact hypersensitivity, the production of IL-10 by mast cells contributes significantly to the ability of mast cells to reduce many features of inflammation in the affected sites[87]. Whether similar anti-inflammatory or immunosuppressive actions of mast cells can be elicited in the context of IgE-associated allergic inflammation remains to be determined. However, several types of innate and adaptive immune cells that infiltrate sites of allergic inflammation (including eosinophils and various populations of regulatory T cells) can produce mediators, cytokines, chemokines and growth factors that could reduce inflammation or promote repair at these sites. Such products include the resolvin and protectin lipid mediators[88], IL-4 (which can have anti-inflammatory effects[89]), TGF-β[90,91], TGF-α[92], IL-10 (refs 16, 87, 89, 91, 93) and IL-35 (ref. 93).

Allergen-specific regulatory T cells have been reported in patients after allergen-specific immunotherapy[10,11,16,93]. In addition, there is evidence from animal models of allergy and

asthma that both antigen-specific regulatory T cells and naturally occurring regulatory T cells can limit disease, in part by IL-10- and TGF-β-dependent mechanisms[16,93]. However, the extent to which particular populations of regulatory T cells can limit allergic inflammation at the times of exposure to specific allergen, or help to resolve allergic inflammation when exposure to allergen ceases, and the mechanisms by which the regulatory T cells exert these effects remain to be fully understood.

Management of allergies and allergic inflammation

The two key elements of allergy management are preventing the exposure of sensitized individuals to allergen and treating these individuals with therapeutic agents appropriate to the disorder. For example, antihistamines that target the H_1 histamine receptor are a mainstay of treatment for allergic rhinitis but have been of limited value in asthma[7,9]. Asthma is generally treated with inhaled corticosteroids (which suppress many of the pathways that contribute to inflammation) and agonists of β-adrenergic receptors (which induce bronchodilation). These treatments are effective in many (but not all) subjects[7,9]. Some patients with asthma are helped by drugs that target cys-LTs[7,9]. Omalizumab, which targets IgE, helps some subjects with moderate or severe asthma[81] and is being evaluated in other settings[82].

The extent to which pharmacogenetic approaches can be used to understand the basis of variable clinical responses to the same agent, and to identify subjects who will benefit from particular treatments, is an area of active investigation[94]. Allergen-specific immunotherapy should be considered in situations in which this approach has been shown to be beneficial[10,11].

Many new pharmacological or biological agents that target the various steps in the cell and mediator pathways implicated in allergic inflammation are being investigated[7,9]. Some of these compounds are designed to exploit endogenous mechanisms to suppress effector-cell activation during allergic inflammation, such as co-engagement of FcεRI with the inhibitory receptor FcγRIIB[95], or to take advantage of other mechanisms that can negatively regulate FcεRI-dependent signalling[8,36].

Strategies to reduce sensitization and promote tolerance to common allergens are also being considered. One example is reducing exposure to allergens through routes that favour the generation of T_H2-cell responses (for example, the skin and respiratory tract) while increasing exposure through routes that favour the production of tolerance (the gastrointestinal tract)[96]. Other approaches include attempting to devise vaccines that can be used (carefully) to induce tolerance to substances before natural sensitization can occur[7,9–11], using probiotics to promote the development of a ‘healthy’ immune system (that is, biased to T_H1-cell responses or modified T_H2-cell responses) [12], and using data derived from epidemiological studies to promote aspects of lifestyle that may reduce the risk of developing allergic disorders. Examples of this last approach include reducing exposure to common aeroallergens[97], increasing exposure to certain pets (such as dogs)[98], and increasing exercise and outdoor activities[99].

What next?

The recent progress in our understanding of the genetic, environmental, tissue-specific and immunological factors that contribute to the development of allergic disorders and allergic inflammation has suggested possible new approaches for managing, treating or even preventing these disorders. Will more specific or potent targeting of additional mediators, their receptors, IgE, FcεRI or effector cells (such as mast cells, T cells and natural killer T cells), used alone or in combination, afford a substantial improvement over current

approaches? Will marshalling the current knowledge of the immunobiology of allergy and tolerance allow researchers to devise ways to prevent allergic sensitization (for example, by improving epithelial barrier function in individuals in whom it is impaired) or to induce tolerance by safer and more effective forms of allergen-specific immunotherapy? Time will tell. Such efforts are important because, although most patients with allergic disorders can be helped by current management strategies, these complex 'disorders of advanced civilization' have so far been difficult to control in many patients, let alone to prevent or cure.

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References

1. von Pirquet C. Allergie. Münch Med Wochenschr. 1906; 53:1457–1458.
2. Silverstein AM. Clemens Freiherr von Pirquet: explaining immune complex disease in 1906. Nature Immunol. 2000; 1:453–455. [PubMed: 11101860]
3. Holgate ST. The epidemic of allergy and asthma. Nature. 1999; 402:B2–B4. [PubMed: 10586888]
4. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med. 2001; 344:30–37. [PubMed: 11136958]
5. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006; 355:2226–2235. [PubMed: 17124020]
6. Sampson HA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol. 2005; 115:584–591. [PubMed: 15753908]
7. Barnes PJ. New therapies for asthma. Trends Mol Med. 2006; 12:515–520. [PubMed: 17011826]
8. Kraft S, Kinet JP. New developments in FcεRI regulation, function and inhibition. Nature Rev Immunol. 2007; 7:365–378. This review of FcεRI-dependent signalling in mast cells and basophils considers how the biology and functional properties of FcεRI might be exploited for the development of new therapeutics. [PubMed: 17438574]
9. Holgate ST, Polosa R. Treatment strategies for allergy and asthma. Nature Rev Immunol. 2008; 8:218–230. [PubMed: 18274559]
10. Larché M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. Nature Rev Immunol. 2006; 6:761–771. This review discusses the history, immunological mechanisms and future prospects of improving allergen-specific immunotherapy. [PubMed: 16998509]
11. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol. 2007; 119:780–791. [PubMed: 17321578]
12. Kukkonen K, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2007; 119:192–198. [PubMed: 17208601]
13. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science. 2002; 296:490–494. [PubMed: 11964470]
14. Galli, SJ.; Askenase, PW. The Reticuloendothelial System: A Comprehensive Treatise. In: Abramoff, P.; Phillips, SM.; Escobar, MR., editors. Hypersensitivity. Vol. IX. Plenum; 1986. p. 321-369.
15. Fallon PG, Mangan NE. Suppression of T_H2-type allergic reactions by helminth infection. Nature Rev Immunol. 2007; 7:220–230. [PubMed: 17318233]
16. Hawrylowicz CM, O'Garra A. Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. Nature Rev Immunol. 2005; 5:271–283. This review provides an introduction to the mechanisms by which regulatory T cells that produce the anti-inflammatory and immunosuppressive cytokine IL-10 might limit the pathology associated with allergy and allergic inflammation of the airways in asthma. [PubMed: 15775993]

17. Romagnani S. Coming back to a missing immune deviation as the main explanatory mechanism for the hygiene hypothesis. J Allergy Clin Immunol. 2007; 119:1511–1513. [PubMed: 17556059]
18. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nature Rev Immunol. 2004; 4:978–988. [PubMed: 15573132]
19. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nature Rev Immunol. 2008; 8:169–182. This review presents the current understanding of the many genes that have been implicated in asthma and allergy, including evidence that exposure to the same microbial products may have opposite effects on susceptibility to developing allergic disorders, depending on an individual's genotype. [PubMed: 18301422]
20. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. Nature Rev Immunol. 2003; 3:721–732. [PubMed: 12949496]
21. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nature Rev Immunol. 2008; 8:205–217. This review describes the complex role of IgE and its receptors in allergy and asthma, including evidence that IgE and its receptors may contribute to epitope spreading in, and therefore exacerbation of, allergic disorders. [PubMed: 18301424]
22. Herrick CA, Bottomly K. To respond or not to respond: T cells in allergic asthma. Nature Rev Immunol. 2003; 3:405–412. [PubMed: 12766762]
23. Dickey BF. Exoskeletons and exhalation. N Engl J Med. 2007; 357:2082–2084. [PubMed: 18003965]
24. Saxon A, Diaz-Sanchez D. Air pollution and allergy: you are what you breathe. Nature Immunol. 2005; 6:223–226. [PubMed: 15716966]
25. Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. Nature Rev Immunol. 2008; 8:193–204. [PubMed: 18301423]
26. Platts-Mills TA, Woodfolk JA, Erwin EA, Aalberse R. Mechanisms of tolerance to inhalant allergens: the relevance of a modified T_H2 response to allergens from domestic animals. Springer Semin Immunopathol. 2004; 25:271–279. [PubMed: 15007631]
27. Sandilands A, Smith FJ, Irvine AD, McLean WH. Filaggrin's fuller figure: a glimpse into the genetic architecture of atopic dermatitis. J Invest Dermatol. 2007; 127:1282–1284. [PubMed: 17502856]
28. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol. 2007; 120:1279–1284. [PubMed: 17949801]
29. Ying S, Meng Q, Corrigan CJ, Lee TH. Lack of filaggrin expression in the human bronchial mucosa. J Allergy Clin Immunol. 2006; 118:1386–1388. [PubMed: 17157670]
30. Jeong SK, et al. Mite and cockroach allergens activate protease-activated receptor 2 and delay epidermal permeability barrier recovery. J Invest Dermatol. 2008; 128:1930–1939. [PubMed: 18305573]
31. McKerrow JH, Caffrey C, Kelly B, Loke P, Sajid M. Proteases in parasitic diseases. Annu Rev Pathol. 2006; 1:497–536. [PubMed: 18039124]
32. Min B, Paul WE. Basophils: in the spotlight at last. Nature Immunol. 2008; 9:223–225. [PubMed: 18285768]
33. Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. Nature Immunol. 2008; 9:310–318. This paper identifies a key role for basophils in the initiation of T_H2-cell responses to exogenous proteases. [PubMed: 18300366]
34. Marshall JS. Mast-cell responses to pathogens. Nature Rev Immunol. 2004; 4:787–799. [PubMed: 15459670]
35. Galli SJ, et al. Mast cells as 'tunable' effector and immunoregulatory cells: recent advances. Annu Rev Immunol. 2005; 23:749–786. This review discusses many aspects of mast-cell biology, including mast-cell phenotypic heterogeneity and function, and the roles of mast cells as effector and potential immunoregulatory cells in innate and adaptive immune responses. [PubMed: 15771585]
36. Gilfillan AM, Tkaczyk C. Integrated signalling pathways for mast-cell activation. Nature Rev Immunol. 2006; 6:218–230. [PubMed: 16470226]
37. Rivera J, Gilfillan AM. Molecular regulation of mast cell activation. J Allergy Clin Immunol. 2006; 117:1214–1225. [PubMed: 16750977]

38. Dvorak AM. Ultrastructural studies of human basophils and mast cells. J Histochem Cytochem. 2005; 53:1043–1070. [PubMed: 15923353]
39. Caughey GH. Mast cell tryptases and chymases in inflammation and host defense. Immunol Rev. 2007; 217:141–154. [PubMed: 17498057]
40. Pejler G, Abrink M, Ringvall M, Wernersson S. Mast cell proteases. Adv Immunol. 2007; 95:167–255. [PubMed: 17869614]
41. Stevens RL, Adachi R. Protease-proteoglycan complexes of mouse and human mast cells and importance of their beta-tryptase-heparin complexes in inflammation and innate immunity. Immunol Rev. 2007; 217:155–167. [PubMed: 17498058]
42. Bradding P, Holgate ST. The mast cell as a source of cytokines in asthma. Ann NY Acad Sci. 1996; 796:272–281. [PubMed: 8906234]
43. Saito H, Nakajima T, Matsumoto K. Human mast cell transcriptome project. Int Arch Allergy Immunol. 2001; 125:1–8. [PubMed: 11385282]
44. Boyce JA. Mast cells and eicosanoid mediators: a system of reciprocal paracrine and autocrine regulation. Immunol Rev. 2007; 217:168–185. [PubMed: 17498059]
45. Finkelman FD. Anaphylaxis: lessons from mouse models. J Allergy Clin Immunol. 2007; 120:506–515. [PubMed: 17765751]
46. Wills-Karp M. Immunologic basis of antigen-induced airway hyperresponsiveness. Annu Rev Immunol. 1999; 17:255–281. [PubMed: 10358759]
47. Sarin S, Undem B, Sanico A, Togias A. The role of the nervous system in rhinitis. J Allergy Clin Immunol. 2006; 118:999–1016. [PubMed: 17088122]
48. Cevikbas F, Steinhoff A, Homey B, Steinhoff M. Neuroimmune interactions in allergic skin diseases. Curr Opin Allergy Clin Immunol. 2007; 7:365–373. [PubMed: 17873574]
49. Lalloo UG, Barnes PJ, Chung KF. Pathophysiology and clinical presentations of cough. J Allergy Clin Immunol. 1996; 98:S91–S96. discussion S96–S97. [PubMed: 8939182]
50. MacGlashan D Jr, Gauvreau G, Schroeder JT. Basophils in airway disease. Curr Allergy Asthma Rep. 2002; 2:126–132. [PubMed: 11892092]
51. Marone G, Triggiani M, de Paulis A. Mast cells and basophils: friends as well as foes in bronchial asthma? Trends Immunol. 2005; 26:25–31. [PubMed: 15629406]
52. Galli SJ, Grimbaldeston MA, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nature Rev Immunol. 2008; 8:478–486. [PubMed: 18483499]
53. Sayed BA, Christy A, Quirion MR, Brown MA. The master switch: the role of mast cells in autoimmunity and tolerance. Annu Rev Immunol. 2008; 26:705–739. [PubMed: 18370925]
54. Bradding P, Walls AF, Holgate ST. The role of the mast cell in the pathophysiology of asthma. J Allergy Clin Immunol. 2006; 117:1277–1284. [PubMed: 16750987]
55. Brown JM, Wilson TM, Metcalfe DD. The mast cell and allergic diseases: role in pathogenesis and implications for therapy. Clin Exp Allergy. 2008; 38:4–18. [PubMed: 18031566]
56. Larché M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. J Allergy Clin Immunol. 2003; 111:450–463. [PubMed: 12642820]
57. Kay AB, et al. Airway expression of calcitonin gene-related peptide in T-cell peptide-induced late asthmatic reactions in atopics. Allergy. 2007; 62:495–503. [PubMed: 17441790]
58. Bonness S, Bieber T. Molecular basis of atopic dermatitis. Curr Opin Allergy Clin Immunol. 2007; 7:382–386. [PubMed: 17873576]
59. Doherty T, Broide D. Cytokines and growth factors in airway remodeling in asthma. Curr Opin Immunol. 2007; 19:676–680. [PubMed: 17720466]
60. Holgate ST. Epithelium dysfunction in asthma. J Allergy Clin Immunol. 2007; 120:1233–1244. This review discusses the role of the airway epithelium and its function (and dysfunction) in the development and pathology of asthma. [PubMed: 18073119]
61. Mauad T, Bel EH, Sterk PJ. Asthma therapy and airway remodeling. J Allergy Clin Immunol. 2007; 120:997–1009. [PubMed: 17681364]
62. Ollerenshaw SL, Jarvis D, Sullivan CE, Woolcock AJ. Substance P immunoreactive nerves in airways from asthmatics and nonasthmatics. Eur Respir J. 1991; 4:673–682. [PubMed: 1716217]

63. Chanez P, et al. Bronchial mucosal immunoreactivity of sensory neuropeptides in severe airway diseases. Am J Respir Crit Care Med. 1998; 158:985–990. [PubMed: 9731035]
64. Joos GF, De Swert KO, Schelfhout V, Pauwels RA. The role of neural inflammation in asthma and chronic obstructive pulmonary disease. Ann NY Acad Sci. 2003; 992:218–230. [PubMed: 12794061]
65. Lewis MJ, Short AL, Lewis KE. Autonomic nervous system control of the cardiovascular and respiratory systems in asthma. Respir Med. 2006; 100:1688–1705. [PubMed: 16524708]
66. Brightling CE, et al. Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med. 2002; 346:1699–1705. [PubMed: 12037149]
67. Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. Annu Rev Immunol. 2004; 22:789–815. [PubMed: 15032597]
68. Gern JE, Busse WW. Relationship of viral infections to wheezing illnesses and asthma. Nature Rev Immunol. 2002; 2:132–138. [PubMed: 11910895]
69. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest. 2004; 113:651–657. [PubMed: 14991059]
70. Pawankar R, Nonaka M, Yamagishi S, Yagi T. Pathophysiologic mechanisms of chronic rhinosinusitis. Immunol Allergy Clin North Am. 2004; 24:75–85. [PubMed: 15062428]
71. Takano K, et al. HLA-DR- and CD11c-positive dendritic cells penetrate beyond well-developed epithelial tight junctions in human nasal mucosa of allergic rhinitis. J Histochem Cytochem. 2005; 53:611–619. [PubMed: 15872054]
72. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003; 112:S118–S127. [PubMed: 14657842]
73. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nature Rev Immunol. 2008; 8:183–192. [PubMed: 18274560]
74. Kawakami T, Galli SJ. Regulation of mast-cell and basophil function and survival by IgE. Nature Rev Immunol. 2002; 2:773–786. [PubMed: 12360215]
75. Yu M, et al. Mast cells can promote the development of multiple features of chronic asthma in mice. J Clin Invest. 2006; 116:1633–1641. This paper presents evidence that mast cells can contribute to multiple features of the pathology in a mouse model of chronic asthma both by mechanisms that do or do not require the antibody (IgE and/or IgG1)-dependent activation of mast cells through the FcRγ chain shared by mast-cell FcεRI and FcγRIII. [PubMed: 16710480]
76. Jacobsen EA, et al. Allergic pulmonary inflammation in mice is dependent on eosinophil-induced recruitment of effector T cells. J Exp Med. 2008; 205:699–710. [PubMed: 18316417]
77. Peters-Golden M. The alveolar macrophage: the forgotten cell in asthma. Am J Respir Cell Mol Biol. 2004; 31:3–7. [PubMed: 15208096]
78. Kasperska-Zajac A, Rogala B. Platelet activation during allergic inflammation. Inflammation. 2007; 30:161–166. [PubMed: 17570045]
79. Akbari O, et al. $CD4^+$ invariant T-cell-receptor$^+$ natural killer T cells in bronchial asthma. N Engl J Med. 2006; 354:1117–1129. [PubMed: 16540612]
80. Vijayanand P, et al. Invariant natural killer T cells in asthma and chronic obstructive pulmonary disease. N Engl J Med. 2007; 356:1410–1422. [PubMed: 17409322]
81. Holgate ST, Djukanovic R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy. 2005; 35:408–416. [PubMed: 15836747]
82. Casale TB, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. J Am Med Assoc. 2001; 286:2956–2967.
83. Leung DY, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003; 348:986–993. [PubMed: 12637608]
84. Akdis CA, Blaser K, Akdis M. Apoptosis in tissue inflammation and allergic disease. Curr Opin Immunol. 2004; 16:717–723. [PubMed: 15511663]
85. Ryan JJ, et al. Mast cell homeostasis: a fundamental aspect of allergic disease. Crit Rev Immunol. 2007; 27:15–32. [PubMed: 17430094]

86. Medoff BD, Thomas SY, Luster AD. T cell trafficking in allergic asthma: the ins and outs. Annu Rev Immunol. 2008; 26:205–232. This is a comprehensive review of the molecular regulation and consequences of T-cell migration in allergic inflammation of airways. [PubMed: 18304002]
87. Grimbaldeston MA, Nakae S, Kalesnikoff J, Tsai M, Galli SJ. Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B. Nature Immunol. 2007; 8:1095–1104. [PubMed: 17767162]
88. Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. Annu Rev Pathol. 2008; 3:279–312. [PubMed: 18233953]
89. Opal SM, DePalo VA. Anti-inflammatory cytokines. Chest. 2000; 117:1162–1172. [PubMed: 10767254]
90. Letterio JJ, Roberts AB. Regulation of immune responses by TGF-β. Annu Rev Immunol. 1998; 16:137–161. [PubMed: 9597127]
91. Li MO, Flavell RA. Contextual regulation of inflammation: a duet by transforming growth factor-β and interleukin-10. Immunity. 2008; 28:468–476. [PubMed: 18400189]
92. Burgel PR, et al. Human eosinophils induce mucin production in airway epithelial cells via epidermal growth factor receptor activation. J Immunol. 2001; 167:5948–5954. [PubMed: 11698473]
93. Vignali DAA, Collison LW, Workman CJ. How regulatory T cells work. Nature Rev Immunol. 2008; 8:523–532. [PubMed: 18566595]
94. Hall IP, Sayers I. Pharmacogenetics and asthma: false hope or new dawn? Eur Respir J. 2007; 29:1239–1245. [PubMed: 17540786]
95. Zhu D, et al. A chimeric human–cat fusion protein blocks cat-induced allergy. Nature Med. 2005; 11:446–449. [PubMed: 15793580]
96. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. N Engl J Med. 2003; 348:977–985. [PubMed: 12637607]
97. Platts-Mills TA, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the Third International Workshop. J Allergy Clin Immunol. 1997; 100:S2–S24. [PubMed: 9438476]
98. Ownby DR, Johnson CC. Does exposure to dogs and cats in the first year of life influence the development of allergic sensitization? Curr Opin Allergy Clin Immunol. 2003; 3:517–522. [PubMed: 14612678]
99. Lucas SR, Platts-Mills TA. Physical activity and exercise in asthma: relevance to etiology and treatment. J Allergy Clin Immunol. 2005; 115:928–934. [PubMed: 15867847]

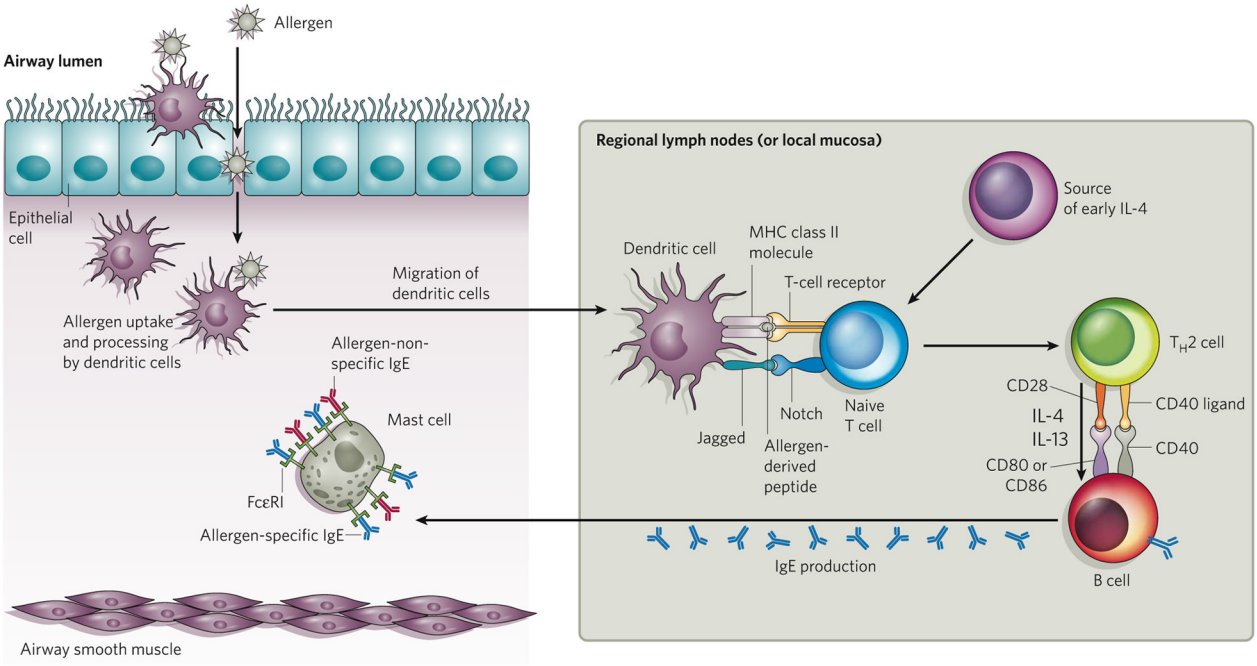

Figure 1. Sensitization to allergens in the airway

Allergen can be sampled by dendritic cells in the airway lumen, and can enter tissues through disrupted epithelium (not shown) or, for some allergens with protease activity, can gain access to submucosal dendritic cells by cleaving epithelial-cell tight junctions. Activated dendritic cells mature and migrate to regional lymph nodes or to sites in the local mucosa, where they present peptides derived from the processed allergen in the context of major histocompatibility complex (MHC) class II molecules to naive T cells. In the presence of 'early interleukin 4' (IL-4) (potentially derived from a range of cells, including basophils, mast cells, eosinophils, natural killer T cells and T cells), naive T cells acquire the characteristics of T helper 2 (T_H2) cells, a process that may be enhanced by engagement of Notch at the surface of T cells with Jagged on dendritic cells). T_H2 cells produce IL-4 and IL-13. In the presence of these cytokines and the ligation of suitable co-stimulatory molecules (CD40 with CD40 ligand, and CD80 or CD86 with CD28), B cells undergo immunoglobulin class-switch recombination, in which the gene segments that encode the immunoglobulin heavy chain are rearranged such that antibody of the IgE class is produced. Basophils and mast cells also can produce IL-4 and/or IL-13, and can stimulate B cells through CD40 (not shown). IgE diffuses locally and enters the lymphatic vessels. It subsequently enters the blood and is then distributed systemically. After gaining access to the interstitial fluid, allergen-specific or non-specific IgE binds to the high-affinity receptor for IgE (FcεRI) on tissue-resident mast cells, thereby sensitizing them to respond when the host is later re-exposed to the allergen. Sensitization does not produce symptoms (for example, if sensitization occurs by way of the airways, bronchoconstriction does not occur). This T_H2-cell response to allergen can be downregulated or modified by various mechanisms (not shown).

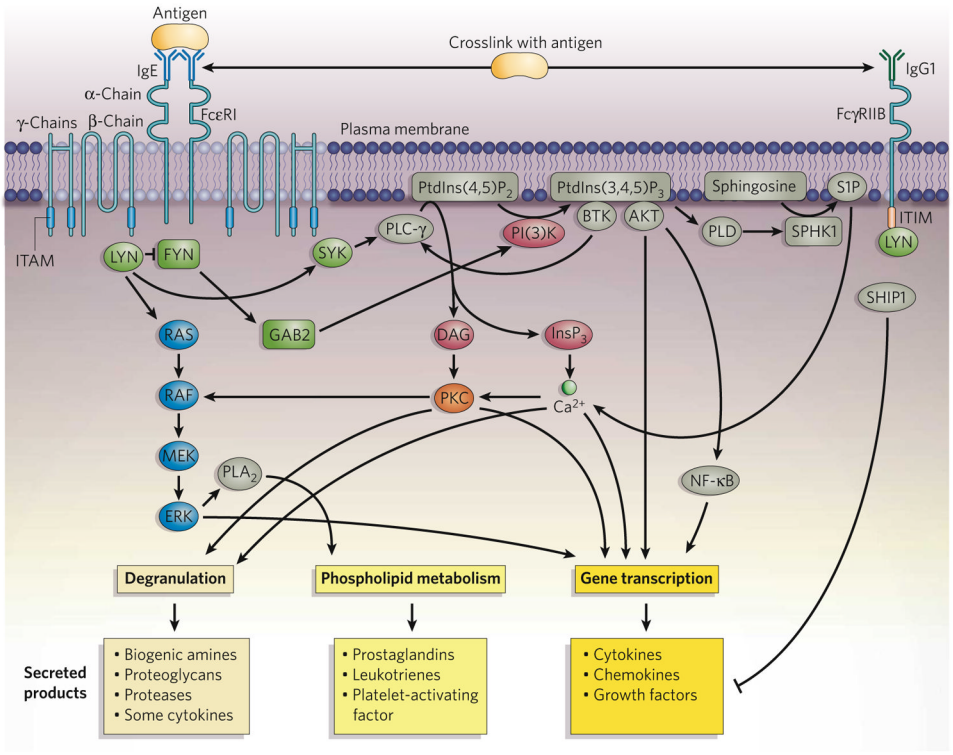

Figure 2. Highly simplified scheme of FcεRI signalling events in mast cells

Crosslinking of FcεRI-bound IgE with antigen induces aggregation of two or more FcεRI molecules and activates the protein tyrosine kinases LYN and FYN. LYN, in turn, phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs) in FcεRI and activates the protein tyrosine kinase SYK (after SYK has bound to an ITAM). FYN phosphorylates the adaptor GAB2, activating the phosphatidylinositol-3-OH kinase (PI(3)K) pathway. LYN and SYK phosphorylate many adaptor molecules (such as LAT, not shown) and enzymes, thereby regulating the activation of the RAS–MAPK (mitogen-activated protein kinase), phospholipase C-γ (PLC-γ) and PI(3)K pathways, as well as other pathways. (LYN also can negatively regulate FYN activity.) The RAS–MAPK pathway — a protein-kinase cascade that involves RAS, RAF, MEK and ERK — activates transcription factors (thereby regulating the synthesis of protein mediators) and activates PLA_2, which participates in arachidonic acid metabolism (thereby regulating the production of lipid-derived mediators). PLC-γ activation regulates calcium (Ca^{2+}) responses, by generating inositol-1,4,5-trisphosphate ($InsP_3$), and protein kinase C (PKC) activation, by generating diacylglycerol (DAG). The PI(3)K product phosphatidylinositol-3,4,5-trisphosphate ($PtdIns(3,4,5)P_3$) is an important lipid mediator that regulates the formation of other lipid mediators, such as DAG and sphingosine 1-phosphate (S1P), and the activity of various enzymes, such as Bruton's tyrosine kinase (BTK) and AKT. FcεRI can be induced to co-aggregate with FcγRIIB (a low-affinity receptor for IgG), for example when IgE and IgG1 are bound to the same antigen. This process inhibits FcεRI signalling events, and therefore mast-cell activation and product secretion, through the LYN-mediated phosphorylation of the FcγRIIB ITIM (immunoreceptor tyrosine-based inhibitory motif) and the recruitment of the inositol phosphatase SHIP1 (which catalyses the hydrolysis of $PtdIns(3,4,5)P_3$ to $PtdIns(3,4)P_2$) (not shown). Some arrows do not indicate direct interactions or targets. NF-κB, nuclear factor-κB; SPHK1, sphingosine kinase 1.

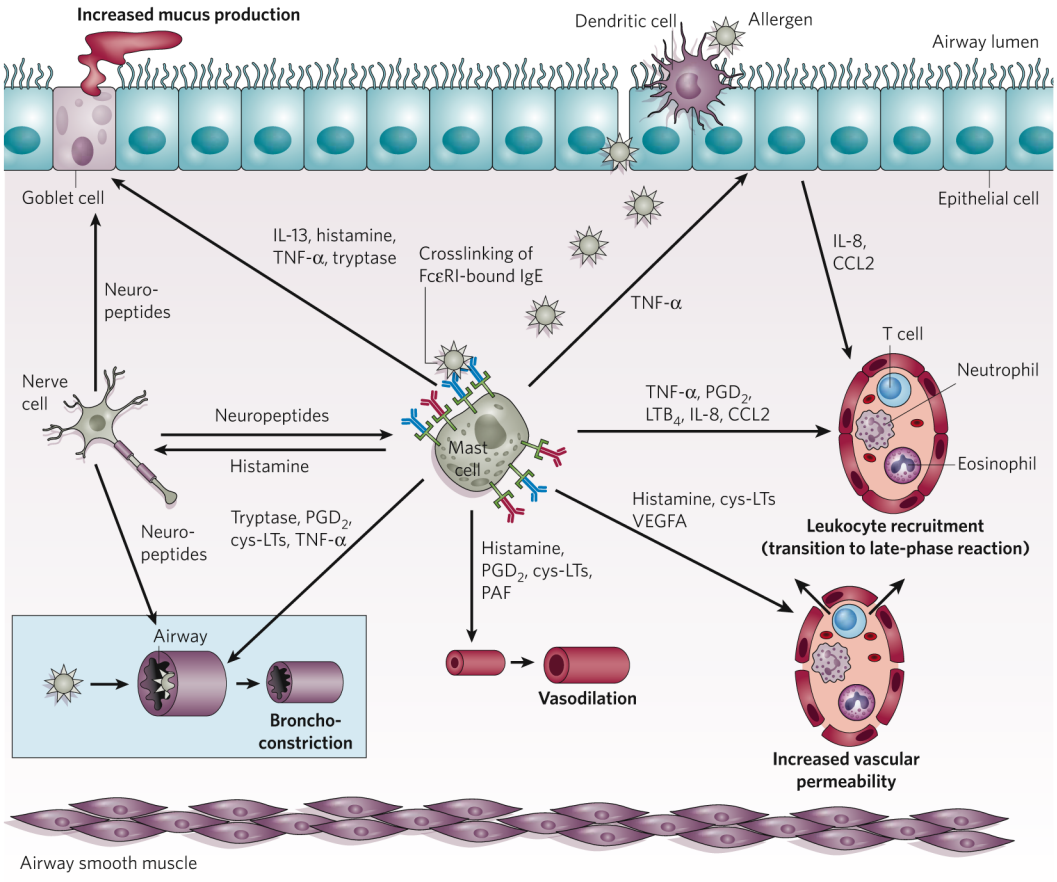

Figure 3. Early phase of allergen-induced airway inflammation

The individual IgE molecules that are bound to the FcεRI molecules on a single mast cell can be specific for different antigens. The recognition of a particular allergen by FcεRI-bound IgE specific for antigen derived from that allergen (allergen-specific IgE) induces FcεRI aggregation, which activates mast cells to secrete preformed mediators and lipid-derived mediators and to increase the synthesis of many cytokines, chemokines and growth factors. The rapidly secreted mediators result in bronchoconstriction (lower left), vasodilation, increased vascular permeability and increased mucus production. Mast cells also contribute to the transition to the late-phase reaction (Fig. 4) by promoting an influx of inflammatory leukocytes, both by upregulating adhesion molecules on vascular endothelial cells (for example, through TNF-α) and by secreting chemotactic mediators (such as LTB_4 and PGD_2) and chemokines (such as IL-8 and CC-chemokine ligand 2 (CCL2)).

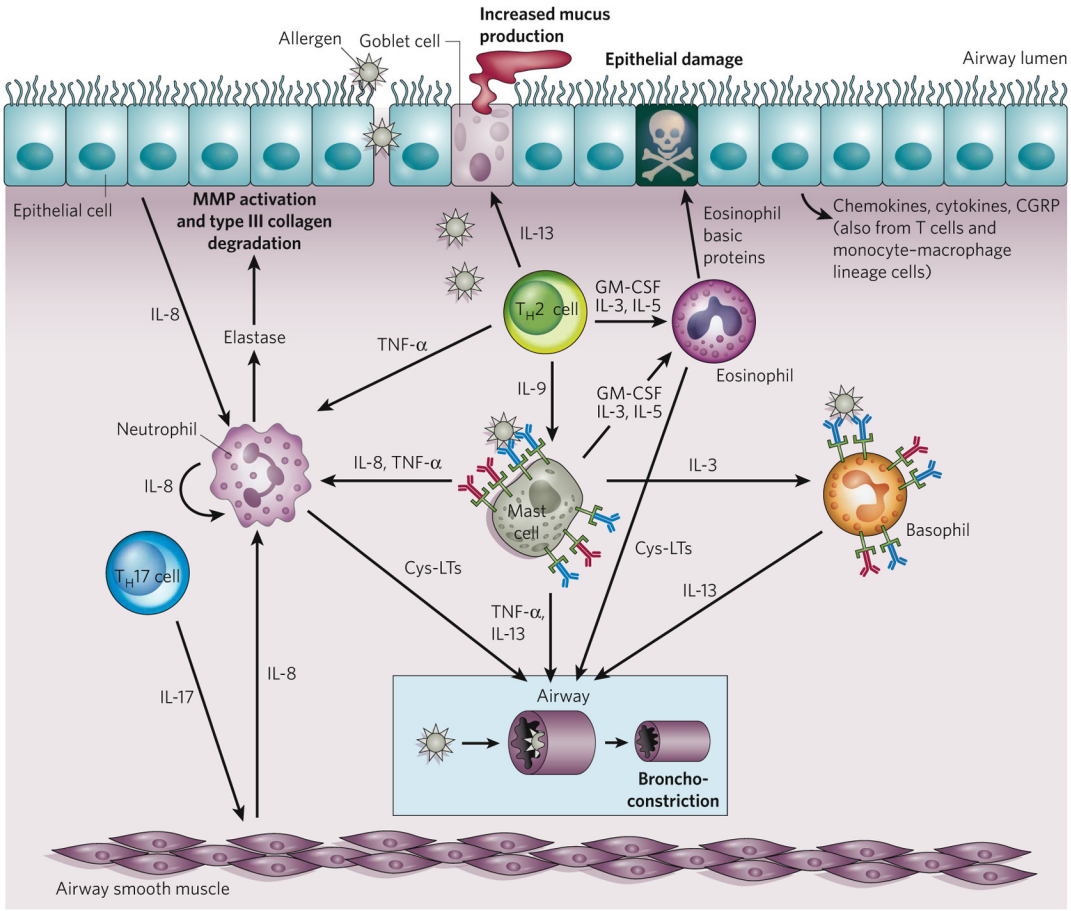

Figure 4. Late phase of allergen-induced airway inflammation

Late-phase reactions have many features in common with early-phase reactions (Fig. 3). But late-phase reactions typically occur hours after allergen challenge and are thought to reflect the actions of innate and adaptive immune cells that have been recruited from the circulation, as well as the secretion of inflammatory mediators by tissue-resident cells. The innate immune cells include neutrophils, monocytes (not shown), eosinophils and basophils. Other cells that secrete inflammatory mediators include mast cells that have been activated by IgE- and allergen-dependent FcεRI aggregation, and tissue-resident or recruited T cells that recognize allergen-derived peptides. Therefore, in a late-phase reaction, for example, elastase released by neutrophils promotes the activation of matrix metalloproteinases (MMPs) and the degradation of type III collagen. In addition, basic proteins released by eosinophils can injure epithelial cells, and several other mediators produced by recruited or tissue-resident cells can induce bronchoconstriction. CGRP, calcitonin-gene-related peptide; GM-CSF, granulocyte–macrophage colony-stimulating factor; T_H17 cell, IL-17-producing T_H cell.

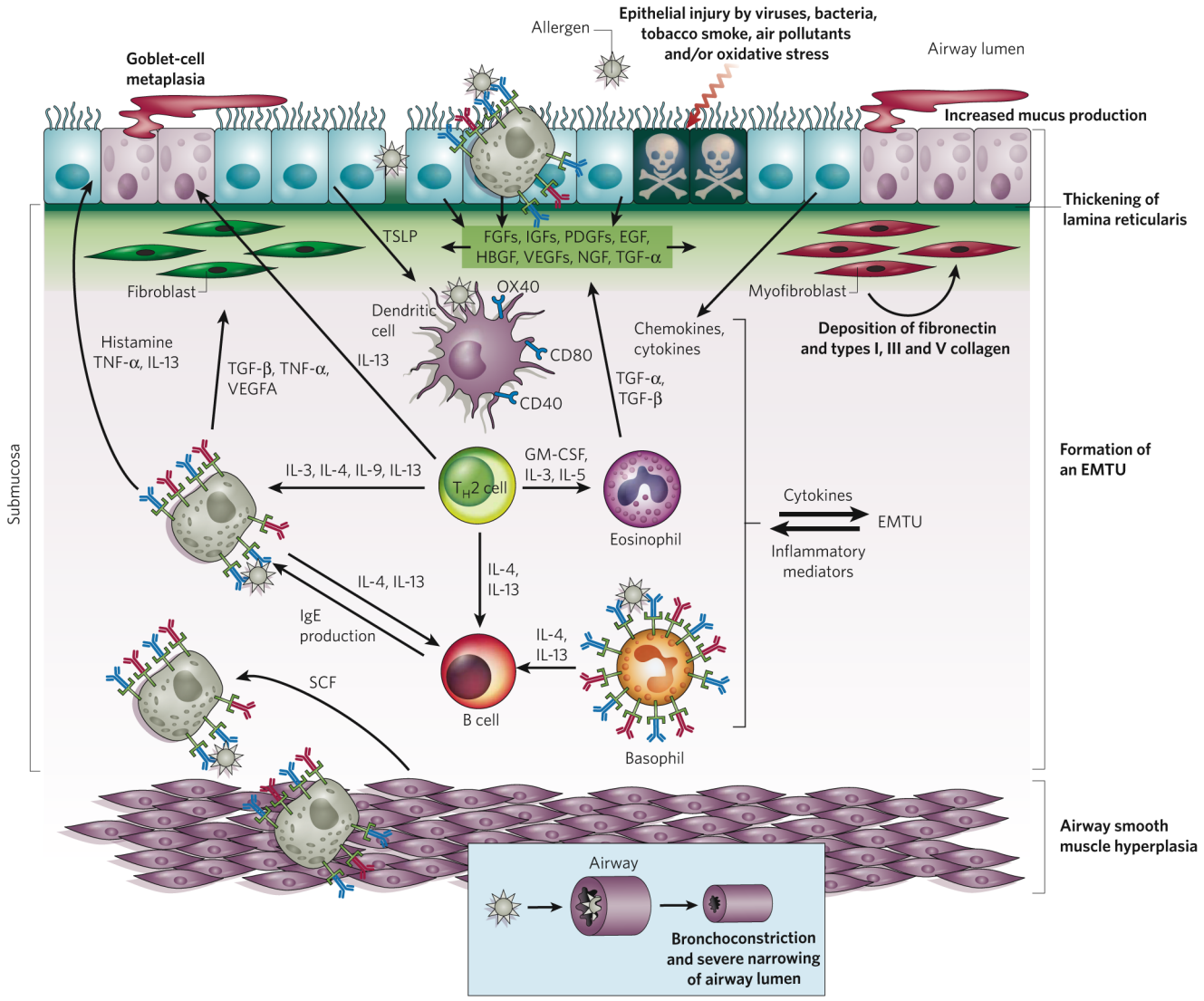

Figure 5. Chronic stage of allergen-induced airway inflammation

In chronic allergic inflammation, repetitive or persistent exposure to allergens has several effects. Innate immune cells (including eosinophils, basophils, neutrophils and monocyte–macrophage lineage cells) and adaptive immune cells (including T_H2 cells, other types of T cells, and B cells) take up residence in the tissues. In addition, more mast cells develop in the tissue, and these cells display large amounts of IgE bound to FcεRI and have an altered anatomical distribution. Last, complex interactions are initiated between recruited and tissue-resident innate and adaptive immune cells, epithelial cells and structural cells (such as fibroblasts, myofibroblasts and airway smooth muscle cells) and blood vessels and lymphatic vessels, and nerves (not shown). Repetitive epithelial injury due to chronic allergic inflammation can be exacerbated by exposure to pathogens or environmental factors, and the consequent repair response results in an epithelial–mesenchymal trophic unit (EMTU) being established. This unit is thought to sustain T_H2-cell-associated inflammation, to 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), and to regulate the airway remodelling process. These processes result in many functionally important changes in the structure of the affected

tissue. These changes include substantial thickening of the airway walls (including the epithelium, lamina reticularis, submucosa and smooth muscle), increased deposition of extracellular-matrix proteins (such as fibronectin, and type I, III and V collagen), and hyperplasia of goblet cells, which is associated with increased mucus production. In individuals who have such thickened airway walls, bronchoconstriction can result in more severe narrowing of the airway lumen than occurs in airways with normal wall thickness. In some individuals, especially those with severe asthma, T_H17 cells (which secrete IL-17) may also contribute to the recruitment of neutrophils to sites of inflammation (not shown). EGF, epidermal growth factor; FGF, fibroblast growth factor; HBEGF, heparin-binding EGF-like growth factor; IGF, insulin-like growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor; SCF, stem-cell factor (also known as KIT ligand).

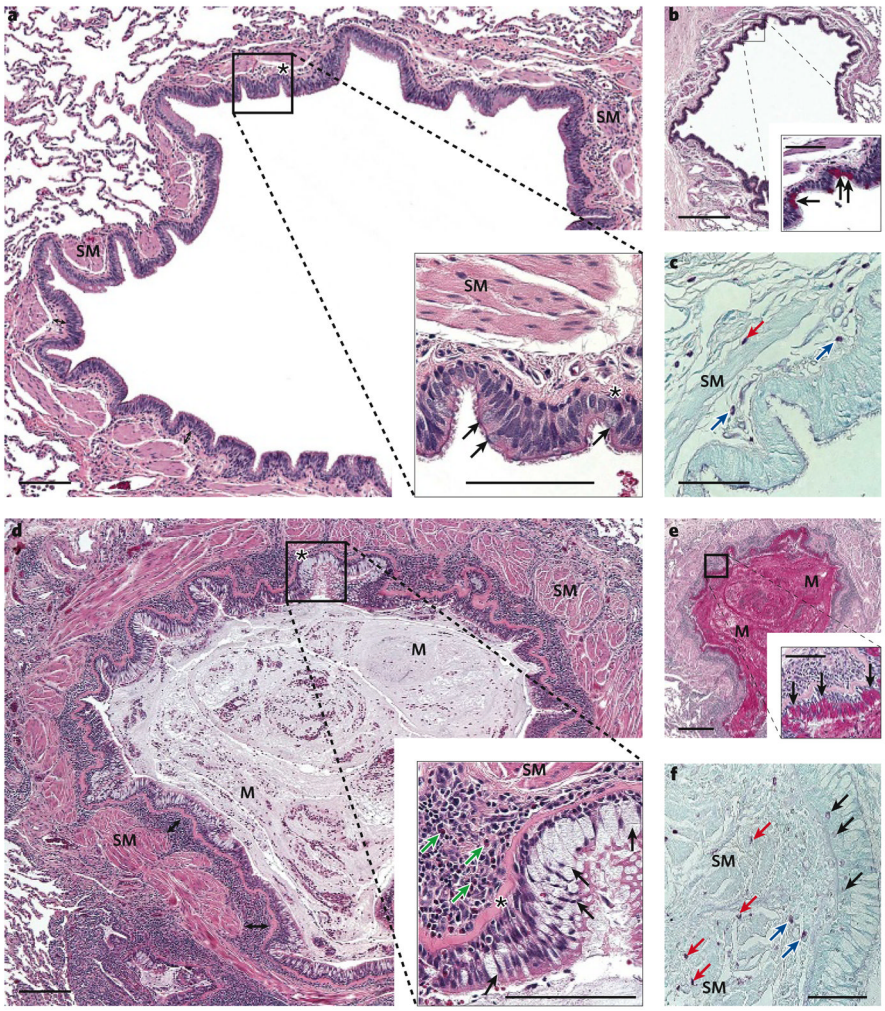

Figure 6. Chronic allergic inflammation and tissue remodelling in asthma

Tissue sections from the airway of a non-asthmatic person (**a–c**) and a patient with severe asthma (**d–f**) are shown. Specimens were taken from lung resections (carried out for other indications), fixed in 10% neutral buffered formalin and processed routinely; sections 5 μm thick, from the same area of tissue, were stained with haematoxylin and eosin (**a** and **d**), periodic acid–Schiff with diastase (to stain mucus red; **b** and **e**), or pinacyanol erythrosinate (to stain mast cells purple; **c** and **f**). Scale bars, 500 μm (**a** and **d**), 100 μm (inset **a** and **d**), 400 μm (**b** and **e**), 100μm (inset **b** and **e**) and 100 μm (**c** and **f**). **a–c**, A normal small bronchus. There are few goblet cells (black arrows in insets) in the epithelium. The basement membrane and underlying lamina reticularis (at asterisk in **a**, hardly visible at this magnification) are normal. The submucosa (the length of the double-headed arrows in **a**) contains few leukocytes and the occasional mast cell (blue arrows in **c**), and the bronchial smooth muscle (SM) has few adjacent mast cells (red arrow in **c**). **d–f**, A small bronchus from a patient with a history of severe asthma. Mucus (M) fills the airway lumen (**d** and **e**). There are many goblet cells (black arrows in insets) and the occasional intra-epithelial mast cell (black arrows in **f**). The lamina reticularis (asterisk in inset in **d**) is markedly thickened. The submucosa (double-headed arrows in **d**) contains many eosinophils (green arrows in inset in **d**) and other leukocytes, as well as mast cells (blue arrows in **f**). There is more bronchial smooth muscle (SM) than in **a–c**, and there are many mast cells (red arrows in **f**)

among bundles of smooth muscle cells. (Figure courtesy of G. J. Berry, Stanford University, California.)