

## REVIEW ARTICLE

# Can anti-IgE therapy prevent airway remodeling in allergic asthma?

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## Abstract

Airway remodeling is a central feature of asthma. It is exemplified by thickening of the lamina reticularis and structural changes to the epithelium, submucosa, smooth muscle, and vasculature of the airway wall. Airway remodeling may result from persistent airway inflammation. Immunoglobulin E (IgE) is an important mediator of allergic reactions and has a central role in airway inflammation and asthma-related symptoms. Anti-IgE therapies (such as omalizumab) have the potential to block an early step in the allergic cascade and therefore have the potential to reduce airway remodeling. The reduction in free IgE levels following anti-IgE therapy leads to reductions in high-affinity IgE receptor (FcεRI) expression on mast cells, basophils, and dendritic cells. This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia and levels of granulocyte macrophage colony-stimulating factor, interleukin (IL)-2, IL-4, IL-5, and IL-13. Considering the previously demonstrated anti-inflammatory effects of anti-IgE therapy, along with results from a small study showing continued benefit after discontinuation of long-term treatment, a larger study to assess its effect on markers of airway remodeling is underway.

Asthma is a disorder of the airways involving multiple inflammatory cells and mediators (1) and is characterized by chronic inflammation and structural alterations in the airways (2). Allergic asthma is characterized by the presence of immunoglobulin E (IgE) antibodies against common allergens such as house dust mite, animal dander, pollens, and moulds (1). There is a strong association between atopy and asthma, and the risk of asthma increases with increasing serum IgE levels, independent of allergic sensitization (3).

IgE has a central role in the induction and maintenance of chronic allergic airway inflammation and asthma-related symptoms (4). In patients with allergic asthma, exposure to allergens to which they are sensitized results in the rapid release of pro-inflammatory mediators that stimulate contraction of airway smooth muscle and increase mucus production, manifesting as the symptoms of asthma: wheezing, coughing, chest tightness and shortness of breath, collectively known as the early asthmatic response. The release of pro-inflammatory mediators, chemokines, and growth factors

attracts inflammatory cells, which release more pro-inflammatory mediators, resulting in the late asthmatic response, characterized by inflammation, bronchoconstriction and tissue damage.

Airway remodeling is a central feature of asthma (2). It is exemplified by thickening of the lamina reticularis and structural changes to the epithelium (epithelial shedding, subepithelial fibrosis, and inflammatory cell infiltration), submucosa (goblet cell hyperplasia, myofibroblast proliferation), smooth muscle (hyperplasia and hypertrophy), and vasculature (neovascularization) of the airway wall. These features and, as a consequence, the physiologic phenomenon of airway hyper-responsiveness (AHR) are characteristic of severe disease (1, 5), although subphenotypes with distinct structural, physiologic, and clinical characteristics (e.g. eosinophil positive and negative) can be identified within the severe asthma phenotype (6).

The causes of airway remodeling in asthma are complex, and a variety of environmental agents, cells, and mediators are involved. Airway remodeling is implicated in the acceler-

ated decline in lung function observed in adult asthma patients over time (7). Agents with the potential to attenuate or reverse remodeling could therefore play an important role in the management of asthma. The effects of several asthma pharmacotherapies and other interventions on airway remodeling have been reviewed previously (2, 8). Although some data are conflicting, inhaled corticosteroids,  $\beta_2$ -agonists, leukotriene modifiers, and chromones have been shown to affect various indices of remodeling in animal models and human biopsy studies. Evidence supporting changes in remodeling through environmental allergen avoidance are limited, although avoidance of occupational sensitizers has been reported to reverse remodeling. Mechanical reduction in airway smooth muscle mass by bronchial thermoplasty has improved measures of lung function and AHR to methacholine, but long-term effects are not known (8).

Because the presence and persistence of allergic inflammation appear to be necessary for airway remodeling to occur, and because IgE is central to allergic inflammation, it is conceivable that anti-IgE therapies may influence the remodeling process. To explore this hypothesis, this paper will review the current knowledge on the structural changes and inflammatory mechanisms in airway remodeling in asthma, with particular emphasis on those mediators involved in the allergic cascade, and consider whether disrupting the allergy cascade by targeting IgE might prevent structural changes from taking place. This review, which was intended to explore the literature and discuss the authors' opinions, did not employ a systematic approach. Literature searches were conducted using the MedLine database (1970–2009) and a variety of keywords, including airway remodeling, anti-IgE, asthma, collagen, eosinophil, IgE, inflammation, interleukin (IL) 13, IL-4, IL-5, mast cell, omalizumab, platelet, subepithelial thickening, T-helper type 2 (Th2) cell, eosinophilia, transforming growth factor (TGF), vascular endothelial growth factor (VEGF). The titles of retrieved articles were assessed to remove obviously irrelevant material, and the abstracts of the remainder were reviewed to identify articles that could be considered for inclusion. Articles were ultimately included in the review if, in the opinion of the authors of this review, they provided insight into or were illustrative of the topics under discussion.

### The allergic cascade

The allergy cascade has been reviewed in full elsewhere (9–11). In brief, allergic sensitization begins when antigens are presented to naïve T cells by antigen-presenting cells, which directs their development to the Th2 phenotype and stimulates release of Th2-type cytokines. IL-4 recruits more Th cells to the Th2 lineage, maintains Th2 cells in that lineage, and, along with IL-13, triggers B cells to release IgE. IgE binds to the high-affinity IgE receptor (FcεRI) on mast cells, sensitizing them to the allergen. Subsequent allergen exposure leads to cross-linking of mast-cell-bound IgE, inducing degranulation (release of histamine, leukotrienes, and platelet-activating factors) that results in acute allergic symptoms (early allergic response) and the release of cyto-

kines and chemokines that recruit macrophages, eosinophils, and basophils to the site of inflammation (late allergic response; Fig. 1). Ultimately, the allergic cascade in asthma results in AHR, mucus hypersecretion, airway inflammation, and airway fibrosis/remodeling.

### Airway remodeling

Remodeling has been attributed to repetitive injury to the airway wall arising from cycles of inflammation and repair (12) and may occur in response to chronic inflammation (13–20) and immune-mediated events such as viral infections (21). The main features of airway remodeling are reviewed below.

### Epithelial shedding

Epithelial cells are found in increased amounts in asthmatic sputum (22). Epithelial shedding may be attributed to increased susceptibility to oxidative stress-induced apoptosis (23), increased epithelial cell permeability following exposure to ozone or nitrogen dioxide (24) or abnormal prolongation of epithelial repair processes because of increased expression of the cyclin-dependent kinase inhibitor, p21(waf), induced by TGF- $\beta$  (25). Damaged epithelial cells release cytokines, growth factors, and other inflammatory mediators, which contribute to the inflammatory process.

### Goblet cell hyperplasia

As airway remodeling progresses, numbers of mucus-secreting goblet cells and submucosal glands increase, leading to mucus secretion and narrowing of the airway lumen (26). Figure 2 shows tissue sections from nonasthmatic and severe asthmatic airways (note that these images do not illustrate a longitudinal progression), illustrating the increased numbers of goblet cells, thickening of the basement membrane and

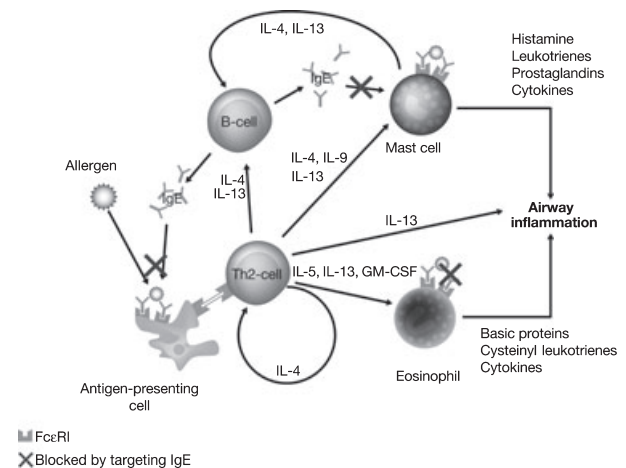


**Figure 1** Key mediators in the allergic cascade and the Th2 pathway. Crosses indicate steps in the cascade, which may be inhibited targeting IgE. Adapted from Holgate and Polosa (9).

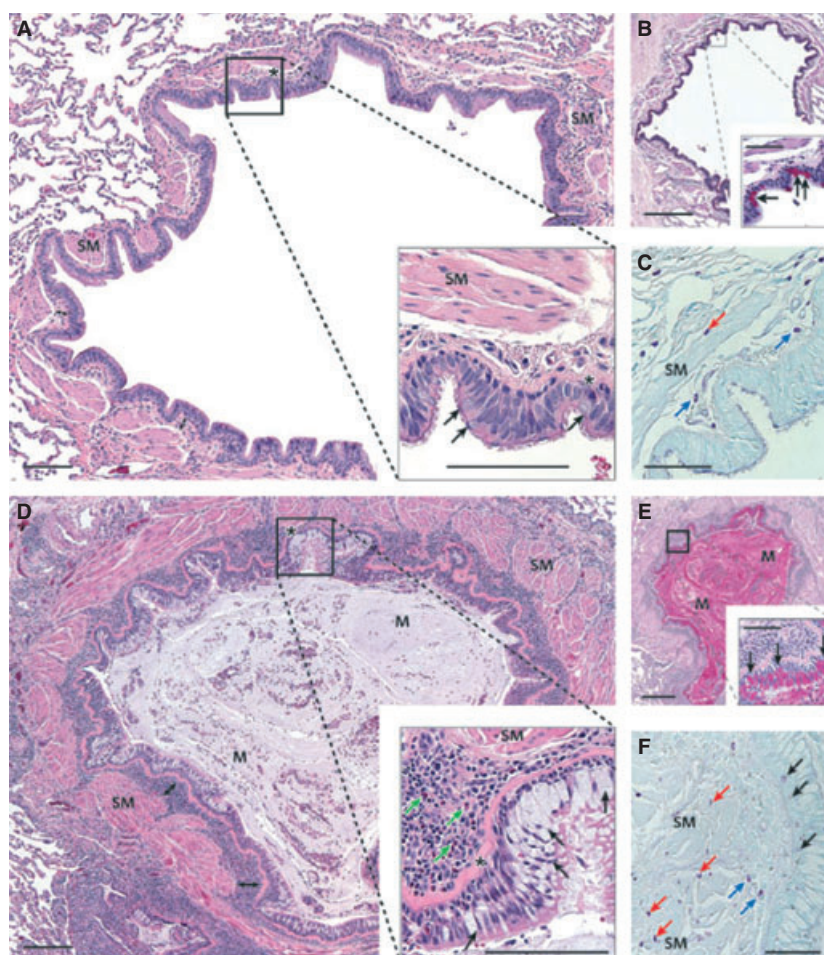


**Figure 2** Tissue sections from nonasthmatic (A–C) and severe asthmatic (D–F) airways. Scale bars: 500  $\mu$ m (A and D), 100  $\mu$ m (inset A and D), 400  $\mu$ m (B and E), 100  $\mu$ m (inset B and E, C, and F). The asthmatic airway shows increased goblet cells (black arrows in insets), basement membrane and lamina reticularis thickening (asterisks), increased mast cells (blue arrows), eosinophils (green arrows in inset D), and other leukocytes in the submucosa

(the length of the double-headed arrows). Increased mast cells (red arrow in C) can be seen adjacent to the bronchial smooth muscle (SM) and in the epithelium (black arrows in F). Mucus (M) fills the airway lumen (D and E). Bronchial smooth muscle is increased, and there are many mast cells (red arrows in F) among smooth muscle cells. Reproduced from Galli et al. 2008 (27).

lamina reticularis and increased numbers of mast cells, eosinophils and other leukocytes in the submucosa in the asthmatic airway (27).

Goblet cell metaplasia may occur through activation of mucin glycoprotein genes and the immunohistochemical expression of these genes, particularly *mucin 5AC* (*MUC5AC*) (28). The epidermal growth factor (EGF) ligand family may also play a role in mucin production, as EGF receptor (EGFR) expression correlates positively with *MUC5AC*-positive cells ( $r = 0.725$ ) and is upregulated in asthmatic patients (28). Other studies have suggested a role of Th2 cytokines in goblet cell metaplasia. In a murine model comparing airway remodeling parameters in IL-4/5/9/13<sup>-/-</sup> ovalbumin-sensitized mice, IL-4, IL-5, and IL-9 were thought to contribute to goblet cell hyperplasia, as following allergen challenge, goblet cells were increased in IL-13<sup>-/-</sup> mice, but less so in IL-4/5/9/

13<sup>-/-</sup> mice, compared with controls (29). In human epithelial cell cultures, IL-9 increased goblet cell hyperplasia and mucus production compared with controls (30). Research in a rat model showed that IL-13 increased goblet cells (as measured by *MUC5AC* expression), tumor necrosis factor (TNF)- $\alpha$  expression, and the number of neutrophils, compared with controls. In addition, goblet cell production was blocked by an IL-13 inhibitor, and TNF- $\alpha$  expression was blocked by cyclophosphamide. Based on these observations, it was suggested that IL-13 induced production of an IL-8-like chemoattractant, which recruited neutrophils into the epithelium. Tumor necrosis factor- $\alpha$  released from neutrophils induced EGFR expression, and oxygen-free radicals, also released from neutrophils, then activated EGFR resulting in mucin production from goblet cells (31). Another study using human bronchial epithelial cell cultures found that IL-13 did

not directly stimulate release of TNF- $\alpha$ , and exogenous TNF- $\alpha$  did not increase *MUC5AC* expression, but IL-13 and EGFR reduced the expression of the FOXA2 protein (which is known to inhibit mucus production) on goblet cells (32).

### Myofibroblast proliferation

Transforming growth factor- $\beta$  stimulates the phenotypic change of fibroblasts to myofibroblasts (33, 34). In an *in vitro* co-culture of human myofibroblasts and epithelial cells, following chemical injury of epithelial cells, levels of several growth factors (basic fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor-1, TGF- $\beta$ 2, and endothelin-1) were shown to increase, along with myofibroblast proliferation. Blockade of these growth factors inhibited myofibroblast proliferation (33). A study using house dust-mite extract challenges in a murine model suggested that TGF- $\beta$  may regulate allergen-induced chronic airway inflammation, but not remodeling. In this model, anti-TGF- $\beta$  had no effect on submucosal collagen deposition, smooth muscle thickness, or mucus production, but increased eosinophilic infiltrate and airway hyperreactivity (35). However, mice challenged with ovalbumin over 8 weeks showed prolonged TGF- $\beta$ 1 production and marked peribronchial fibrosis after cessation of challenge (36), indicating that a minimum duration of allergen exposure may be required for more long-term changes to develop (24). Transforming growth factor- $\beta$ 1 and histamine have been shown to upregulate production of connective tissue growth factor (CTGF) and enhance proliferation of lung fibroblast cells (37). Overexpression of CTGF is linked to many fibrotic diseases, but its exact role in airway remodeling is unknown (38).

### Smooth muscle hyperplasia and hypertrophy

It has been postulated that AHR in asthma may be attributed to increased airway smooth muscle mass (Fig. 3). Biopsies from airways of patients with mild-to-moderate asthma have been found to have twofold higher numbers of smooth muscle cells and 50–83% more smooth muscle in the submucosa, compared with controls; however, no differences in genes encoding phenotypic markers or cell size were found (39). Another study found that smooth muscle cell size was increased in severe asthmatic patients compared to those with milder disease and correlated negatively with postbronchodilator forced expiratory volume in one-second (FEV<sub>1</sub>) (40). In a comparison of airway smooth muscle cell cultures from asthmatic and control patients, cell numbers from asthmatic patients were found to be increased at 3, 5, and 7 days compared with those from controls, and more were in the G<sub>2</sub> + M phase. The researchers suggested that these results indicated an intrinsic abnormality in the proliferation characteristics of airway smooth muscle cells from asthmatic patients (41). The Th2 cytokines IL-4, IL-5, IL-9, and particularly IL-13 have recently been shown to be implicated in smooth muscle hyperplasia. Airway smooth muscle hyperplasia was inhibited to a similar extent in both IL-13<sup>-/-</sup> and IL-4/5/9/13<sup>-/-</sup> ovalbumin-sensitized mice, compared with controls (29).

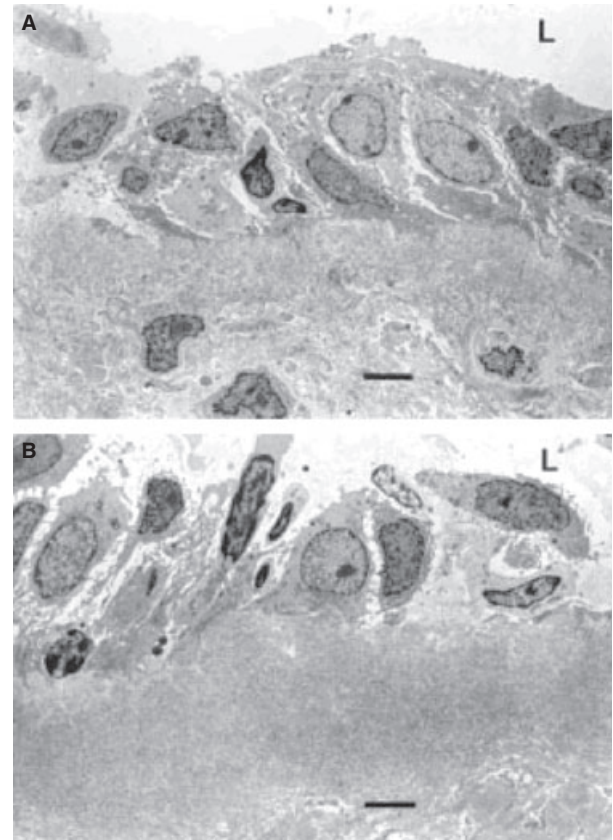


**Figure 3** Transmission electron micrograph of the basement membrane region of bronchial biopsy specimens from a control subject (top) and an asthmatic subject (bottom) showing an increase in the thickness and density of subepithelial collagen in the asthmatic subject. L = lumen. Original magnification  $\times 3600$ . Reproduced from Hoshino et al. 1998 (42).

### Subepithelial fibrosis

The epithelial basement membrane consists of two layers, the basal lamina and the deeper lamina reticularis. The lamina reticularis tends to be thicker in patients with asthma compared with healthy individuals (Fig. 4) (42) and in those with severe compared with mild asthma (43). Thickening appears to result from increased deposition of collagen and extracellular matrix owing to an imbalance between collagen-degrading matrix metalloproteases (MMPs) and their inhibitors, tissue inhibitors of metalloproteases (TIMPs). MMP-9 and TIMP-1 are thought to be particularly relevant, as they are both increased in bronchoalveolar lavage fluid (BALF) from asthmatic patients, and the ratio of MMP-9 to TIMP-1 correlates with airway obstruction (44). Matrix metalloproteases produced by structural and inflammatory cells may be at least partly responsible for injury to epithelial basement membrane as a consequence of cell transmigration through the membrane during acute allergic airway inflammation: administration of TIMP-2 (and additionally dexamethasone) reduced

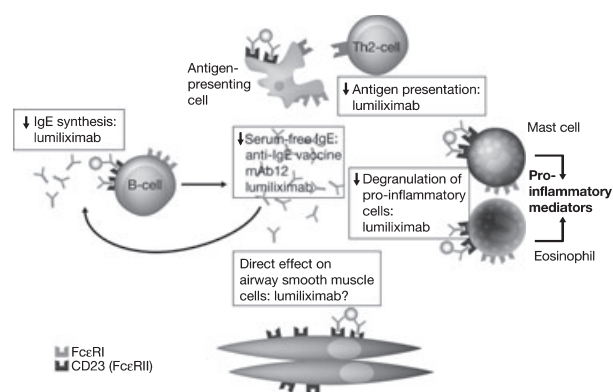


**Figure 4** The site of action and potential effects of other anti-IgE strategies currently under investigation and in development.

inflammatory cells in BALF from ovalbumin-challenged mice compared with controls (45).

As well as being synthesized by epithelial cells, TGF- $\beta$  is synthesized by macrophages, eosinophils, and fibroblasts. The expression of TGF- $\beta$  mRNA, particularly in eosinophils, has been shown to be greater in asthmatic patients than in control subjects and increases with increasing asthma severity; fibrosis was also found to be greater in asthmatic patients and correlated with a decline in FEV<sub>1</sub> ( $r = 0.78$ ) (46).

### Inflammatory cell infiltration

A major feature of airway remodeling is the infiltration of multiple inflammatory cells (Fig. 2). Mast cells appear to play a partial role in allergen-induced subepithelial fibrosis (47). In a murine model of allergic asthma, following repeated antigen exposure, no significant differences were observed between ovalbumin-sensitized mast cell-deficient mice and congenic litter mates in total leukocytes, eosinophils, and lymphocytes in BALF and lung tissue. No difference was seen in antigen-specific serum IgE, TGF $\beta$ 1, and AHR. However, collagen deposition was significantly lower in mast-cell-deficient mice and, after reconstitution of tissue mast cells with bone marrow-derived mast cells, was comparable to the congenic mice.

It is thought that eosinophils play a key role in airway inflammation and remodeling (48–50). They are recruited to the airways by the release of IL-5 following allergen-induced activation of mast cells and Th2 cells (9, 11, 50, 51), and IL-5 may prolong their presence (52). In addition, mast cells release prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), a potent chemoattractant for eosinophils, during allergic responses (53). The chemotactic effects of PGD<sub>2</sub> are mediated by the chemoattractant receptor homologous molecule of Th2 cells (CRTH2). Accumulation of eosinophils in the airways may damage mucosal surfaces through release of cytotoxic substances (54), and they are a rich source of fibrogenic factors, including IL-11, IL-17, IL-25, TGF $\alpha$ , MMP-9, and particularly TGF $\beta$ 1 (55–57). Several cytokines, including IL-4, IL-13 and TGF- $\beta$ , are known to have pro-fibrotic activity mediated via the recruitment, activation,

and proliferation of fibroblasts, macrophages, and myofibroblasts, resulting in a pathogenic fibrotic response (58).

Interleukins play a key role in allergic responses and probably in airway remodeling. As mentioned previously, IL-5 is involved in eosinophil recruitment, which may be specifically involved in airway remodeling (9, 11, 50, 51). Gene-targeted IL-4/13<sup>-/-</sup> mice also exhibited markedly diminished eosinophil recruitment and airway remodeling, as well as absence of AHR (59). IL-4 stimulates synthesis and release of IgE from B cells (10), and BALF taken from segmentally challenged asthma patients demonstrated that IL-4 caused a dose-dependent increase in alpha-smooth muscle actin and collagen III synthesis, which could indicate that IL-4 is a mediator of asthmatic airway remodeling (34). In a study in which bronchial fibroblasts from asthma patients and normal controls were stimulated with IL-4, it was emphasized that IL-4 may be considered as a link between inflammation and collagen deposition in the airways (60).

### Maintenance and reversibility of airway remodeling

Studies examining the role of continued antigenic challenge in the maintenance of the airway inflammation and remodeling indicate that remodeling persists after antigenic challenge is removed. One murine model of chronic asthma using low antigen concentrations for 3 days per week over 8 weeks found that inflammation reversed on cessation of antigenic challenge, while remodeling (subepithelial fibrosis and epithelial hypertrophy) persisted throughout the 4-week follow-up period (61). In a murine model of tissue remodeling (created using daily allergen challenge for up to 55 days), collagen deposition, airway smooth muscle proliferation, goblet cell hyperplasia, and TGF- $\beta$ 1 (fibrotic mediator) secretion were still evident at 80 days (62).

Pretreatment or concurrent treatment with established asthma therapies in allergen challenge models has been found to alter the course of airway remodeling. Corticosteroids may slow the progression of airway remodeling. In a murine model, lung expression of the extracellular matrix protein, laminin, was reduced with dexamethasone (63), and airway structural changes (wall area, fibronectin deposition, epithelial cell proliferation, goblet cell hyperplasia, and AHR) were reduced with fluticasone, although established remodeling was not affected (64). Beclomethasone has also been shown to reduce bronchial fibroblast proliferation *in vitro*, with greater effects when used in combination with salbutamol or formoterol (65). Similarly, 6 months of budesonide and formoterol in combination decreased expression of VEGF and its receptor in patients with asthma, and bronchial biopsy samples showed decreased submucosal gland hyperplasia, smooth muscle mass, thickness of reticular basement membrane, neovascularization, and subepithelial fibrosis (66). Montelukast, a cysteinyl leukotriene<sub>1</sub> (CysLT<sub>1</sub>) receptor antagonist, also significantly reduced the airway eosinophilia, mucus plugging, smooth muscle hyperplasia, and subepithelial fibrosis in murine models. Furthermore, in mice with established airway remodeling (3 months after allergen challenges), montelukast reversed airway smooth muscle mass

increases and subepithelial collagen deposition. CysLT<sub>1</sub> expression was also reduced (67, 68).

### Anti-IgE – a disease-modifying therapy?

The presence of IgE in the serum and airways of the atopic individual has numerous consequences because of its key role in the allergic cascade (4). Anti-IgE therapy, therefore, has the potential to disrupt the mechanisms involved in the allergic cascade. Several anti-IgE agents have been developed or are in development to target IgE either directly (e.g. omalizumab, monoclonal antibody 12, and anti-IgE vaccines) or indirectly (e.g. lumiliximab).

CD23 (also known as FcεRII) is the low-affinity IgE receptor. Expressed on antigen-presenting cells, lymphocytes, macrophages, eosinophils, and smooth muscle cells, the CD23 receptor plays a role in the regulation of IgE production and allergy-induced immune and inflammatory responses (69, 70). Lumiliximab (also known as IDEC-152) is a primate (*cynomolgus macaque*) variable regions and human constant regions. This monoclonal antibody has been shown to block IgE synthesis in human B cells (71), reduce serum IgE concentrations (72), and may be involved in modulating antigen-presenting cells and reducing Th2-type immune responses (Fig. 4.) (73). Monoclonal antibody 12 is a high-affinity anti-human IgE antibody, which has been shown to remove IgE and IgE-bearing cells from peripheral blood and may thus be used for extracorporeal depletion of IgE (74). Various IgE vaccines are in development, which may also lead to the development of viable anti-IgE therapies (75).

A number of studies have assessed the efficacy and safety of anti-IgE therapy (omalizumab) in asthma. Treatment has been shown to be well tolerated and clinically effective in the management of moderate-to-severe allergic asthma (76–81). Anti-IgE therapy acts by reducing serum-free IgE and expression of FcεRI, thereby reducing the amount of IgE binding to mast cells, basophils, and eosinophils (4). This prevents the degranulation of allergen-bound mast cells, which would otherwise result in the release of pro-inflammatory cytokines (including IL-4, IL-13 and IL-5) associated with airway remodeling. Prevention of this step also has the potential to limit subsequent eosinophilia and further IgE production.

Recent data have suggested that IgE may promote mast cell survival through autocrine production of IL-6 (82). Survival assays performed on cultures of human lung mast cells provided further evidence that IgE and IL-6 contribute to the pathogenesis of asthma, and it is speculated that anti-IgE therapy might achieve its therapeutic effect through this mechanism.

Anti-IgE therapy has also been shown to attenuate tissue mast cell function (4). In subjects with dust-mite allergy, treatment resulted in a 100-fold increase in the dose of antigen required to evoke a positive skin-prick test response equal to pretreatment (83). In another study, patients with mild, persistent, atopic asthma showed a reduced infiltration of mast cells into bronchial smooth muscle from 10.04 cells/

mm<sup>2</sup> before treatment to 4.94 cells/mm<sup>2</sup> at 16 weeks following treatment (84). In patients with mild-to-moderate persistent asthma, anti-IgE therapy resulted in median reductions in sputum eosinophils from 4.8% at baseline to 0.6% at week 16, as well as reductions in submucosal cell counts for eosinophils (–3.95 cells/mm<sup>2</sup>), FcεRI+ cells (–21.26 cells/mm<sup>2</sup>), cells staining for IL-4 on the cell surface (–15.28 cells/mm<sup>2</sup>), CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T cells (–36.96, –27.81 and –8.95 cells/mm<sup>2</sup>, respectively), and B cells (–0.83 cells/mm<sup>2</sup>) (85). In another study in which samples were collected 24 h after allergen challenge, reductions from baseline in eosinophilia were significantly greater in biopsies (from 15 to 2 cells/0.1 mm<sup>2</sup>) and sputum (from 4 to 0.5%) following 12 weeks of therapy in patients with mild persistent asthma (86). In addition, anti-IgE therapy has been shown to prevent the production of pro-inflammatory cytokines and growth factors, and as a result, the authors of that study concluded that it probably contributes to decreased airway remodeling in patients with asthma (87).

Another mechanism by which anti-IgE may affect inflammatory cells and mediators is through inhibition of antigen processing and presentation to T cells by downregulating FcεRI expression on antigen-presenting cells such as dendritic cells (88). IgE binds to dendritic cells and enhances allergen uptake and presentation to T cells (89). It has been reported that dendritic cells in patients with mild atopic asthma bind significantly more IgE than cells taken from healthy individuals (90), and FcεRI receptors are known to be upregulated on dendritic cells (as well as eosinophils, mast cells, and macrophages) in patients with seasonal allergic rhinitis (91).

A small study examining clinical and cellular changes in patients who discontinued therapy after long-term use provided preliminary evidence of an alteration in the long-term course of asthma progression. Patients (*n* = 18) with cat or mite allergy initially received anti-IgE therapy for approximately 6 years as part of a clinical trial in severe allergic asthma. After treatment cessation, clinical evaluations and basophil allergen sensitivity (as measured by CDsens) were analyzed monthly for 6 months and again at approximately 12–14 months and 36 months (92, 93). During the 12–14 months' withdrawal period, patients' asthma was clinically stable. At 1 year, 12 of 18 patients judged symptoms to be improved or the same as on treatment, with no increase in night symptoms and no emergency visits. Only four patients increased medication use (none required oral corticosteroids). Basophil sensitivity was significantly reduced at 1 month (CDsens = 0.1), 6 months (CDsens = 1.1), and 1 year (CDsens = 0.3) after the last anti-IgE therapy injection, compared with control patients (CDsens = 6.8) (92). The clinical picture remained similar 3 years after withdrawal, with 12 patients still reporting improved or unchanged asthma symptoms, 16 reporting no increase in nightly symptoms, and medication increased in only four patients (93). With the majority of patients maintaining a good level of asthma control some time after withdrawal, this result suggests that such treatment may have the potential to modify the course of asthma. Further tests are required to confirm

the findings from Nopp et al. (92, 93) and to test the hypothesis that anti-IgE therapies are disease modifying.

Markers of inflammation and airway remodeling (from bronchial biopsy, sputum, and blood samples) are currently being studied in patients with moderate-to-severe persistent allergic asthma who will receive 78 weeks of anti-IgE therapy with omalizumab [the EXPLORE study (ClinicalTrials.gov identifier: NCT00670930)]. The study aims to investigate the effect of treatment on the number of tissue eosinophils and other markers of airway inflammation and remodeling, including thickness of the lamina reticularis. Identification of markers of airway remodeling based on the results of this study may provide a simple, noninvasive method for evaluating patients at risk of developing airway remodeling or those already exhibiting airway remodeling, which should enable identification of suitable candidates for asthma disease-modifying therapy.

### Considerations with anti-IgE therapy

It has been suggested that there may be an association between monoclonal antibodies of murine origin and anaphylaxis (94). Typical manifestations of anaphylaxis reported in patients receiving anti-IgE therapy with omalizumab [which comprises <5% residues of murine origin (94)] include combinations of angioedema of the throat or tongue, bronchospasm, hypotension, syncope, and urticaria (95). Several hypotheses have been proposed to explain the occurrence of anaphylaxis, including the presence of pre-existing anti-allopic or anti-idiotypic antibodies (IgE or IgG) to anti-IgE or development of an antibody after initial exposure or during cumulative exposure to the drug (95). In an assessment of data from 7500 patients with asthma, rhinitis or related conditions treated in clinical trials for up to 4 years, anaphylaxis occurred in 0.14% of patients receiving omalizumab, compared with 0.07% of the control group (94). Assessment of adverse event reports submitted to the US Food and Drug Administration's Adverse Event Reporting System database identified 124 cases of anaphylaxis among 57 300 patients treated with omalizumab (frequency 0.2%), with the onset of symptoms often occurring more than 2 h after treatment (96).

There have also been concerns regarding the potential for molecules that target the immune system to increase the risk of neoplasm because of long-term immunosuppression (94). In clinical trials, it has been noted that there was a numerical imbalance in cancers in omalizumab-treated patients, compared with control (97). In these trials, malignancies occurred in 0.5% of treated patients, which is similar to the incidence expected in the general population but higher than the incidence in the control group (0.2%).

Concerns have also been expressed regarding the risk of parasitic infections in patients receiving anti-IgE therapy (94). Infection by a parasitic helminth results in the production of IgE, which is a key component of immune responses to such infections (98). Blocking or reducing the activity of IgE might therefore weaken immune responses to helminth infection (94). A study of patients with a high risk of helminth infection

indicated that the risk of helminth infection was modestly increased by anti-IgE treatment (omalizumab), compared with controls, although the increase was not statistically significant and responses to anthelmintic treatment were unaffected (99).

### Conclusions

The release of IgE by B cells is a key step in the allergic cascade and results in the sensitization of mast cells to allergens. Subsequent exposure to the allergen stimulates mast cells to release histamine, leukotrienes, and platelet-activating factors that cause the characteristic symptoms of the early allergic reaction. Further release of cytokines and chemokines leads to the late allergic reaction, which is characterized by recruitment of inflammatory cells. Chronic allergic inflammation is believed to result in airway remodeling because of a repetitive cycle of injury and repair in the airway wall. Features of this remodeling process include epithelial shedding (which results in the release of additional cytokines, growth factors, and other inflammatory mediators), goblet cell hyperplasia, myofibroblast proliferation, smooth muscle hyperplasia and hypertrophy, subepithelial fibrosis, and inflammatory cell infiltration. Several studies indicate that this remodeling process continues after the removal of the original antigenic challenge.

The interaction between anti-IgE therapy and free IgE interrupts a key step in the allergic inflammatory cascade. Given the central role of IgE in airway inflammation, and the likely inflammatory component involved in the development and maintenance of airway remodeling, it is plausible that therapies that target IgE may influence the remodeling process, either by attenuating its progress or by reversing long-term changes.

A small study has highlighted the possible role of anti-IgE therapy in improving the course of asthma, with clinical improvements still seen 3 years after treatment withdrawal (92, 93). A larger study is underway to assess the effect of anti-IgE therapy on markers of airway remodeling and may allow further characterization of the patients most likely to benefit. The ongoing EXCELS study will also provide additional information on the natural history of moderate/severe asthma and the efficacy and safety of anti-IgE therapy (100).

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K. Rabe has been consulting, participated in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer, Chiesi Pharmaceuticals, Pfizer, Novartis, Nycomed, MSD, and GSK. He holds no stock or other equities in pharmaceutical companies. K. Rabe was the head of The

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Roche and GSK in the years 2005 until 2009. W. Calhoun has been on the Genentech speakers bureau and has a current grant award from Genentech/Novartis. N. Smith and P. Jimenez are employees of Novartis.

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