

## REVIEW OPEN ACCESS

# The Direct and Indirect Role of IgE on Airway Epithelium in Asthma

Christian Domingo<sup>1</sup> | William W. Busse<sup>2</sup>  | Nicola A. Hanania<sup>3</sup> | Muyesser Ertugrul<sup>4</sup> | Lauren A. Millette<sup>5</sup> | Tina Maio-Twofoot<sup>6</sup> | Xavier Jaumont<sup>6</sup> | Oscar Palomares<sup>7</sup> 

<sup>1</sup>Department of Pulmonary Medicine, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain | <sup>2</sup>Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA | <sup>3</sup>Section of Pulmonary, Critical Care and Sleep Medicine, Baylor College of Medicine, Houston, Texas, USA | <sup>4</sup>Novartis Pharma, Istanbul, Turkey | <sup>5</sup>Genentech Inc, San Francisco, California, USA | <sup>6</sup>Novartis Pharma AG, Basel, Switzerland | <sup>7</sup>Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University of Madrid, Madrid, Spain

**Correspondence:** Christian Domingo ([cdomingo@tauli.cat](mailto:cdomingo@tauli.cat))

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## ABSTRACT

Asthma is a chronic airway inflammatory disorder, affecting over 350 million people worldwide, with allergic asthma being the most common form of the disease. Allergic asthma is characterized by a type 2 (T2) inflammatory response triggered by numerous allergens beginning in the airway epithelium, which acts as a physical barrier to allergens as well as other external irritants including infectious agents, and atmospheric pollutants. T2 inflammation is propagated by several key cell types including T helper 2 (Th2) cells, eosinophils, mast cells, and B cells. Immunoglobulin E (IgE), produced by B cells, is a key molecule in allergic airway disease and plays an important role in T2 inflammation, as well as being central to remodeling processes within the airway epithelium. Blocking IgE with omalizumab has been shown to be efficacious in treating allergic asthma however, the role of IgE on airway epithelial cells is less communicated. Developing a deeper explanation of the complex network of interactions between IgE and the airway epithelium will facilitate an improved understanding of asthma pathophysiology. This review discusses the indirect and direct roles of IgE on airway epithelial cells, with a focus on allergic asthma disease.

## 1 | Introduction

Asthma is a common chronic respiratory disease, with a prevalence previously shown to be 5.5% [1–3]. Asthma is a heterogeneous disease which may present as one of several endotypes and clinical phenotypes, based on the underlying biological mechanisms of the disease [4]. Allergic asthma is the most common asthma phenotype, it is characterized by early disease onset, immunoglobulin E (IgE) sensitisation to the causative allergen and a type 2 (T2) inflammatory response [5].

The airway epithelium actively protects against irritants such as infectious agents, allergens, and pollutants, serving as the first line of defense [6]. It consists of multiple cell types including basal cells, ciliated columnar epithelial cells, mucus-secreting goblet cells, and surfactant-secreting club cells [7–9]. Persistent inflammation following allergen inhalation leads to bronchial epithelial damage. This results in the release of T2 cytokines driving a cascade of events, including activation of airway epithelial cells, chemoattraction of effector cells (eosinophils and basophils), and remodeling of the airway and epithelium [10].

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T2 inflammation is mediated by several key cell types including T helper 2 (Th2) cells, T2 innate lymphoid cells (ILC2), eosinophils, basophils, mast cells and IgE producing B cells [10–12]. Following inhalation of allergens into the airway epithelium, the epithelial cytokines (also known as alarmins) interleukin (IL)-33, IL-25 (which was found to belong to the IL-17 family), and thymic stromal lymphopoietin (TSLP) are released. These signals programme dendritic cells (DCs) to mount Th2-cell-mediated immunity resulting in an overproduction of the T2 cytokines IL-4, IL-5, and IL-13 as well as an increase in ILC2, basophil, and mast cell function [10, 13]. Stimulation of DCs with IL-33, IL-25 and TSLP also promotes activation of adapted immune responses [14].

IgE plays a key role in allergic asthma [15], with an allergic asthma T2 inflammatory response associated with increased serum IgE levels [6]. Elevated IgE production in allergic asthma has also been shown to lead to persistent symptoms, risks for exacerbations, and reduced quality of life for patients with allergic asthma [16]. IgE, produced by B cells, functions in the development of a T2 inflammatory response and is mediated through interaction with its two receptors: the high-affinity receptor, FcεRI, and the low-affinity FcεRII/CD23 receptor [17]. During the effector phase of allergic asthma, IgE bound to FcεRI receptors expressed on the surface of inflammatory dendritic cells amplifies antigen presentation by presenting allergens to memory Th2 lymphocytes [18].

Omalizumab is a monoclonal antibody directed against circulating IgE [17, 19, 20], and is established as an efficacious targeted therapy for the treatment of patients with moderate-to-severe allergic asthma. Omalizumab reduces serum and tissue levels of free IgE and downregulates expression of IgE receptors [19]. Anti-IgE therapy for the treatment of asthma has demonstrated a favorable long-term efficacy and safety profile [21–23]. The effectiveness of omalizumab treatment demonstrates the potential of improved asthma control via targeting of IgE [15].

There has been accumulating evidence that IgE plays an important role on the epithelial cells in asthma. In this review, we will

provide an outline of our current understanding of the role of IgE on epithelial cells, and its clinical implications, in the context of the airway epithelium and allergic asthma.

## 2 | Airway Epithelial Cells

Airway epithelial cells lie at the interface between the host and the environment and represent the first line of defense against inhaled microorganisms and allergens [24]. A major role of the airway epithelium is to act as a highly regulated, physical barrier to restrict allergens from penetrating the mucosa lamina propria of the airway. For inhaled allergens to gain access to immune effector cells in the lamina propria, they must first cross the airway epithelium [25–27].

Normally, the airway epithelium consists of multiple cell types, including basal cells, ciliated columnar epithelial cells, mucus-secreting goblet cells, and surfactant-secreting club cells (Figure 1) [7–9].

Basal cells, located below the surface epithelial cell layer, are key modulators of epithelial regeneration following injury [28]. These cells also serve as progenitors from which ciliated, secretory, and goblet cells differentiate during repair. Ciliated cells are found throughout the airway and play an important role in establishing airway homeostasis by trapping and expelling microorganisms, mucus, and other debris through mucociliary clearance. Goblet cells are the major mucus-producing cells of the airway, together with ciliated cells they facilitate mucociliary clearance. Increased mucus production by goblet cells is a common feature of asthma [28]. Club cells, previously known as Clara cells, are dome-shaped cells that can give rise to both ciliated and goblet cells [29]. Collectively, these cells form a highly regulated and impermeable epithelial barrier, the integrity of which is made possible by the presence of the apical junctional complex, which is formed by tight junctions, adherens, and desmosomes (cell-to-cell adhesion structures). The apical junctional complex keeps airway epithelial cells together and maintains apicobasal polarity [29, 30] (Figure 2). In people with asthma, the airway epithelial

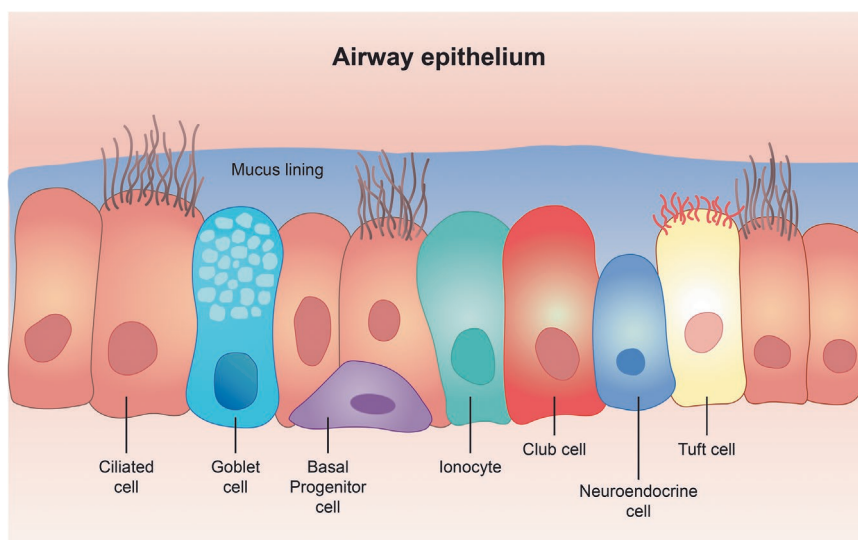


**FIGURE 1** | Key cell types in the airway epithelium.

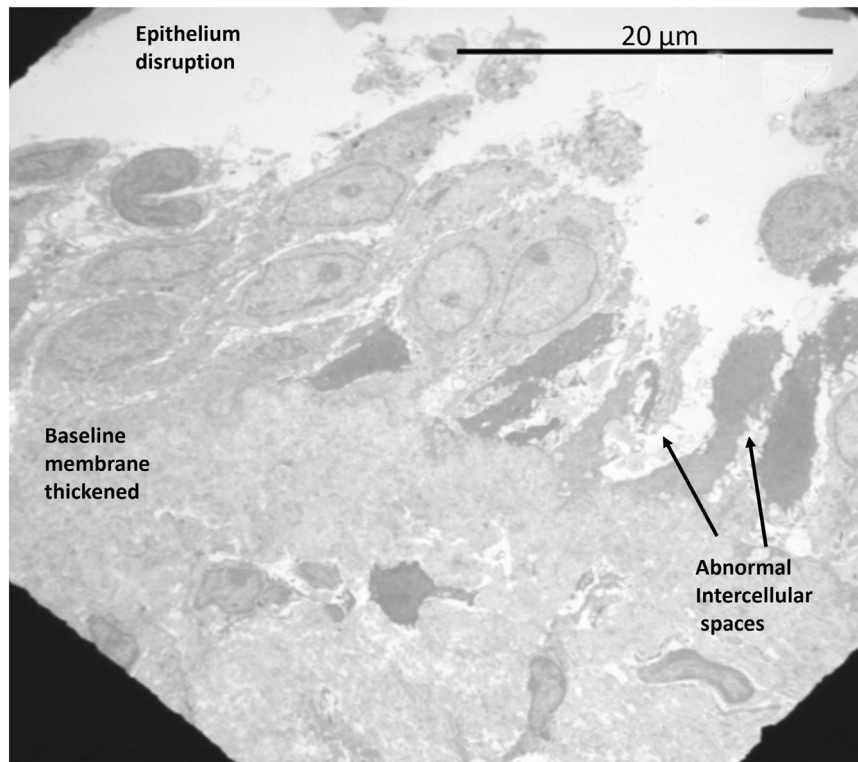


**FIGURE 2** | Electron microscopy image showing bronchial biopsy of a patient with severe allergic asthma. (image is at 3000× magnification). [This figure belongs to the personal collection of Drs Domingo and Mirapeix].

barrier is compromised through disruption of the tight junctions of the epithelium [24, 31].

Rare cell populations, comprising less than 1% of airway epithelial cells, have been identified using single-cell transcriptomic analysis. These include pulmonary neuroendocrine cells (PNECs), tuft cells, and ionocytes that perform specific roles relevant for the maintenance of the epithelium integrity [9]. PNECs are found within the surface epithelium of the trachea, bronchi, and bronchioles and are a rich source of neuropeptides and neurotransmitters that stimulate immune cells to cause physiological effects such as the maintenance of bronchial and vascular smooth muscle tone and coordination of immune system responses [9, 32]. Tuft cells are chemosensory epithelial cells that, together with enteroendocrine cells, coordinate interactions with the external environment [9]. Interestingly, the tuft cell-specific marker *Rgs13* has been identified as a risk gene for asthma in genome-wide association studies [33] and is associated with asthma and IgE-mediated mast cell degranulation, thus implying a possible contributory role in asthma and T2 inflammation [34].

In addition to acting as a barrier against pathogen and allergen invasion, the airway epithelium functions in immune activity. Indeed, airway epithelial cell activation has been demonstrated to be a key trigger of innate and adaptive immune responses following inhalation of allergens [25, 31]. Airway epithelial cells express pattern recognition receptors (PRRs) that detect and respond to pathogen-associated molecular patterns (PAMPs) found on microbes, as well as to damage-associated molecular patterns (DAMPs) released upon cell death or following tissue damage within the airway. The activation of epithelial PRRs, in

response to PAMPs and DAMPs, leads to the release of cytokines that attract and activate innate and adaptive immune cells [31].

Airway epithelial cells further contribute to T2 inflammation following allergen exposure [31]. Upon allergen stimulation, airway epithelial cytokines such as TSLP, IL-25 and IL-33 are released [31]. These cytokines stimulate a T2 immune response by DC activation of Th2 cells, resulting in an increase in ILC2 [35]. This T2-inflammatory response is further characterized by IgE-mediated release of immune mediators and dysfunction of epithelial barriers [35]. Notably, omalizumab may restore virus-induced IFN $\alpha$  responses, potentially preventing exacerbations associated with respiratory viruses [36].

### 3 | IgE and the IgE Receptors

The immunoglobulin class IgE was officially recognized and published over 50 years ago during a meeting at the World Health Organization Immunoglobulin Reference Laboratory ([37, 38]). IgE is the least abundant class of human immunoglobulins and has a molecular structure consisting of two identical heavy chains and two identical light chains [39]. The biological effects of IgE are mediated through its two receptors [23]: a membrane high-affinity receptor, Fc $\epsilon$ RI, and a membrane bound and soluble, low-affinity Fc $\epsilon$ R2/CD23 receptor [17] (Figure 3). IgE exhibits the highest affinity for its specific receptors among all immunoglobulin receptors, particularly Fc $\epsilon$ RI. Free IgE preferentially binds to Fc $\epsilon$ RI due to this high affinity. The cross-linking of Fc $\epsilon$ RI by IgE and allergens triggers intracellular signaling, leading to the degranulation of effector cells such as basophils and mast cells. The mediators released during this process are responsible for the characteristic

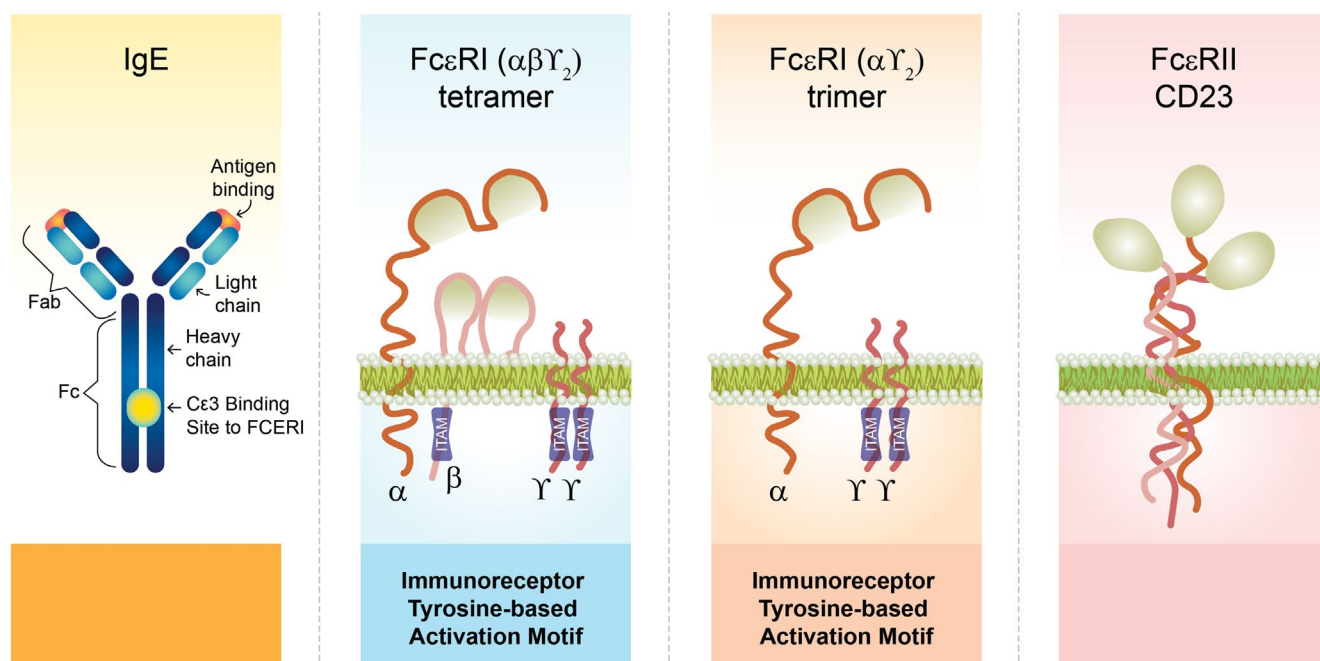


**FIGURE 3** | Structure of IgE and the IgE receptors. The IgE molecule has two receptors: A membrane high-affinity receptor, FcεRI, and a low-affinity FcεRII/CD23 receptor. The FcεRI is expressed on dendritic cells, mast cells and basophils, while the FcεRII/CD23 receptor is primarily expressed on B-cells, T-cells and antigen-presenting cells.

symptoms of allergies [40]. Both receptors are highly selective for IgE, and thus, exposure to even small amounts of allergens can induce significant levels of inflammation [41].

The IgE receptor, FcεRI, is a member of the multi-chain immune recognition receptor family and signals through cytoplasmic tyrosine kinases. The receptor is expressed either as an αβγ<sub>2</sub> tetramer (on basophils, mastocytes and smooth muscle cells) or as an αγ<sub>2</sub> trimer (on the surface of antigen-presenting cells and monocytes) [42]. The α chain of the receptor, a member of the immunoglobulin superfamily, contains the binding site for IgE [42–44] and consists of an extracellular domain, a transmembrane domain, and a short cytoplasmic tail with no signaling motifs. The γ subunits contain an immunoreceptor tyrosine-based activation motif (ITAM) and form a disulfide-linked dimer. The β subunit consists of four transmembrane domains with single ITAMs [45] (Figure 3). FcεRI expression has been observed on numerous cell types including mast cells, eosinophils, antigen-presenting cells, and epithelial cells. However, understanding of the mechanisms underlying the receptor's functional role in allergic asthma remains poor [46].

The low affinity IgE receptor FcεRII, also known as CD23, is a calcium-dependent lectin that is expressed on B cells, T cells, macrophages, monocytes, eosinophils, and epithelial cells. It is a type II membrane glycoprotein and its carboxyl terminus consists of a C-type lectin head that binds to IgE in a calcium-dependent manner [47]. The FcεRII/CD23 receptor is transcribed in two spliced isoforms, CD23a and CD23b. CD23a is constitutively expressed on B cells, while CD23b is expressed on several cell types including eosinophils, neutrophils, and human bronchial epithelial cells [48–51].

Although less is known about the signaling mechanisms of the low-affinity FcεRII/CD23 receptor than the FcεRI receptor, it is thought that it may act as an adhesive molecule [52]. The low-affinity FcεRII/CD23 receptor may also act as an IgE sink, as CD23 expressed on B cells has been shown to be involved in the regulation of free serum IgE [53]. CD23 activation is central to IgE regulation, differentiation of B cells, and antigen presentation. It is possible that this receptor structure influences a range of biological processes, including cellular apoptosis, regulation of T- and B- lymphocyte differentiation, release of anti-inflammatory mediators, and transcytosis of IgE-allergen complexes [54]. Interestingly, patients with allergic disorders have shown increased expression of membrane bound CD23 and ensuing soluble CD23 [45].

Both the FcεRI and the FcεRII/CD23 receptors play important roles in the pathogenesis of airway allergic inflammation. Expression of both FcεRI and FcεRII/CD23, receptors have been observed on a variety of human epithelial cells, including bronchial, nasal, tracheal, and intestinal [48, 55, 56]. Studies have also found that the expression of FcεRI is increased in the airway epithelium of patients with asthma when compared with control subjects [57, 58].

FcεRII/CD23 can be induced by a range of immune cells, including activated B cells, eosinophils, and airway epithelial cells [39]. FcεRII/CD23 was shown to be capable of transporting human IgE or IgE-derived immune complex across polarized human airway epithelial monolayers [54, 59]. Further, both FcεRI and FcεRII/CD23 receptors are expressed by human intestinal epithelial cells [56, 60, 61], with the CD23a receptor demonstrating a role in activation of intestinal sub-epithelial mast cells in the presence of IgE [60]. It has been

suggested that FcεRII contributes to immunosurveillance of the intestinal mucosa [61].

## 4 | IgE Directly Affects Airway Epithelial Cells

The complex mechanisms through which the IgE network directly affects airway epithelial cells remain poorly understood [62] [Table 1]. Both FcεRI and FcεRII/CD23 IgE receptors are directly expressed on human bronchial epithelial cells [48, 55], with elevated numbers of high-affinity IgE receptor-bearing cells a feature of bronchial biopsies of both allergic and non-allergic asthmatic subjects [58]. Further evidence demonstrates elevated expression of mature IgE heavy chain transcripts in the bronchial mucosa of allergic, as well as in non-allergic, asthma patients compared with normal controls [64]. Indeed, anti-IgE therapy with omalizumab reduced bronchial mucosal IgE+ mast cells in patients with non-allergic asthma [65]. IgE plays a key role in the interaction between airway mucosa and allergens due to transcytosis across the epithelial cells on submucosal connective tissue in the airway lumen; this process is mediated by the low-affinity FcεRII/CD23 receptor expressed on airway epithelial cells [54, 59]. Epithelial CD23 plays a central role in the development of allergic inflammation [54]. A study by Palaniyandi et al. used knock-out mice to demonstrate that without functional CD23, airway epithelial cells are unable to directly capture allergens. This, in turn, prevented allergen transportation across the epithelial barrier, activation of immune cells by IgE allergens and subsequent development of asthma and allergy symptoms. The group further suggested that blocking CD23 function in airway epithelial cells may have potential as a novel therapeutic strategy for allergic asthma [54].

## 5 | Role of the IgE Network on Airway Epithelium in the Pathophysiology of Asthma

The biological role of IgE in allergic asthma is complex. IgE is involved in both the early and late inflammatory response to an allergen and is a key mediator of allergic inflammation [35] (Figure 4).

However, the exact mechanisms responsible for the crosstalk between allergen/IgE, epithelial cells, and immune effector cells in the airway remain poorly understood.

### 5.1 | Alarmins

The airway epithelium mediates a complex inflammatory process in response to allergen exposure and epithelial damage, which includes the release of the epithelial cytokines TSLP, IL-25, and IL-33, also known as alarmins [35, 66, 67]. In addition to being important mediators of inflammation, alarmins play a major role in asthma [68]. Expression levels of TSLP and IL-33 are higher in patients with asthma than in healthy individuals and correlate with disease severity, indicating a key role for these cytokines in asthma T2 inflammation [69, 70].

TSLP potently activates DCs which prime naïve T helper cells to produce the T2 cytokines IL-4, IL-5, and IL-13 [71]. TSLP is part

of the IL-2 cytokine family and binds to a high-affinity receptor complex consisting of the thymic stromal lymphopoietin receptor (TSLPR) and an IL-7Rα subunit that is expressed on airway epithelial cells [71]. Cross-linking of IgE to the FcεRI receptor in mast cells has been shown to result in TSLP secretion [71]. IgE directly activates airway smooth muscle cells to produce IL-4, IL-5, IL-13, and TSLP, leading to airway remodeling [72].

Both IL-25 and IL-33 play an important role in the T2 inflammatory response with overexpression of T2 cytokines, including IL-4, IL-5, and IL-13. Both IL-4 and IL-13, secreted from polarized Th2 cells, activate B cells which subsequently produce IgE. This interaction can then result in airway hyperresponsiveness and mast cell degranulation [73]. The expression of FcεRII/CD23 receptor has also been shown to be increased under the influence of IL-4 in airway epithelial cells [59, 74]. The IL-4 cytokine has further been determined to enhance CD23-dependent trans-epithelial transport of IgE across airway epithelial cells [59] and to stimulate mast cell production of the IL-6 family cytokine oncostatin M (OSM) [75]. In vitro studies of nasal epithelium have shown that OSM has direct effects on epithelial function by causing a reduction in epithelial tight junction expression [76].

### 5.2 | Dendritic Cells

DCs are the major antigen-presenting cells of the airway. They express a wide range of receptors on their cell surface and play a crucial role in the immune response to inhaled allergens [77]. Airway epithelial activation is a key triggering event in the recognition of inhaled allergens, which, in turn, activates local DCs that coordinate the subsequent immune response [77]. This has been shown to occur via epithelial toll-like receptor (TLR)-4 activation [78]. Willart and colleagues found primary human bronchial cells produce DC-attracting chemokines, granulocyte-monocyte colony-stimulating factor (GM-CSF), and IL-33 in response to house dust mite allergen exposure [79]. In addition, DCs can form tight junctions with airway epithelial cells, and some allergens have been shown to access DCs by disrupting these tight junctions [80, 81]. Different subtypes of airway DCs contribute different roles in airway allergic inflammation. For example, inflammatory DCs are necessary for induction of T2 immunity in asthma [82], while conventional DCs (cDCs) express higher levels of CC-chemokine receptor 7 (CCR7) compared to other DC subtypes [83]. DCs have been found to express FcεRI, suggesting a role for IgE [84]. The expression of FcεRI on DCs directly correlates with serum levels of total IgE [85]. IgE bound to FcεRI receptors expressed on the surface of DCs amplifies antigen presentation by the presentation of allergens to memory Th2 lymphocytes [18]. Research by Platzer and colleagues demonstrated that humanized mice expressing FcεRI on DCs carry IgE similar to non-allergic humans and do not develop spontaneous allergies. The crosslinking of antigen-specific IgE/FcεRI does not trigger maturation or the production of inflammatory mediators in either human DCs or FcεRI-humanized DCs. Additionally, expressing FcεRI on DCs reduces asthma severity in relevant disease models, indicating that IgE/FcεRI signals may have anti-inflammatory effects [86].

Stimulation of the FcεRI IgE receptor on plasmacytoid DCs (pDCs) inhibits influenza induced interferon (IFN)-α release

**TABLE 1** | Source literature identifying direct effects of IgE on epithelial cells.

| Authors                         | Journal                                                    | Title                                                                                                                                       | Main findings                                                                                                                                                                                                         |
|---------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Campbell et al., (1994) [48]    | Immunology                                                 | Low-affinity receptor for IgE on human bronchial epithelial cells in asthma.                                                                | Demonstrated low affinity FcεRII/CD23 IgE receptor to be directly expressed on human bronchial epithelial cells                                                                                                       |
| Humbert et al., (1996) [58]     | American Journal of Respiratory and Critical Care Medicine | High-affinity IgE receptor (FcεpsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma.                              | Demonstrated elevated numbers of high-affinity IgE receptor-bearing cells on bronchial biopsies of patients with both allergic and non-allergic asthma                                                                |
| Campbell et al., (1998) [55]    | American Journal of Respiratory Cell and Molecular Biology | Expression of the high-affinity receptor for IgE on bronchial epithelial cells of asthmatics                                                | Demonstrated that bronchial epithelial cells of subjects with asthma express the high affinity FcεRI IgE receptor on their surface                                                                                    |
| Ying et al., (2001) [64]        | Journal of Allergy and Clinical Immunology                 | Local expression of ε germline gene transcripts and RNA for the ε heavy chain of IgE in the bronchial mucosa in atopic and nonatopic asthma | Demonstrated elevated expression of mature IgE heavy chain transcripts, in the bronchial mucosa of nonatopic as well as atopic patients when compared with control subjects                                           |
| Palaniyandi et al., (2011) [59] | Journal of Immunology                                      | CD23-dependent transcytosis of IgE and immune complex across the polarized human respiratory epithelial cells                               | Demonstrated that CD23 (FcεRII) is constitutively expressed in primary human airway epithelial cells, and its expression is significantly upregulated when airway epithelial cells were subjected to IL-4 stimulation |
| Palaniyandi et al., (2015) [54] | Mucosal Immunology                                         | Inhibition of CD23-mediated IgE transcytosis suppresses the initiation and development of allergic airway inflammation                      | Demonstrated that airway epithelial cells are unable to directly capture allergens without functional CD23                                                                                                            |
| Pillai et al., (2016) [65]      | European Respiratory Journal                               | Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma                                                    | Demonstrated that anti-IgE therapy with omalizumab reduced bronchial mucosal IgE+ mast cells in patients with non-allergic asthma                                                                                     |

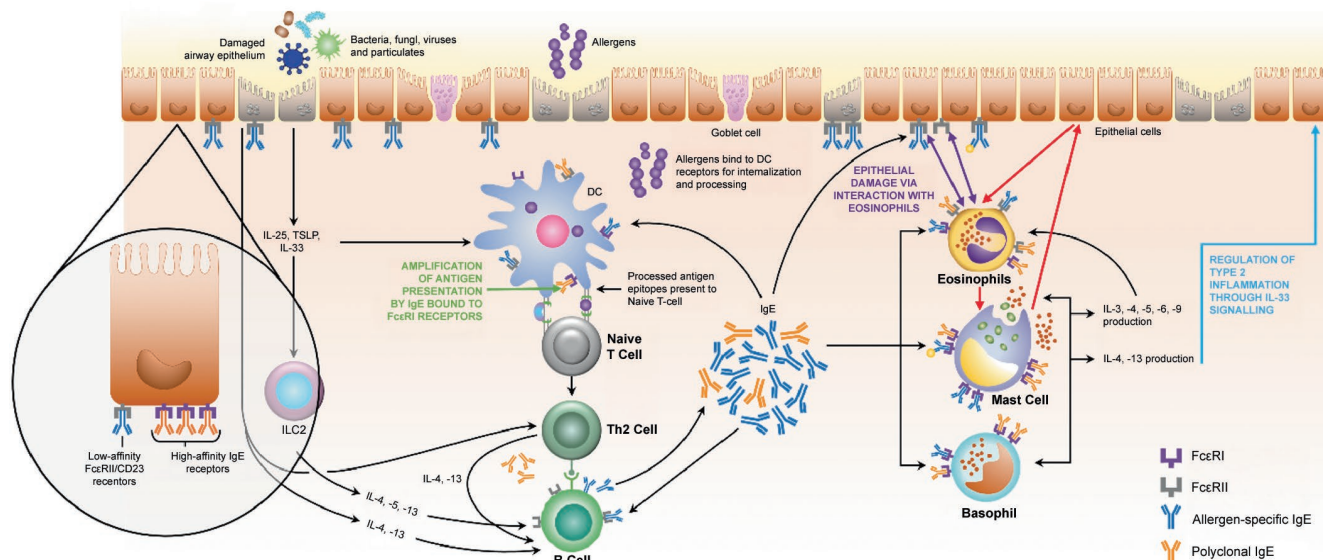


**FIGURE 4** | Role of the IgE network on airway epithelium in the pathophysiology of asthma. Following allergen exposure, dendritic cells present allergen-specific antigens to activated T cells, which differentiate into T helper 2 (Th2) cells. Th2 cells produce the type 2 (T2) cytokines interleukin (IL)-4, IL-5, and IL-13, which, in turn, prompt B cells to produce allergen-specific immunoglobulin E (IgE). IgE acts on the FcεRI receptors of tissue-resident mast cells, stimulating the release of histamine, prostaglandin, and cell growth factors and recruitment of proinflammatory cells including eosinophils and basophils. Elevated numbers of high-affinity FcεRI receptors are a feature of bronchial biopsies of both allergic and non-allergic asthmatic subjects. Low-affinity FcεRII/CD23 receptors mediate transcytosis across the epithelial cells on submucosal connective tissue in the airway lumen.

and blocks TLR signaling. Decreasing serum IgE with omalizumab in patients with allergic asthma restores the capacity of human pDCs to produce IFN- $\alpha$  which correlates with improved clinical outcomes [87, 88]. This also leads to an increase in the antiviral activity of pDCs, which subsequently enables the generation of functional regulatory T cells (Tregs). Consequently, omalizumab treatment increases the frequency of Tregs in children with asthma, which then correlates with improved asthma control [89]. Lopez-Abente and colleagues recently identified an association between IgE- FcεRI cross-linking on human pDCs, and an impaired capacity of pDCs to polarize Tregs in vitro. This ability was found to be restored following in vitro treatment with omalizumab, and was associated with a clinical improvement in asthma, suggesting a potential role for anti-IgE therapy in the treatment of immune conditions in which Tregs are involved [87, 90, 91]. Further research has demonstrated that lige-lizumab, an anti-IgE monoclonal antibody with a higher affinity for IgE than omalizumab, exhibits a greater ability to block the binding of free IgE to FcεRI on human pDCs. Additionally, lige-lizumab was been shown to restore the capacity of pDCs to generate Trags [90].

### 5.3 | Eosinophils

Eosinophils, basophils, and mast cells are key players in the development of allergic inflammation as well as in innate and adaptive immunity. During a T2 inflammatory response the T2 cytokines IL-5 and IL-13 enhance eosinophil recruitment. Eosinophils release additional IL-5, which, in turn, enhances the recruitment of circulating eosinophils to maintain and amplify the inflammatory response [15]. DCs have been shown to induce Th2-dominated sensitization to inhaled antigen, further

leading to eosinophilic airway inflammation [87]. Eosinophils induce airway epithelial remodeling through airway smooth muscle proliferation and through interactions with mast cells and epithelial cells [92, 93]. Eosinophils are considered important epithelial-damaging cells in allergic and non-allergic asthma [94]. Eosinophils have been demonstrated to be directly influenced by both FcεRI and FcεRII/CD23 receptors [95], suggesting that IgE may indirectly affect airway epithelial cells through interactions with eosinophils, as evidenced by omalizumab-induced apoptosis in these cells [95].

### 5.4 | Mast Cells and Basophils

Mast cells are located throughout the lung and are increased within the airway epithelium of patients with asthma [96, 97]. They play an essential role in the immune response to PAMPs and DAMPs. Mast cells have been shown to interact with epithelial cells through IL-33 signaling to regulate T2 inflammation [96]. Like basophils, mast cells express the IgE receptor FcεRI [98]. As well as regulating IgE, the T2 cytokine IL-4 stimulates the migration and activation of mast cells [15]. The interaction between allergen-IgE complex and the FcεRI receptor on the surface of mast cells triggers mast cell degranulation and the release of inflammatory mediators including histamine, prostaglandins, cell growth factors and tryptase [15, 99, 100]. Additionally, tryptase released by mast cells interacts with extracellular IL-33, producing a more mature and active form of IL-33 [101].

Basophils represent the least abundant granulocyte population in mammals and share phenotypic similarities with mast cells [63]. An accumulation of basophils has been reported in allergic

asthma [102] and an increase in basophil development has been observed *in vivo* during a T2 cytokine-mediated inflammatory response [103]. Basophils are known to bind IgE through the IgE receptor FcεRI, which results in the subsequent release of histamine [104, 105]. Although predominantly regulated by IgE-activated IL-3, recent studies have shown that some basophil populations are regulated by the epithelial cytokine TSLP in an IgE-independent manner [63, 103].

## 6 | Airway Epithelial Remodeling

Structural changes to the airway wall, also known as airway remodeling, are a hallmark feature of allergic asthma in some patients and reflect a consequence of sustained airway inflammation [106, 107]. These changes consist of an increase in the smooth muscle mass surrounding the airway wall, a thickening of the epithelial reticular basement membrane, a breach in the integrity of the airway epithelium and an increase in mucus-producing goblet cells in the epithelium or submucosal glands [31]. The airway smooth muscle (ASM) is now recognized to play a crucial role in the modulation of airway inflammation and remodeling. Previous studies have established a molecular link between ASM and IgE, demonstrated by the expression of FcεRI in primary human ASM cells both *in vitro* and *in vivo* within bronchial biopsies of allergic asthmatic subjects [44]. Exposure to IgE, whether it is antigen-bound or independent, and its subsequent cross-linking with FcεRI on ASM cells, triggers the release of proinflammatory cytokines IL-4, IL-5, and IL-13 [44, 108]. Indeed, over a decade ago, Roth et al. demonstrated that IgE dose-dependently increased extracellular matrix and collagen deposition by airway smooth muscle cells as well as their proliferation [109]. IgE may also directly interact with IgE receptors on airway epithelium cells causing epithelium damage, as well as leading to the additional release of alarmins following inflammatory signaling [67]. It has been proposed that given the central role of IgE in persistent airway inflammation, anti-IgE therapies may influence the airway remodeling process by interrupting the allergic inflammatory cascade [110]. To this end, recent studies have demonstrated direct associations between IgE or anti-IgE treatment with features of airway remodeling [67, 111]. Riccio and colleagues showed that after 1 year

of omalizumab treatment a substantial proportion of patients with severe asthma had reduced bronchial reticular basement membrane thickness [112]. This was further confirmed after 36 months of omalizumab treatment [113]. Recently, in a randomized open label study, Domingo et al. (CHOC study) further demonstrated a corticosteroid-sparing capacity of omalizumab to facilitate airway epithelium repair Figure 5A–C. and reduce both lung function impairment and disease exacerbations, in corticosteroid-dependent asthma patients [114].

## 7 | Clinical Implications

IgE plays a central role in the pathogenesis and clinical course of various allergic diseases, including asthma, and is an important target for these conditions [115, 116]. Omalizumab is a humanized monoclonal anti-IgE antibody, that neutralizes free-form IgE, blocking its interaction with FcεRI and FcεRII/CD23 receptors on airway epithelial cells [46, 67]. This blockade inhibits the development of allergic inflammation in the respiratory tract [117]. Omalizumab has also been shown to inhibit the release of TNF-α and TNF-β in human airway epithelial cells [118].

Omalizumab has proven to be efficacious and well tolerated in the treatment of moderate-to-severe asthma in both adult and pediatric populations, with > 2.25 million patients-years of exposure [119, 120]. It is associated with both improvements in lung function and a reduction in disease exacerbations [19, 121, 122]. The Inner-City Anti-IgE Therapy for Asthma (ICATA) study was a year-long trial that assessed the effectiveness of omalizumab on inner-city children, adolescents, and young adults with persistent asthma [123]. The Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study also examined inner-city children with allergic asthma but took place during the fall season only to examine asthma exacerbations when children return to school [36]. In both trials omalizumab reduced exacerbations and improved asthma control, through prevention of mast cell activation as well as the modification of IgE's action on antiviral properties [36, 123].

Patients with allergic asthma show impaired interferon responses to viruses and this may account for the susceptibility

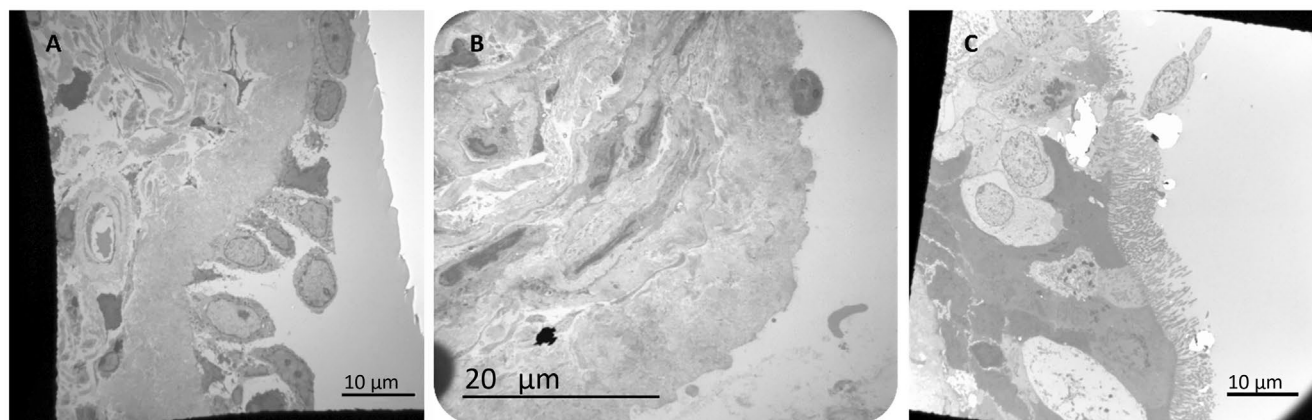


**FIGURE 5** | (A) shows the disruption of the bronchial epithelium (loss of cilia, intercellular spaces, loss of cells, thickness of the bronchial mucosa of a patient with severe asthma. (B) shows the total loss of epithelium, only an enlarged basement membrane persists. (C) shows the restore of the bronchial epithelium (reappearance of cilis, ciliated cells, absence of intercellular space) after one year of treatment with omalizumab [114].

to virus-induced asthma exacerbations seen in children with severe asthma and high serum IgE levels [124]. Omalizumab has been shown to reduce the severity of asthma exacerbations [125]. IgE production in patients with allergic asthma has been shown to decrease following long-term anti-IgE treatment [126].

## 8 | Conclusions

Bronchial epithelial cells and IgE play key roles in allergic asthma through a complex network of interactions. IgE plays a key role in the interaction between airway mucosa and allergens and, both directly and indirectly, affects epithelial cells. Directly, both FcεRI and FcεRII/CD23 IgE receptors are expressed on human bronchial epithelial cells and elevated numbers of FcεRI receptors are a hallmark feature of bronchial biopsies from asthma patients [48, 55, 58]. While indirectly, IgE plays an important role in T2 inflammation and consequently is central to remodeling processes within the airway epithelium [114].

IgE has a broad range of biological effects and successful treatment of asthma and other allergic diseases with the IgE-specific antibody omalizumab, demonstrates the efficacy of targeting IgE for therapy [46]. Omalizumab interferes with the interaction of IgE antibodies with both high- and low-affinity IgE receptors, as well as influencing early and late phases of allergic reaction and preventing the development of allergic inflammation in the respiratory tract [17]. Anti-IgE therapy has further been shown to facilitate airway epithelium repair in patients with asthma [114].

The direct and indirect effects of IgE on airway epithelial cells may play an important role as a key early step in the T2 inflammatory cascade in allergic asthma. These interactions provide an additional mode of action for omalizumab in the treatment of asthma as clinical efficacy may also be related to the effects of IgE on epithelial cells resulting in disruption of downstream signaling.

### Author Contributions

All authors contributed to the conception, structure, development, and review of the manuscript.

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### Conflicts of Interest

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### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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