Development of Adaptive Immunity and Its Role in Lung Remodeling.

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Abstract

Asthma is characterized by airflow limitations resulting from bronchial closure, which can be either reversible or fixed due to changes in airway tissue composition and structure, also known as remodeling. Airway remodeling is defined as increased presence of mucins-producing epithelial cells, increased thickness of airway smooth muscle cells, angiogenesis, increased number and activation state of fibroblasts, and extracellular matrix (ECM) deposition. Airway inflammation is believed to be the main cause of the development of airway remodeling in asthma. In this chapter, we will review the development of the adaptive immune response and the impact of its mediators and cells on the elements defining airway remodeling in asthma.

Keywords

Asthma · Mucins · Airway smooth muscle · Lung remodeling · Extracellular matrix (ECM) · Cytokine · Adaptive immunity · Fibroblast · Innate lymphoid cell · Matrix metalloproteinase · Epithelial cell · Eosinophil · Neutrophil · Mast cell · Dendritic cell · Allergen · Lymphocyte

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A. R. Brasier, N. N. Jarjour (eds.), *Precision Approaches to Heterogeneity in Asthma*, Advances in Experimental Medicine and Biology 1426,
https://doi.org/10.1007/978-3-031-32259-4_14

Abbreviations

AEC	Airway epithelial cells
AHR	Airway hyperreactivity
APC	Antigen-presenting cell
ASM	Airway smooth muscle
BALF	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BEC	Bronchial epithelial cells
CysLT	Cysteinyl leukotrienes
DC	Dendritic cell
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
ELANE	Neutrophil elastase
ET	Endothelin
FEV_1	Forced expiratory volume in 1 second
FGF	Fibroblast growth factor
IFN	Interferon
IGF	Insulin-like growth factor
IL	Interleukin
ILC	Innate lymphoid cell
MAIT	Mucosal-associated invariant T
MMP	Matrix metalloproteinase
NK	Natural killer
PDGF	Platelet derived growth factor
PG	Prostaglandin
SBP-Ag	Segmental bronchoprovocation with an allergen
T2	Type-2
TGF	Transforming growth factor
Th1	Type 1 T helper lymphocyte
VEGFA	Vascular endothelial growth factor
γ/δ	Gamma-delta
αSMA	Alpha-smooth muscle cell actin

Introduction

Pulmonary insults by aero-allergens, microbes, or pollutants disrupt the bronchial epithelial barrier leading to vascular leakage in the airways and bringing inflammatory cells, growth and coagulation factors, and matrix proteins to stop the leakages and start tissue repair. This is followed by accumulation and activation of contractile and extracellular matrix protein-producing fibroblasts to enhance the repair process. While these processes favor lung protection and healing, exaggerated or prolonged response can lead to scarring and fibrosis, which are detrimental to proper lung function. Concomitantly, these events are partially orchestrated by the innate

immune response that involves inflammatory cells, such as macrophages, innate lymphoid cells (ILC), and neutrophils. This primary innate response may also participate in the development of an adaptive immune response that involves antigen-presenting cells (e.g., dendritic cells) to ultimately produce antigen-specific memory B and T lymphocytes that will remember the specific initiator of the insult and more efficiently react to the next exposure from the same aggressor. This adaptive response that generates large amounts of numerous cytokines and other factors, further enhances the innate immune response, and, in the case of allergies, leads to eosinophilia and specific IgE/IgE receptors binding on mast cells.

Asthma is characterized by airflow limitations resulting from bronchial closure, which can be either reversible (e.g., airway smooth muscle contraction) or fixed due to a change in airway tissue composition and structure, also known as remodeling. In asthma, airway remodeling is defined as increased presence of mucins-producing epithelial cells (goblet cell hyperplasia), increased thickness of airway smooth muscle cells (ASMC) layer (ASMC hyperplasia and hypertrophy), angiogenesis, increased number and activation state of fibroblasts (subepithelial fibrosis) and extracellular matrix (ECM) deposition. Airway remodeling has been implicated in increased airway hyperresponsiveness (AHR) [1], decline in lung function [2], and decreased responsiveness to asthma therapies. Importantly, except for bronchial thermoplasty which is a treatment option to reduce the airway smooth muscle (ASM) layer [3], current therapeutics for asthma including the corticosteroids, do not directly target airway remodeling [4, 5]. However, because therapeutics targeting products from the immune response (e.g., biologics) exist or are being developed, in this chapter, we will describe how the adaptive immune response affects lung remodeling, particularly fibroblast, ASMC activation, and mucus production by bronchial epithelial cells (BEC).

Evidence of Remodeling in Asthma

Fibroblast Activation and Accumulation of Extracellular Matrix Proteins in the Airways

Fibroblasts are the main cell type that produces ECM proteins, and they are the direct culprit for subepithelial thickness or fibrosis. Subepithelial fibrosis is a prominent feature of airway remodeling in asthma [6, 7], particularly in severe asthma [8], and is a direct product of fibroblasts. Fibroblasts are mesenchymal cells present in the connective tissue at the base of the airway epithelial layer and have an important role in tissue repair. Following airway insults and injuries, activated local and newly recruited fibroblasts divide and differentiate into contractile (alpha-smooth muscle producers) [9] and ECM-producing myofibroblasts due to activation by transforming growth factor-β1 (TGF-β1) and other mediators [10–13]. Activated fibroblasts and myofibroblasts produce large amounts of ECM proteins (e.g., collagens, fibronectin, etc.), leading to accumulation and changes in the biochemical

properties of the matrix. Fibroplasia and ECM proteins stiffnesses are important elements of lung fibrosis and the irreversible loss of lung function in asthma [14]. In addition, fibroblasts and fibrocytes differentiation into myofibroblasts participate in hyperplasia of ASM [15].

Increased deposition of collagen under the basement membrane was observed in lung biopsies from both patients who died from status asthmaticus and asymptomatic subjects with asthma, suggesting irreversibility of ECM deposition after asthmatic attacks [16]. Later, Davidson et al. noticed marked fibrosis in lung biopsies from living patients with asthma [17]. Electron microscopy and immunohistochemical analyses of subepithelial fibrosis in asthma revealed noticeable presence of collagens (I, II and V) and fibronectin in the thickened lamina reticularis [18]. Furthermore, Brewster et al. [19] found a strong correlation and co-localization of bronchial subepithelial collagen thickness and the number of α-smooth muscle actin (αSMA)-producing myofibroblasts in asthma. Later, in 1997, histopathologic features of bronchial biopsies in allergic asthma showed that subepithelial fibrosis (basement membrane thickening/collagen deposition) was associated with metacholine airway responsiveness, asthma severity, and decline in forced expiratory volume in 1 second (FEV_1) [20, 21]. Furthermore, increased peribronchial fibrosis in asthma is associated with the number of eosinophils, the thickness of basement membrane, and goblet cell area [22]. In rodents, prolonged allergen exposure leads to goblet cell hyperplasia, ECM deposition, and thickening of the airway walls [23, 24]. In bronchoalveolar lavage fluids (BALF) from subjects with mild asthma elongated, highly mobile, and ECM- and αSMA-producing fibroblasts have been found along elevated numbers of eosinophils [25]. These fibroblasts were not found in the nonasthma control group [25]. Besides fibroblasts, a circulating cell called fibrocytes possesses fibroblast-like features, including the generation of ECM and αSMA [26–28]. Fibrocytes retain antigen-presenting capabilities [29] and can further differentiate into fibroblasts and myofibroblasts in the airways in asthma [15], where their number correlates with the basement membrane thickness [30]. In asthma also, the count of vascular endothelial growth factor (VEGFA) positive cells and the vascular area is higher than in healthy individuals [31]. In that study, VEGFA level was associated with basement membrane thickness, indicating that VEGF may play a role in subepithelial fibrosis [31], and indicating that promotion of new blood vessel growth is likely part of lung remodeling.

In allergic asthma, segmental bronchoprovocation with an allergen (SBP-Ag) in subjects with mild asthma induced fivefold the amount of a locally produced ECM protein, fibronectin in BALF, which correlated with early release of histamine and accumulation of inflammatory cells [32]. In that same model, SBP-Ag increased BALF basic fibroblasts growth factor-2 (bFGF, aka FGF2), an activator of fibroblasts, and ASMC, as well as matrix metalloproteinase (MMP)-9 [33, 34], which cleaves ECM proteins and allows migration of inflammatory cells and the release of VEGFA, fibrotic factors such FGF2, active TGF-β1, platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF) [35–40].

Smooth Muscle Cells

Smooth muscle cells are present from the central airway to the most peripheral parts of the lung. Increased airway smooth muscle mass is a pathological feature of asthma, with further increase airway smooth muscle area in severe versus moderate asthma [41–43]. Both hyperplasia and hypertrophy of ASMC are strongly increased in asthma versus control individuals [44–47], particularly in the more severe cases [48–50]. In vitro, ASMC from asthma subjects display a higher ability to proliferate than ASMC from nonasthmatic subjects, indicating a different and stable phenotype in asthma [51]. ASMC contraction is opposed to elastic recoil of the airways that limits bronchoconstriction, and ASM hypertrophy correlates to AHR to histamine in asthma [52]. Thus, changes of ASMC in asthma are likely a major cause of increased AHR, excessive bronchoconstriction, and airway narrowing [53, 54]. Peribronchial smooth muscle hypertrophy is often concomitant to the deposition of collagen and subepithelial fibrosis in asthma [16]. In vitro, ASMC activated with serum from asthmatic subjects produce an increased amount of ECM, compared to ASMC activated with serum from nonasthmatic individuals [55]. ASMC, particularly injured ASMC produce TGF-β and TGF-β receptors, which in an autocrine way enhances their production of glycosaminoglycans and ECM, such as collagens, and the pro-neutrophilic cytokine, IL-8 [56–59]. Furthermore, mechanical stress that mimics force generated by mechanical bronchoconstriction in asthma leads to release of endothelin-1 (ET-1) and endothelin-2 (ET-2) by epithelial cells, which can stimulate ASMC to further enhance bronchoconstriction [60–62]. Therefore, there are tight interconnections between fibrosis and ASMC activity in asthma.

Mucus Accumulation

The role of mucus plugging in asthma is addressed by Schiebler et al. (Part II, Chap. 8) of this volume. Here, we provide a brief description of mucus production and potential effects on asthma.

In the 1960s, Dunnill et al. described the presence of mucus plugs associated with the loss of ciliated mucosal cells are features of subjects dying in *status asthmaticus* [63, 64]. Later, it was proposed that the presence of bronchial mucus plugs may be due to reduced mucociliary clearance in asthma compared to control individuals [65]; and bronchial epithelial goblet cells hyperplasia with mucus accumulation was observed after death by asthma attack [66]. More recently, state-of-the-art imaging was implemented to quantify mucus plugs in asthma and examine their associations with its clinical features such as predisposition for exacerbation and presence of airway obstruction [67]. The formation of mucus plugs involves the release of gel-forming mucin proteins (e.g., MUC5AC and MUC5B). MUC5AC is produced by BEC with the implication of IL-13, epidermal growth factor receptor (EGFR) signaling pathways and neutrophil elastase (ELANE) [68–71]. In addition

to gel-forming mucin proteins, mucus plugs in asthma contain fibrin clots, which have also been observed in fatal asthma [72, 73], suggesting tight imbrication between mucin proteins and fibrogenesis for the formation of mucus plugs and airway obstruction in asthma. While mucus plugging is now well-established as a major contributor to asthma pathophysiology, including the risk of exacerbation and disease severity, there are no specific therapies to date that directly address mucus plugging in asthma, making this one of the important areas for future investigation.

Development of Adaptive Immunity in Asthma

Mucosal surface in the airways is a barrier to the development of adaptive immune responses to external agents such as aero-allergens, microbes, and pollutants. The epithelial barrier may, however, suffer some damage and allow the development of an innate immune response that involves macrophages, neutrophils, basophils, dendritic cells (DC), natural killer (NK) cells, NKT cells, gamma-delta (γ/δ) T cells, mast cells, and eosinophils as well as proteins such as proteins part of the complement. Following the innate immune response, an adaptive immune response takes place, but the response can be limited by mechanisms of lymphocyte unresponsiveness such as anergy, and ultimately adaptive tolerance. However, the adaptive immune response can fully grow, producing memory T and B lymphocytes, which can amplify a damaging succeeding response to the same original external agents.

The Role of the Epithelium and the Innate Immune Cells

The development and role of the innate immune response in lung tissue remodeling are addressed in the chapter by Brasier (Part III, Chap. 13) of this volume. Yet, to put the adaptive immune response into perspective in the complex global events occurring after an airway challenge in asthma, some of the cells of the innate immune response and their products will be briefly described here vis-à-vis their role in lung remodeling and the development of an adaptive immune response.

Airway Epithelial Cells (AEC)

AEC form the main first barrier between the host and inhaled factors involved in asthma development, and they have a critical early role in the immune response against these agents. Airway inflammation is believed to be the main cause for the development of airway remodeling in asthma [74, 75]; however, AEC, particularly those from the small airways, can directly participate in promoting remodeling [see Brasier (Part III, Chap. 13) of this volume]. Allergen challenges in rats increase the number of AEC [76]. During asthma exacerbation, there is both recruitment of inflammatory cells and AEC damage, which leads to the release of proteolytic enzymes, oxygen radicals, and profibrotic factors, including TGF-β and epidermal growth factor (EGF) [77–80]. Injured epithelial cells can release TGF-β1 from the

ECM to activate myofibroblast differentiation and survival [81–83]. Also, AEC produces MMP-2 which induces the proliferation of subepithelial fibroblasts [84]. Furthermore, mechanical stress of AEC that can occur during bronchoconstriction of the airways leads to the production and release of ET-1 and ET-2 [60]. Notably, among the AEC types, enhanced differentiation of mucus-producing goblet cells is one of the main characteristics of airway remodeling, and hyperplasia and hypertrophy of the goblet cells are associated with the severity of the disease [66, 85]. In asthma, AEC display increased protease-activated receptor-2 (PAR-2) and constitutively produce the enhanced amount of cytokines (IL-8 and GM-CSF), which increases their release of MMP-9 and GM-CSF [86, 87] that stimulate neutrophil recruitment and prolong eosinophil survival, respectively [88–92]. Finally, asthma subjects display increased VEGF and VEGF receptor expression on BEC that correlates with airway remodeling (mucus-producing cells, subepithelial fibrosis, and airway smooth muscle hyperplasia), airflow obstruction, and AHR [93].

AEC also has an important role in developing the adaptive immune response. Following interactions with environmental factors, including allergens, microbes, and other aero-particles, AEC release cytokines, such as the innate cytokines thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 (IL17B), which are important activators if the mucosal surface-enriched innate lymphoid cells-2 (ILC2) that produce IL-13, IL-4, IL-5, and IL-9 [94]. Through the release of these type 2 (T2) cytokines, ILC2 not only acts directly on IgE and mucus production, fibroblasts and ASMC activation, and vascular permeability [95] but also contributes to the development of the type 2 adaptive immune response [96–98]. In addition, in an ILC2-independent manner, the AEC-derived cytokines, TSLP and IL-33 also have a direct critical role in promoting a T2 adaptive immune response by activating antigen-presenting cells (APC) to promote a T2 immune response when presenting antigen to antigen-specific CD4+ T lymphocytes [99–101]. Furthermore, besides releasing TSLP and IL-33, AEC produces many chemokines including CCL2 (MCP-1), which is elevated in the airways in asthma [102]. CCL2 attracts T lymphocytes [103], favors T2 development [104], and activates the release of T2 cytokines by mast cells [105].

Eosinophils and TGF-β

The numerous effects of the eosinophil on tissue remodeling and the regulation of the adaptive immune response are well-discussed in a review by Lee et al. [106]. Eosinophils are a hallmark of asthma [107, 108], and their number in the airways correlates with asthma severity [108, 109]. Postmortem observations demonstrate lung tissue eosinophilia in patient who died from severe asthma compared to those without asthma [110]. Many more peribronchial eosinophils are observed by electron microcopy in severe symptomatic asthma versus asymptomatic asthma, indicating the role of eosinophils in asthma exacerbation [16]. Eosinophil granule toxic proteins are present in mucus plugs on damaged epithelial surfaces in patients who died from asthma, suggesting tissue damaging functions from the eosinophil products [111]. In the airways, eosinophil extracellular traps augment goblet cell hyperplasia and mucus production and activate pulmonary neuroendocrine cells to amplify allergic immune response via neuropeptides and neurotransmitters [112].

In mice, IL-5 and eotaxin are critical for eosinophil differentiation and recruitment into the lung to induce AHR [113, 114]. Conversely, the elimination of eosinophils leads to a significant reduction in IL-13 production during an allergic response [115], indicating that while the T2 immune response induces eosinophilia, eosinophils have in turn a role in T2 cytokines production. Evidence for eosinophils to affect the adaptive immune response come from their ability to interact with T lymphocytes and to release numerous cytokines and growth factors that control the T1, T17 and T2 immune responses [116–118]. Eosinophils themselves can release IL-4 and IL-13 and thus perpetuate both the T2 immune response and directly lung remodeling [118, 119]. Eosinophils release multiple other factors including IL-1β [117], a pro-T17 cytokine, and they activate fibroblasts in an IL-1α-dependent manner [120]. The sum of the factors released by eosinophils changes fibroblasts into both a pro-inflammatory and profibrotic phenotype with the significant secretion of pro-neutrophilic factors, IL-6, IL-8, and CXCL1 [120–123]. Notably, both IL-1β and IL-6 may induce hyperplasia and hypertrophy of ASMC [124].

Eosinophils are a principal source of TGF-β1 in the airways in asthma, and their granule toxic proteins may activate fibroblasts to produce more TGF-β1 [21, 125, 126]. TGF-β1 stimulates fibroblast proliferation, differentiation into myofibroblasts, and their production of collagens (types I and III), fibronectin, glycoaminoglycans, and elastin [127–130]. TGF-β induces ASMC hypertrophy [131] and increases the level of smooth muscle α-actin in SMC, enhancing their capacity to contract and migrate [132–134]. In mouse, treatment with an anti-TGF-β neutralizing antibody reduced airway ECM deposition, ASMC proliferation, and mucus production after chronic allergen challenges [135]. BAL TGF-β1 protein is high in the airways in atopic asthma, is enhanced by SBP-Ag [136], and its expression is associated with eosinophilia and asthma severity (i.e., fibrosis and lung function decline) [21]. Hoshino et al. found that subepithelial thickness correlated with the number of fibroblasts in the submucosa, which was correlated with TGF-β1 expression in asthma [137]. TGF-β1 can also convert human BEC into an elongated fibroblasts-like shape, producing α-SMA, F-actin stress fibers, collagen I and losing the epithelial marker E-cadherin, an indication of epithelial-to-mesenchymal transition (EMT) [138].

Macrophages/Monocytes

Macrophages in the lung are a first defense against pathogens due to their high phagocytosis capacities and the production of cytokines such as type I interferons. Local lung tissue macrophages may present phagocytized and processed antigens to lung DC [139] and thus amplify specific adaptive immune responses. However, depending on the number of macrophages, they can also suppress the antigen presentation from DC to T lymphocytes [139]. Macrophages also promote adaptive immunity by presenting antigens to naïve CD8+ and CD4+ T lymphocytes via major histocompatibility complex (MHC) class I and MHC class II surface molecules and the co-stimulatory molecules, CD40, CD80, and CD86 [140]. As for T lymphocytes, macrophages have different functions depending on the cytokine environment. IL-10-producing regulatory macrophages have anti-inflammatory

function, and macrophages in a T2 environment (M2) have wound healing and fibrotic functions via their production of TIMP, MMP, PDGF, TGF-β1, and chitinase-like proteins [141–147]. These airway M2 macrophages also produce CCL11 (eotaxin 1), CCL17 (TARC) and CCL22, which recruits eosinophils [148] and T2 lymphocytes [149]. Alveolar macrophages can produce IL-13 [150] and may be critical to maintain IL-13-dependent lung fibrosis [151]. As major producers of IL-1β and IL-23, macrophages likely act on IL-17A and T17 immune response generation [152, 153], which are known to induce pulmonary fibrosis [154]. It is however important to note that the M2 macrophages may be more predisposed to resolve inflammation and fibrosis via the production of IL-10 and pro-resolving lipids (reviewed in Ref. [155]) [156].

As part of the myeloid cells along with macrophages and DC, monocytes have similar properties, and they can mature into macrophages to replenish tissue macrophages, present antigens to CD8+ and CD4+ T lymphocytes via MHC class I and MHC class II surface molecules, as well as be pro- or anti-inflammatory (reviewed in Ref. [157]). Monocytes accumulate in the airways during an asthma attack [158]. In addition, circulating CD14+ monocytes can transform into fibroblast-like cells, fibrocytes, which migrate to injured tissues where they are matured by TGF-β1, produce ECM (Fibronectin, collagens), and promote wound contraction [15, 27, 159]. Circulating fibrocytes number and activation state are elevated in asthmatic patients following an exacerbation [160]. Monocytes also present antigens to T lymphocytes to induce differentiation into T1, T2, and T17 lymphocytes [157]. In an airway inflammation mouse model, newly airway recruited monocytes primed the antigen-specific CD4+ T lymphocytes to become T2 type [161]. Lastly, in an autoimmune mouse model, granulocyte-macrophage colony-stimulating factor (GM-CSF)-activated monocytes produce IL-6 and IL-1β to differentiate T lymphocytes into a T17 phenotype [162].

Neutrophils and MMP-9

In a cohort enriched in patients with severe asthma, 16% of the population displayed a neutrophilic phenotype as defined by ≥76% of neutrophils in sputum samples [163], while typically, only ~40% of immune cells in sputum samples are neutrophils in healthy individuals [164]. Mixed granulocytic inflammation (>2% eosinophils plus >40% neutrophils in sputum samples) in severe asthma is associated with lower lung function, worse asthma control, increased symptoms, and health care requirements compared to patients with only increased eosinophils, neutrophils, or none [165, 166]. In addition, the number of neutrophils in BALF increases by >20-fold 48 h after SBP-Ag in subjects with mild asthma [167], suggesting that neutrophils have an active role in allergic asthma. There is evidence showing that neutrophils can enhance lung remodeling. For instance, a specific product from neutrophils, neutrophil elastase (ELANE), increases mucin gene expression, mucus-producing BEC hypertrophy and hyperplasia, and disrupts the epithelial barrier [168–171]. Also, ELANE increases the migration of fibroblasts toward epithelial cells in vitro [172]. Neutrophil extracellular DNA traps (NET) level associated with asthma severity likely via AEC damage and eosinophil degranulation [173, 174].

NET are also associated with myofibroblast differentiation [175], and they activate macrophages to produce IL-1β [176], which directly activate fibroblasts and may increase the production of IL-17A by memory CD4+ T lymphocytes [117, 152]. Furthermore, through the release of exosomes, activated neutrophils enhance ASMC proliferation [177]. Activated neutrophils release many proteases that can degrade the matrix and contribute to lung remodeling, including MMP-9 (gelatinase) [178, 179]. MMP-9 activity is critical for antigen-uptake by dendritic cells (DC) in the airways [180]. In the lung, MMP-9 may be produced by most of stimulated cell types, and it is present in endobronchial biopsies in all asthmatic subjects, while absent in healthy individuals [107]. Notably, MMP-9 can mature IL-1β release by eosinophils [181], and thus participates in the activation of memory Th-17 [117, 152]. Although MMP-9 is predominant in asthma, all MMP-2 (collagenase A), MMP-3 (stromeolysin-1), and MMP-12 (metalloelastase) are elevated in the asthmatic airways [182]. MMP is associated with enhanced ECM deposition and inflammatory cells in the epithelium and subepithelium region. ECM-degrading collagenases and stromelysins affect the function and migration of inflammatory cells and matrix deposition in asthma [183, 184]. Although MMP could be considered as anti-fibrotic by degrading ECM, by cleaving ECM, they can also facilitate the migration of inflammatory cells and the release of fibrotic factors such as FGF2, active TGF-β1 and insulin-like growth factor (IGF) thus promoting fibrosis [185–188]. The expression of MMP genes is upregulated by cytokines such as IL-1, TNF-α, and TGF-α but is inhibited by TGF-β1 or IL-4. Their latent form requires maturation by cleavage to exert their proteolytic activity.

Besides, neutrophils can directly impact the development of the adaptive immune response by secreting cytokines such as IL-1, IL-23, IL-12, and IFN-γ [189–191], and thus favor T1 and T17 adaptive immune responses. Neutrophils also transport antigens and interact with myeloid APC to activate CD8+ T cells [192] and NET prime CD4+ T lymphocytes as they reduce the lymphocytes activation threshold [193]. Finally, neutrophils produce B-cell-stimulating factors, such as B-cell-activating factor (BAFF), APRIL, and a B-cell-activating molecule, CD40L [194].

Mast Cells and Cysteinyl Leukotrienes (CysLT)

Mast cells are tissue-resident cells. The number of mast cells in bronchial biopsies is higher in asthma than in healthy individuals [31], and it correlates with airway ECM thickness [195]. Mast cell number is increased in fibrotic disease and thus may play an important role in the development of fibrosis [196–199]. In asthma, mast cells are present in the ASM layer, which associates with the severity of the disease [200–202]. Mast cells function in allergic asthma is particularly important following the development of the adaptive T2 immune response that culminates in the production of antigen-specific IgE. Mast cells produce surface high-affinity receptors for IgE (FcεRI) and degranulate by cross-linking of the antigen-IgE complexes attached to FcεRI (reviewed in Ref. [203]) [204]. In mucosal and connective tissues, degranulating mast cells release a long list of preformed and newly produced mediators, including histamine, tryptase, chymase, LTC4, LTB4, PAF, PGD2, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-13, IL-8, IL-16, GM-CSF, MCP, RANTES,

eotaxin, TGF-β1, FGF2, nerve growth factor (NGF), VEGF, and PDGFA, the latter of which being a chemoattractant and mitogenic for fibroblasts (reviewed in Refs. [203, 205]) [206]. Tryptase stimulates fibroblast proliferation and the release of type I collagen production by fibroblasts via TGF-β1 [207–209]. Mast cell and ASMC interaction lead to tryptase-induced ASMC proliferation, activation, and ASMC production of TGF-β1 that enhances their contractibility [210, 211]. Besides tryptase, the reason for the tight association between mast cells and fibrosis is their release of multiple other potential profibrotic factors, such as TNF-α, FGF2, and IL-1β, as well as their interaction with fibroblasts [212], which can lead to increase fibroblast contractility [213]. In addition, mast cells activated via FcεRI also release amphiregulin (AREG), a ligand for the EGF receptor, which increases mucin gene expression in epithelial cells and fibroblast proliferation [214, 215]. Mast cells also promote Th2 cell development due to their secretion of the T2 cytokines, IL-4 and IL-13 [216], and mast cell-derived histamine enhances IL-13 expression in murine T helper-2 lymphocytes via JAK-STAT dependent pathways [217].

Along with eosinophils, neutrophils, and basophils, mast cells are an important source of arachidonic acid products, including cysteinyl leukotrienes (CysLT) [218, 219]. CysLT are powerful bronchoconstrictor agents and promote mucus production and leukocyte inflammation [220]. CysLT are issued from the activation of phospholipase A2 (PLA2), which hydrolyses arachidonic acid (AA) and activates 5-lipoxygenase (5-LO); CysLT are chemoattractants for immune cells and promote eosinophil survival [221–225]. CysLT also favor T2 versus the T1 immune response [226–228]. Furthermore, CysLT activate alveolar macrophages to release profibrotic factors, such as IL-6, FGF, and MMP [229–232]. CystLT receptors are expressed on ASMC and CysLT trigger ASMC migration, contraction, and proliferation alone or associated with EGF [233–237]. Finally, CysLT increase fibroblast chemotaxis, proliferation, and myofibroblast differentiation and activation [238–243]. Therapeutics targeting the CystLT pathways reduce eosinophilia and tissue remodeling and have shown benefits in asthma and airway inflammation [244–248].

Development of Memory T Cells and B Cells by Dendritic Cells and Lymphocytes

Memory T Cells in Asthma

The three different kinds of adaptive immune responses according to the T lymphocyte-generated profile of cytokines are T1, T2, and T17, which are all three dampened by the T-regulatory cells. The main producers of cytokines and drivers of the different immune responses are the polarized memory CD45RO+CD4+ helper T lymphocytes, which are called, type 1 T helper (Th1), type 2 T helper (Th2) and type 17 T helper (Th17) [249–251]. Th1, Th2, and Th17 are the T lymphocytes that mainly define the T1, T2, and T17 immune responses, respectively. Th1 is characterized by the T-box transcription factor (T-bet) and produces the cytokines, IFN-γ, and IL-2; Th2 displays the transcription factor, GATA3 and produce IL-13, IL-4, IL-5, and IL-9; while Th17 produce RORC2, IL-17A and IL17C. The other forth

main CD4+ cell type, composed of the T-regulatory (Treg) cells express Forkhead box P3 (FOXP3) and the anti-inflammatory cytokines, IL-10 and TGF-β. It is, however, important to know that these T-cell populations are more heterogeneous and display plasticity, changing from one type to another type. In addition, these definitions hide more complex situations since, for instance, IL-17A can be produced by FOXP3+ cells [252], and differentiated memory CD4+ T lymphocytes can produce both IL-17A and IL-4 [253]. Other CD4+ T cells called type 0 T helper (Th0) can produce both IL-4 and IFN-γ while the naïve CD45RA+CD4+ T lymphocytes have not encountered a cognate antigen, and thus, they produce low amounts of cytokines. Usually, the T1 response protects against infections from bacteria and viruses, the T2 response protects from parasitic infections and enhances the humoral response (including IgE production) [254], while the T17 response has some anti-infection properties, and it is present in autoimmune diseases and tumors.

The development of a certain type of adaptive immune response is strongly regulated by the persistent cytokine environment. For instance, inhalation of an antigen in mice displaying active and persistent airway T2 inflammation leads to T lymphocyte activation, while in naïve mice, it induces tolerance rather than activation [255]. In agreement, T2 cells differentiate following antigen presentation by DC and the presence of IL-4, while T1 cells develop during antigen presentation and the presence of IL-12 and IFN-γ. The exact cocktail of cytokines required to generate Th17 during antigen presentation remains uncertain but often include IL-1β or α, IL-23, IL-6, and IL21. The increased production of IL-17A from human memory CD4+ T cells usually requires IL-1β or α plus IL-23 [256].

CD8+ T cells or cytotoxic lymphocytes are critical for the defense against intracellular pathogens and the elimination of tumor cells. The cytotoxic activity of CD8+ T cells is particularly important to achieve viral clearance in the lung. Like CD4+ T cells, CD8+ T cells produce cytokines (e.g., IFN-γ and TNF), but they are mostly known for their production of T1 cytokines and toxic proteins (granzyme B and perforin) that kill infected cells and cancer cells. While APC (DC and macrophages) use their major histocompatibility complex class II (MHC-II) to present antigens to CD4+ T cells, CD8+ T cells recognize an antigen via the MHC-I. Co-stimulation during antigen presentation is critical for the development of effector and memory CD8+ T cells (i.e., OX40/OX40L), as well as the presence of cytokines such as common γ-chain cytokines (IL-2, IL-7, and IL-15). Importantly, while CD8+ T cells are predisposed to produce T1 cytokines (i.e., IFN-γ), they can also polarize into T2-producing lymphocytes (IL-13, IL-5, and IL-4) when in a T2 environment [257–261]. These T2 CD8+ T cells have been identified in human individuals including in patients with atopic asthma [262], yet it is uncertain whether the T2 CD8+ T cells can remain long-life memory lymphocytes [263].

Although the role of T1 IFN-γ+ CD8 and CD4 T lymphocytes in asthma remains under investigation, the T1 immune response has been observed particularly in severe asthma [264–267]. IFN-γ and IFN-γ-producing Th1 cells are present in the airways in asthma [268–270]. Whereas IFN-γ is known to antagonize the T2 immune response [271], it has also been shown that IFN-γ-producing Th1 cells

caused severe airway inflammation, principally via activation of macrophages/monocytes, and did not reduce AHR during a T2 immune response [272]. In another study, the transfer of both Th1 and Th2 cells before an allergen challenge resulted in the recruitment of both Th1 and Th2 cells and rapid eosinophilic inflammation in the airways [273]. In any case, the presence of T1 IFN-γ+ CD8 and CD4 T memory lymphocytes in asthma is likely reminiscent of repeated viral and bacterial infections that are a major cause for asthma development and exacerbation [274, 275].

Memory B Cells in Asthma

B cells are the central generators of humoral immunity to protect against pathogens and eliminate unwanted elements that can bind to an antibody. While T cells distinguish between self-antigen versus nonself-antigen with its T-cell receptor (TCR), a B-cell does so by using its immunoglobulin (Ig) B-cell receptor (BCR). B cells are antibody factories that produce IgM and can further class switch into IgG- or IgE-producing cells. Antigen-specific T-cell-dependent IgG+ B cells develop in germinal centers due to isotype-switched recombination, somatic hypermutation, and affinity maturation and migrate to bone marrow as high-affinity memory B cells or long-lived antibody-secreting plasma cells. B cells recognize either small soluble antigens directly via their BCR or larger antigens via a presentation by a professional APC. In addition, during the interaction with T cells, B-cell activation implicates CD40/CD40L and ICOS/ICSOSL connections, MHC class II presentation of the antigen by B cells to T cells, and the presence of cytokines, such as IL-4, IL-21, and IFN-γ. T-cell-generated IL-9 participates in the development of memory B cells [276, 277], while terminally differentiated plasma cells need pro-survival factors such as IL-6 and hyaluronic acid [278]. The strength of the interaction during cell-cell contact is a factor that determines the production of either memory B cells or plasma cells [279].

Allergy is characterized by the production of allergic-specific IgE+ B cells. The recombination switch from IgM to IgE is mainly initiated by B-cell interactions via CD40/CD40L and CD28/CD80 (or CD86) with IL-4- and IL-13-producing T cells during the presentation of allergen by DC. Notably, other factors produced by APC and neutrophils such as BAFF and APRIL also facilitate the IgE isotype switching [280]. The cross-linking of the allergen/IgE complex to FcεRI on mast cells (and basophils) and DC lead to the rapid release of inflammatory factors and to internalization of the allergen followed by its presentation to T lymphocytes, respectively. IgE also binds to B cells and DC via the low-affinity IgE receptor (CD23), which permits the uptake of the allergen and its presentation to T lymphocytes to augment the immune response. Memory B cells are long-lived cells present in circulating blood for decades. Under new exposure to the same antigen, memory B cells can quickly proliferate and differentiate into antibodies-secreting plasma cells. While the existence of memory IgE+ B cells remains controversial, it is however proposed that specific IgE-secreting B cells may be quickly generated by T2 cytokines-activated long-lived memory IgG+ B cells (reviewed in Refs. [281, 282]).

Role of Dendritic Cells

Antigen-presenting cells, such as DC, are part of a heterogeneous population [140, 283] located at mucosal surface, across the epithelial barrier, and in the subepithelial layer, with a key role in connecting the innate with the adaptive immune response. DC are significantly better than other antigen-presenting cells to differentiate naïve T cells into effector T cells [284]. After uptaking inhaled antigens, mucosal matured DC migrate to lymph nodes to present antigens to naïve T cells, which differentiate into polarized CD4+ T lymphocytes [285–287]. DC interactions with naïve lymphocytes via Class II MHC and co-stimulatory surface accessory molecules will activate CD4+ T lymphocytes toward a more or less polarized Th-1, Th-2, Th-17, and T-regulatory lymphocyte phenotype, depending on the cytokine environment, the route, the form and the antigen dose [287–292]. Generally, the stronger is the co-stimulation during DC/T lymphocyte interaction, the most likely the response will skew toward T1 versus T2, which can also be achieved by favoring the interaction of the T-cell CD28 marker with B7.1 (CD80) versus B7.2 (CD86) [293, 294]. However, in asthma, DC isolated from the lungs seem to be potent inducers of a T2 immune response [295, 296], and myeloid DC preferentially skew the immune response toward Th2 [295]. In a mouse model, a DC subset can present antigen to activate Th2 cells up to 5 weeks after antigen challenge, explaining the occurrence of chronic Th2 airway inflammation [297]. The numerous other important co-stimulatory surface molecules interacting during the antigen presentation of DC to T lymphocytes are CD2/LFA-3, ICAM-1/LFA-1, OX-40/OX40L, ICOS/ICOSL, CD27/CD70, CD30/CD30L, 4-1BB/4-1BBL, HVEM/TNFSF14, and GITR/GITRL [298, 299]. Allergen challenges trigger the production of progenitors for DC [76], and in asthma, airway DC are increased in number, and their activation status, as measured by cell surface class II MHC molecules and Fc epsilon RI-alpha (FcεRI), is higher [300–302]. DC activation is partially induced by locally produced CSF-1, GM-CSF, and the interaction of DC with T cells via CD40-CD40 ligands [303, 304]. Studies have shown the link between DC and tissue fibrosis. For instance, the IL-10-producing DC is part of the tolerance process following exposure to antigen, and they reduce cardiac inflammation and fibrosis [305, 306]. CD209+ DC are associated with fibrosis in the heart [307], and accumulation of DC is found in the lung fibrotic area and BALF in idiopathic pulmonary fibrosis (IPF) [308, 309].

The Role of T Cells, B Cells, γ/δ T, NK, and NKT Cells in the Development of Memory Lymphocytes

The development of the adaptive immune response is strongly regulated by the cytokine environment, with T2 and T1 cytokines favoring the development of Th2 and Th1, respectively. With generally increased expression of T2 cytokines, most of the subjects with asthma are classified as T2 high (i.e., high IL-13 signaling) [310]. Of note, human B cells produce the receptor for IL-13 while T cells do not, indicating that IL-13 can play a role in the development of memory B cells but do not participate in the development of memory T lymphocytes [311]. Distinctively, the

IL-4 receptor is produced by both T and B cells. In asthma, CD4+ T helper cells are increased in the airways and expressed activation markers [109, 270]. In the airways, the production of T2 cytokines (IL-4, IL-5, and IL-13) co-localizes with T lymphocytes [312], adding to compelling evidence that CD4+ T cells are the main constitutive source of T2 cytokines in the airways and thus are critical regulators of the adaptive immune response. Yet, via the secretion of IL-4 and IL-13, subsets of Class II MHC-expressing accessory cells, CD8+ T cells, γ/δ T cells and NKT cells can also promote the development of Th2 and IgE+ B cells [312–318]. T lymphocytes also produce IL-9 that participates in the development and activation of T17 lymphocytes and B cells, enhancing IL-4-mediated IgE and IgG by B cells [319, 320]. In addition to the production of T2 cytokines and IL-9, antigen-activated CD4, CD8 and γ/δ T cells can all become IL10- and TGF-β-producing CD25+ T-regulatory cells that downregulate the immune response [321–327]. Additionally, many of the unconventional and innate-like lymphocytes present in mucosal surfaces including γ/δ T cells and NKT produce IL-17A and IL-22 [328–331]. Although only representing <2% of T lymphocytes in BAL fluids in asthma, NKT cells respond to both lipids presented by APC via CD1d and cytokines to produce T2 and T17 cytokines [332, 333]. Indeed, as for the CD4+ T lymphocytes, NKT cells are a source of IL-17A and IL-22 via stimulation of DC-derived IL-1β and IL-23 [330, 334]. NKT cells also produce IFN-γ [335], and they respond to IL-25 and IL-33 to produce T2 (IL-4, IL-13) and T1 (IFN-γ) cytokines [336–339]. Besides NKT cells, NK cells can secrete high amount of IFN-γ [340], and CD161+CD3− NK cells produce IL-17A [341]. Another unconventional T lymphocyte type, the *mucosal-associated invariant T* (MAIT) cell recognizes microbial metabolites via the MHC class I-related MR1 and produces T1 (IFN-γ, IL-12), T17 (IL-17A, IL-23) and T2 (IL-4, IL-13) cytokines [342, 343]. Like NKT cells, MAIT cells can be activated by IL-1β and IL-23 to produce IL-17A, but unlike NKT cells, MAIT cells are in fact abundant in human tissues [344]. Antigen-activated MAIT cells also promote B cells and DC activation via CD40L [345]. Notably, it has been reported that the number of airway MAIT cells appears associated with asthma severity [346], and the number of IL-17-producing MAIT cells are positively correlated with severe asthma exacerbation [347]. Therefore, although the primary role of the unconventional T lymphocytes is to defend the host against pathogens, they also actively participate in the development of the adaptive immune response.

The development of the adaptive immune response described above is summarized in Fig. 1.

Role of Adaptive Immunity on Remodeling

In models of lung injury, recruitment and activation of inflammatory cells precede fibrotic changes [348, 349], suggesting a cause-effect relationship between inflammation and tissue remodeling. In this part of this chapter, we will review how the cells and the products of the adaptive immune response impact tissue remodeling in asthma.

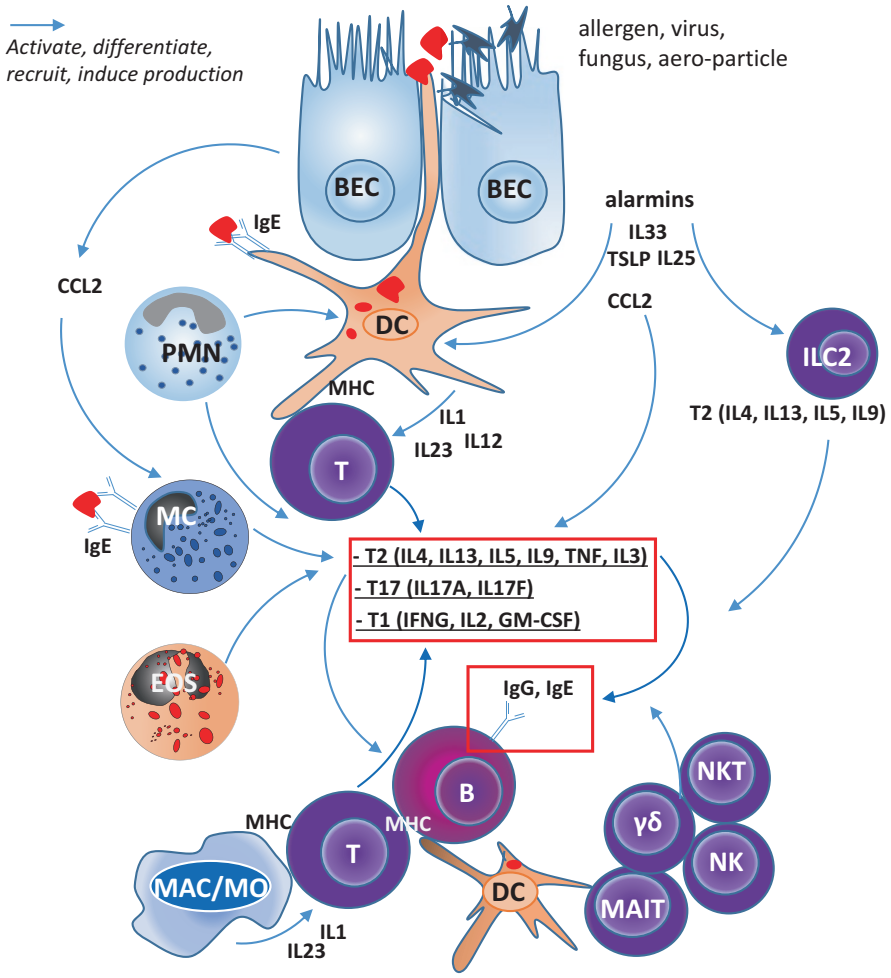

Fig. 1 Development of adaptive immunity in asthma. Adaptive immunity is composed of memory B and T lymphocytes. The different types of adaptive immune responses (T2, T17, and T1) are defined by the profile of cytokines generated by the T lymphocytes (T) and by the type of specific antibodies produced by B lymphocytes (B) as shown in the red rectangles. The fourth subset of T lymphocytes, the T-regulatory cells, produce IL-10 and TGF-β, and inhibit the development of the other three subsets, T1, T2, and T17. The profile of cytokines present in the environment will support the development of its own kind. For instance, the T2 cytokine, IL-4, will favor the development of T2 lymphocytes while the T1 cytokine, IFN-γ, will support the development of T1 lymphocytes. Following interaction with environmental factors, including allergens, microbes, and other aero-particles, the bronchial epithelial cells (BEC) release cytokines, such as the innate cytokines thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 (IL17B), which are important activators of the mucosal surface-enriched innate lymphoid cells-2 (ILC2) to produce IL-13, IL-4, IL-5, and IL-9. Through the release of these type-2 (T2) cytokines, ILC2 act directly on IgE production and the development of the type-2 adaptive immune response. In addition, in an ILC2-independent manner, the BEC-derived innate cytokines also have a direct role in promoting a T2 adaptive immune response by activating dendritic cells (DC) when presenting antigen to antigen-specific T lymphocytes via the major histocompatibility complex (MHC). Furthermore, BEC also

Adaptive Immunity and Fibrosis

T2 Adaptive Immunity

It is well-known that subjects with allergic asthma express high levels of type-2 cytokines in their airways compared to nonasthmatic subjects [350]. It has been proposed by Holgate et al. that impaired epithelial repair in a T2 environment leads to myofibroblast activation, and excessive ECM deposition amplifying airway remodeling in asthma [351]. The T2 transcription factor, GATA3, enhances pulmonary fibrosis in a bleomycin mouse model [352]. Along with TGF-β, among the T2 cytokines, IL-13 predominates in its contribution to the pathophysiology of fibrosis [353]. In allergic asthma, IL-13 level is elevated in the airways compared to control [354–356], and the capacity of cord blood CD4+ T cells to produce IL-13 is a predictor for the development of atopic diseases [357]. IL-13 receptor is composed of the two subunits IL-13Rα1 and IL-4Rα, which is also a subunit of the IL-4 receptor. Presaging of the critical role of IL-13 in tissue remodeling, the IL-13 receptor is expressed on fibroblasts, ASMC, and BEC [358, 359]. The fibrotic response to IL-13 is concomitant with increases MMP and cathepsins that regulate matrix deposition [360]. Unlike HBF from healthy controls, HBF from patients with asthma responds to IL-13 to produce α-SMA and collagen type-1 (COL1A2) downstream of MMP-2 and TGF-β1 [361]. IL-13 augments TGF-β1-induced TIMP-1 expression in primary human airway fibroblasts via SMAD phosphorylation [362]. In an inducible transgenic mouse model, overexpression of lung IL-13 induced eosinophil accumulation in the airway and airway fibrosis, as examined by histology [353]. In the same model, IL-13 leads to prolonged airway inflammation, including eosinophils, neutrophils, lymphocytes, and macrophages, and persistent collagen deposition, weeks after induction of IL-13 [363]. Conversely, a neutralizing anti-IL-13 reduced AHR, subepithelial collagen deposition, and mucus production in an OVA

Fig. 1 (continued) produce CCL2, which attracts T lymphocytes, favors T2 development, and activate the release of T2 cytokines by mast cells. The antigen-presenting cells (APC), DC, macrophages (MAC) and monocytes process and present antigens to T lymphocytes via MHC-II and MHC-I to differentiate the lymphocytes into T1, T2, or T17 lymphocytes. APC secretion of IL-1 and IL-23 favors T17 differentiation, while their secretion of IL-12 favors T1 development. Similar to conventional CD4+ and CD8+ T lymphocytes, activated γδ T lymphocytes, natural killer (NK) cells, NK-T lymphocytes, and mucosal-associated invariant T (MAIT) cells also produce pro-T1, T2, and T17 cytokines and thus influence the development of the adaptive immune response, including the production of antibodies. The granulocytes, neutrophils (PMN), eosinophils (EOS), and mast cells (MC) release numerous cytokines and growth factors that directly or indirectly via APC control the T1, T17, and T2 immune responses. The release of these cytokines and other factors by tissue-resident MC is induced by the cross-linking of the complex IgE/antigen with MC surface FcεRI. B cells recognize either small soluble antigens directly or larger antigens via a presentation by a professional APC. During the interaction with T cells, B cells present antigens to T cells, and they are activated to produce antibodies in the presence of cytokines, such as IL-4 and IFN-γ. T2 cytokines enhance the humoral response leading to the production of IgE by B lymphocytes, and cross-linking of the complex IgE/antigen with DC surface FcεRI leads to the antigen internalization and presentation to T lymphocytes

mouse model [364]. IL-13 stimulation also leads to reduced production of prostaglandin-E2 (PGE2), a prostaglandin that blocks TGF-β-induced effects on fibroblasts [365] as well as to induced collagen contraction by activated fibroblasts [366]. IL-13 upregulates and activates TGF-β1 [367, 368], and it stimulates the proliferation of myofibroblasts via signal transducer and activator of transcription 6 (STAT6) [369]. Subepithelial fibrosis observed in IL-13 transgenic mice is due in part to MMP-9-dependent activation of TGF-β [370]. The innate cytokine, IL-33 amplifies IL-13-induced airway macrophages differentiation toward M2 [371, 372], which produce the profibrotic TGF-β and increase eosinophil recruitment via CCL11 production [148]. Finally, adenosine is the product of the dephosphorylation of adenine nucleotides released from damaged cells and is elevated in blood and airways in asthma [373, 374]. In vivo, IL-13 induces high levels of adenosine and decreases adenosine deaminase (ADA) activity, an adenosine inhibitor which reduces IL-13-induced subepithelial fibrosis in mouse [375].

The cellular sources of IL-13 and IL-4 are mostly identical, and due to their common receptor subunit, the two T2 cytokines have often been examined simultaneously. As for IL-13 and conversely to IFN-γ, IL-4 is typically characterized as a profibrotic cytokine due to IL-4 ability to increase collagen production by fibroblasts [376, 377]. A study by Liu et al. showed that IL-4 and IL-13 increase collagen contraction by human fibroblasts but do not directly activate fibroblasts to produce TGF-β1 and fibronectin [366]. Instead, IL-4 and IL-13-induced profibrotic molecules, such as TGF-β, may occur as a result of epithelial cell activation, which was inhibited by IFN-γ [378, 379]. Besides, IL-4 and IL-13 have additive effects with oncostatin M (OSM) to increase both STAT3 phosphorylation in fibroblasts and fibroblast-mediated collagen gel contraction [380]. IL-4 and IL-13 induce human lung fibroblast-myofibroblast transition as evaluated by induction of α-SMA production through c-jun NH(2)-terminal kinase (JNK) signaling pathway [381]. In another study, both IL-4 and IL-13 increase the expression of α-SMA and collagen-III in human primary lung fibroblasts [382]. Doucet C et al. and others showed evidence that activation of fibroblast with IL-4 and IL-13 led to enhance proliferation, upregulation of cell surface adhesion molecules (integrin and vascular cell adhesion molecule 1 [VCAM-1]) as well as increase production of inflammatory cytokines and chemokines, such as IL-6, GM-CSF and monocyte chemoattractant protein 1 [MCP-1 aka CCL2] [383–385]. Finally, as indicated above, for IL-13, IL-4-activated fibroblasts also release CCL11 [379], a key chemokine for eosinophil recruitment into lung tissue. Thus, both IL-13 and IL-4 trigger intracellular signaling in fibroblasts, yet the effects of these T2 cytokines on fibroblast activation and fibrosis appear to occur partially downstream of MMP, TGF-β, adenosine, and increased granulocytes and macrophages recruitment and activation.

IL-5 is another T2 cytokine produced by memory CD4+ T lymphocytes. However, unlike for IL-13 and IL-4, the IL-5 receptor (IL5Rα) is almost exclusively produced by eosinophils, mast cells, and basophils [386, 387], and thus IL-5 cannot have a direct effect on fibroblasts. In murine models, IL-5 from CD4+ T lymphocytes is essential to develop eosinophilia [388]. In asthmatic subjects, a segmental

bronchoprovocation with an allergen (SBP-Ag) leads to the recruitment of blood CD4+ T cells to the airways [389], which after ex vivo activation, produces an increase among IL-5 compared to a challenge with saline [390]. In the airways, allergic asthmatic subjects have increased levels of both IL-4 and IL-5 associated with elevated IgE and eosinophilia, while nonallergic asthmatic subjects with elevated IL-5 also displayed enhanced eosinophilia [391]. Anti-IL-5 treatments in mild atopic asthma reduce ECM protein deposition (e.g., tenascin, lumican, and procollagen-III) in bronchial subepithelial basement membrane, probably due to decrease presence of TGF-β1 [392]. In addition, IL-5 enhances the presence of surface semaphorin-7A on eosinophils, which has a role in pulmonary and liver fibrosis and can increase the production of α-SMA in HBF [393–395]. Therefore, while IL-5 does not have a direct role on fibroblasts, it may have an indirect impact on fibrosis via eosinophil-derived toxic proteins, TGF-β, profibrotic other cytokines/chemokines as well as the capability for eosinophils to enhance the T2 response including IL-13 production in vivo.

T9 Adaptive Immunity

Although IL-9 is often described as a T2 cytokine, more differentially polarized IL-9-producer cells are named Th9 cells. As for Th2 cells, Th9 cells differentiate under T2 conditions, but they also require TGF-β and IL-2 [396]. Regarding the development of IL-9–producing CD4+ T cells, various cytokine signaling pathways, such as IL-2/STAT5, IL-4/STAT6, type I IFN/STAT1, and TGF-β/SMAD, have been reported to promote IL-9 production in CD4+ T cells [397]. Yet, the two types of cells (Th2 and Th9) remain closely related to each other [398]. In fact, many kinds of cells can produce IL-9, including Th17 cells, regulatory T cells, and other subsets of immune cells, such as ILC2, mast cells, and NKT cells [399, 400]. IL-9 is a pleiotropic cytokine that promotes the development of allergic diseases [399, 401]. IL-9 receptor is present on effector T cells, mast cells, and granulocytes [402–404]. IL-9 potentiates the effect of IL-4 on B cells to produce IgE [320], enhances IL-3-induced proliferation of mast cells, and increases mast cell production of IL-6 [405]. Inducible lung-producing IL-9 mice display a strong accumulation of airway eosinophils, mast cells, and lymphocytes [406], some of these functions being likely indirect effects [407]. The strong correlation between IL-9 mRNA expression level and number of eosinophils suggests a role in eosinophil recruitment and survival [408], but it may also be due to correlations between the expression of IL-9 and the T2 cytokines. IL-9 increases eosinophil differentiation in the presence of IL-3 and IL-5; and enhances the expression of IL-5Rα [409, 410]. In mouse, neutralization of IL-9 in a house dust mite allergen challenge led to reduced airway mature mast cells, TGF-β1, VEGF, and FGF2, and to enhanced lung function [404]. In an Alternaria alternata-induced airway remodeling mouse model, IL-9 overexpression led to further accumulation of collagen and fibronectin with increase eosinophilia, RANTES (eosinophil chemoattractant), and the profibrotic CTGF in the lung [411]. In sum, as for IL-5, it is likely that IL-9 augments lung fibrosis mostly indirectly via granulocyte and mast cell activation.

T17 Adaptive Immunity

Another important mediator involved in airway remodeling is IL-17A. IL-17A is produced by CD4+ T cells, particularly CD4+CD4RO+ and CD8+CD4RO+ memory T cells [412–414]. IL-17A signals via the multimeric IL-17RA and IL-17RC receptor, which is present on fibroblasts and T lymphocytes [412, 415, 416]. IL-17 has a major role in defense against infections, notably by inducing chemoattractant factors for neutrophils and macrophages [417, 418]. Excess IL-17 is associated with lung dysfunction, including excessive airway neutrophilia [419, 420]. For instance, in vivo, neutralization of IL-17 attenuates bleomycin-induced pulmonary fibrosis including collagen deposition, α-SMA expression, and activation of MMP-2, as well as T2 and T17 inflammation [421]. IL-17A is typically associated with a more severe, neutrophilic, and corticosteroid-resistant asthma phenotype [422, 423]. IL-17A is significantly increased in sputum samples and BALF from subjects with asthma compared to healthy individuals [424] and BAL cells after SBP-Ag [117]. In asthma, airway IL-17A and the T17 immune response expression levels correlate with the number of airway neutrophils [425, 426], but it also correlates with the presence of eosinophils [427, 428] and IL-5 expression level [425]. Both IL-17A and T2 cytokines are elevated in sera in severe uncontrolled asthma [429]. As for IL-5 and IL-9, a possible mechanism for IL-17A to increase fibrosis is through the activation of eosinophils to produce TGF-β1 [430]. However, IL-17A also acts directly on fibroblasts to produce TGF-β and collagens [431, 432]. In a mouse model, intranasal instillation of LPS plus ATP-activated DC led to a mixed T2 and T17 immune response with correlation between IL-17A production and airway remodeling [431]. In that same study, IL-17A stimulated mouse fibroblasts to release TGF-β and express collagen in vitro [431]. IL-17A also enhances the effects of IL-13 on gene expression in fibroblasts likely via heightened STAT-6 activation [433]. Additionally, IL-17A increases the production of IL-6, IL-11, and IL-8 by HBF [424], and both IL17A and IL17F enhance CD40L-induced collagen production by blood monocyte-derived fibroblasts [434]. In that latter study, IL17A augmented CD40L-mediated IL-6 production while IL17F increased VEGF and angiogenin [434]. IL-17A induces the production of the chemokine IL-8 from epithelial cells, endothelial cells, fibroblasts, and macrophages, leading to the recruitment of neutrophil granulocytes [435]. Therefore, there is evidence that the T17 cytokines have direct effects on fibroblasts to trigger fibrosis.

T-Regulatory Cells

In humans, Treg cells are typically defined as FOXP3-expressing CD4+CD25^{hi}CD127^{-} T lymphocytes. Naturally occurring Treg cells are generated in the thymus and play a crucial role in the maintenance of self-tolerance by cell-cell interaction [436–439]. Conversely, inducible or adaptive Treg cells are differentiated outside the thymus, probably due to low accessory molecule implication and the presence of TGF-β [440]. Inducible Treg cells express relatively more modest levels of FOXP3 and CD25 compared to the naturally occurring Treg, and they mediate immune suppression [440]. It is well-established that Treg cells produce large amount of IL-10 and TGF-β [441–444]. Treg cells suppress the activity of many different immune cells,

including T cells, B cells, NK cells, NKT cells and APC, by consuming IL2 and producing IL-10 and TGF-β. Both resting (CD45RA+) and activated (CD45RA−) Treg have immunosuppressive activity in vitro [445]. In bronchial biopsies from subjects with asthma, TGF-β1 is present in CD3+ lymphocytes [446], and TGF-β1 is produced by most immune cells [447]. TGF-β1 is an anti-inflammatory cytokine that reduces the activation of macrophages [448], the proliferation and generation of T lymphocytes [449], and the production of type-2 cytokines in T lymphocytes [450]. IL-10, mainly produced by macrophages and Treg cells, inhibits APC activity, T-cell proliferation and activation, and immune cell cytokine expression [451–457]. Treg cells limit lung collagen deposition and likely control tissue fibrosis [458–460]. In accordance with these studies, Treg depletion results in enhanced profibrotic gene expression level in skin tissue [461]. In a TGF-β-induced lung fibrosis mouse model, Treg cells inhibit fibrosis via suppression of FGF9 [462]. Treg cells can also reduce fibrosis by limiting CXCL12 production and, thus, fibrocytes recruitment to lung injury [463]. In asthma, the function of Treg cells seems reduced compared to normal [464–466], and successful immunotherapy (i.e., tolerance to allergen and reduction of symptoms) has been associated with increased Treg cell function [467, 468]. On the other hand, autocrine TGF-β-induced PDGF release by Treg directly activates lung fibroblasts; and the transfer of these Treg in vivo in mouse induced collagen deposition in the lung tissue in a noninflammatory condition [469]. All together, these studies suggest that the benefits of the functions of Treg cells on the reduction of inflammation in vivo dominates their potential induction of tissue fibrosis via TGF-β. Therefore, it seems fair to say that in an inflammatory disease such as asthma, Treg cells do not enhance fibrosis, but conversely, it inhibits fibrosis by controlling inflammation.

T1 Adaptive Immunity (IFN-γ)

Because T2 cytokines are profibrotic factors and IFN-γ enhances the T1 response at the expense of T2 development, it is logical to classify IFN-γ as an anti-fibrotic cytokine. Cell surfaced IFN-γ-enhanced IL-13Rα2, a decoy receptor for IL-13Rα1, reduces IL-13 activity [470, 471]. IFN-γ also strongly reduces T2 cytokine production by ILC2 [472]. In vivo, IFN-γ controls fibrosis in a bleomycin-induced lung fibrosis mouse model, likely by downregulating the expression of TGF-β and the procollagens [473, 474]. However, although IFN-γ decreases the synthesis of collagen by fibroblasts, in the same condition, collagen deposition in the matrix remained high and IFN-γ-activated fibroblasts displayed higher collagen receptor activity [475]. In addition, in another bleomycin mouse model, IFN-γ promotes lung inflammation and collagen accumulation [476]. IFN-γ enhances fibronectin expression level by fibroblasts [477]. In alveolar macrophages, IFN-γ increases the expression of PDGF-B [478], which disulfide-linked homodimer plays an important role in the wound healing process by recruiting fibroblasts, pericytes, and endothelial cells [479–481]. To make the dogma of IFN-γ anti-fibrotic activity more complex, CD4+ T cells that produce both IL-13 and IFN-γ have been identified in patients with pulmonary fibrosis [482]. In asthma, the expression of T2 markers in the airway remains positively correlated with IFN-γ expression, indicating the

concomitant presence of both T2 and T1 immune responses in a subset of patients [426]. Moreover, in subjects with uncontrolled asthma or severe asthma, high amount of IFN-γ in exhaled breath condensate and the elevated number of IFN-γ+CD4+ T cells in BAL fluid have been reported [266, 483]. Adoptive transfer of a Th1 clone in a mouse after allergen challenge, reduced the T2 response but increased the noneosinophilic inflammation, including the accumulation of mononuclear cells [484]. Therefore, the role of IFN-γ in fibrosis in asthma remains unknown. In a disease such as idiopathic pulmonary fibrosis (IPF), IFN-γ therapy was tested on end-stage patients who subsequently suffered from acute respiratory failure following IFN-γ treatment [485]. The lack of efficacy of IFN-γ to treat IPF was further confirmed in other studies [486, 487].

B Cells

Deficiency in CD19 results in diminished B-cell responses and reduce fibrosis in bleomycin-induced lung fibrosis, and in the same model, CD19 overexpression enhances fibrosis [488]. In another study, using that same mouse model, IL-6 deficiency in B cells and blockade of BAFF led to reduced lung fibrosis [489]. Confirming these data, in vitro, IL-6-producing B cells promote collagen secretion by fibroblasts [489]. In co-culture experiments, B cells induce α-SMA and collagen expression in human dermal fibroblasts [490], while B-cell depletion using a therapeutic anti-CD20 antibody ameliorates patients with systemic sclerosis [491]. As with Treg cells, regulatory B cells (Breg) produce TGF-β to potentially enhance fibroblast activation and tissue remodeling [489, 492–494]. As mentioned above, the primary function of B cells is to produce antibodies such as IgG and IgE. Allergen-induced cross-linking of FcεRI bound IgE on the surface of mast cells has a major role in allergic asthma and airway remodeling via mast cell degranulation of numerous factors, including pro-granulocytic cytokines, TGF-β1, FGF2, VEGF, and PDGFA. There is, however, little to no evidence of an effect of B cells and immunoglobulins on fibroblasts in asthma.

The role of the adaptive immune response in fibrosis, as described above, is summarized in Fig. 2.

Adaptive Immunity and ASM Activation

In a group of subjects with asthma and chronic persistent and intermittent airway obstruction (FEV_1 <70% and ≥70%, respectively), the concentration of sputum IL-13, IL-5, IL-12, and IFN-γ is correlated with the smooth muscle area determined

Fig. 2 (continued) recruitment of neutrophils (PMN) that are a major source of MMP, which in turn triggers the release of active TGF-β. Notably, T-regulatory lymphocytes (Treg) inhibit most of the immune responses upstream of fibrosis. B cells co-cultured with fibroblasts induce expression of αSMA and collagen by fibroblasts, possibly via B-cell release of IL6. Finally, the production of specific IgE by B cells leads indirectly to increase fibroblast activation by MC degranulation of profibrotic factors following cross-linking of surface MC FcεRI with the complex IgE/antigen

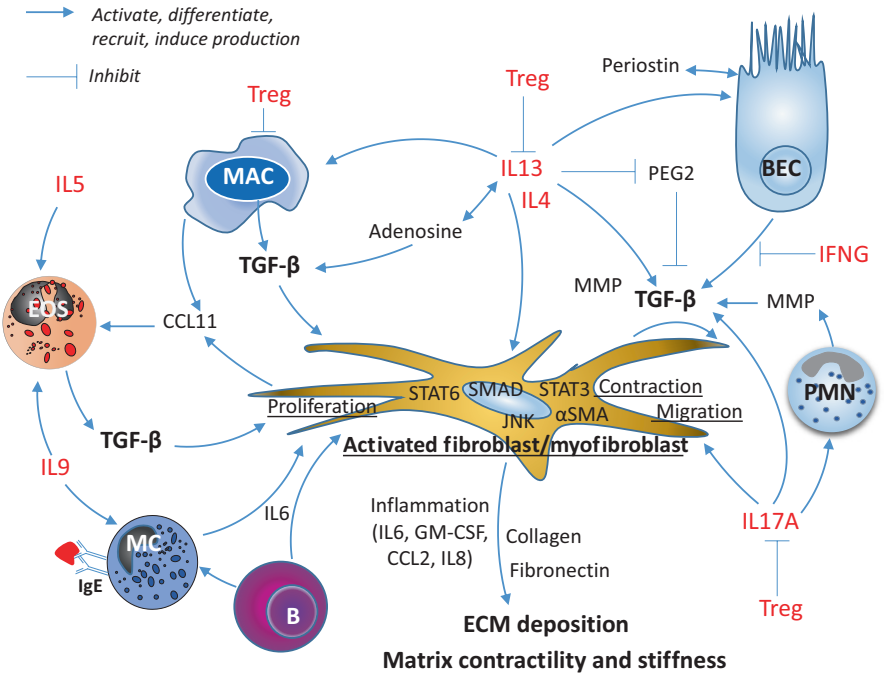

Fig. 2 Adaptive immunity in fibrosis. The fibroblast and its TGF-β-induced differentiated and α-smooth muscle actin (αSMA)-producing form, the myofibroblast, are responsible for lung subepithelial fibrosis, characterized by fibroblast hyperplasia, and increased contractility, the accumulation of extracellular matrix (ECM) proteins (e.g., collagens and fibronectin) and changes in the extracellular matrix biochemical properties (contractility, stiffness). Among the T2 cytokines, IL13 predominates in its contribution to the pathophysiology of fibrosis. Fibroblasts display functional IL13 receptors on their surfaces, and IL13 activates directly or indirectly through TGF-β, fibroblast proliferation, the production of alpha-smooth muscle actin (αSMA), and collagens via intracellular activation of STAT6 and SMAD signaling pathways. In addition, IL13 indirectly induces the production and the activation of the profibrotic factor, TGF-β through macrophages (MAC), MMP activities, and by inhibiting PGE2. IL13-activated macrophages also produce CCL11 that recruits TGF-β-producing eosinophils (EOS). Due to their common receptor subunit, IL4 possesses many similar functions as IL-13 on fibroblasts, and thus, studies have examined IL4 and IL13 functions concomitantly. IL4 and IL13 activate c-jun NH(2)-terminal kinase (JNK) and STAT3 signaling pathways in fibroblasts leading to αSMA production and fibroblast-mediated collagen contraction. Furthermore, IL4 and IL13 increase not only fibroblast proliferation but also their production of pro-inflammatory cytokines and chemokines. Finally, IL-4 and IL-13 activate epithelial cells (BEC) to produce both TGF-β, which in turn activates fibroblasts to produce collagens and fibronectin, and periostin that is part of the ECM. Notably, the induction of TGF-β in BEC by the T2 cytokines is tempered by the T1 cytokine, IFNG. The other main T2 cytokine, IL5, indirectly stimulates fibroblasts via eosinophils. Similarly, IL9 acts on fibroblasts via granulocytes such as EOS and mast cells (MC), and it enhances the T2-induced production of IgE by B lymphocytes, IL3-induced MC proliferation as well as the production of IL6 by MC. The receptor for the major T17 cytokine, IL17A, is present in fibroblasts. IL17A stimulates fibroblasts to produce TGF-β and collagen. IL17A enhances the effects of IL13 via STAT6 activation, and it increases the release of pro-inflammatory cytokines and chemokines (IL6, IL8) by fibroblasts. In vivo, IL17A has an indirect effect on fibrosis through its function on IL8 release by many airway cell types leading to the

in bronchial biopsies [495]. Interestingly, in that same study, the principal component analysis revealed that components that include IL-13, IL-12, and IFN-γ or IL-9, IL-17, and RANTES, were associated with chronic obstruction or intermittent obstruction, respectively. In vitro, contact of activated CD4+ T cells with ASMC induces ASMC proliferation [496]. Therefore, there is evidence on the role of lymphocytes and their products on the ASMC compartment in asthma.

T2 Adaptive Immunity and IL-9

T2-high asthma, as defined by the increased expression of IL-13 and IL-5 in the airway and the level of IL-13-responsive genes in BEC, is associated with increased AHR to methacholine and reticular basement membrane thickness, compared to T2-low asthma [497]. IL-13-deficient mice develop eosinophilia but fail to develop allergen-induced AHR [498], demonstrating the direct role of IL-13 on airway constriction. IL-13 is sufficient to induce AHR and enhance BAL eosinophil numbers and total IgE blood levels in naïve mice [353, 499]. Lack of IL-4 or IL-13 also reduced AHR and the presence of airway alpha-smooth muscle actin in a chronic allergen-induced mouse model [500]. IL-13 can induce AHR by direct effects on ASMC [501–503] or indirectly via STAT6 in BEC [504]. In vitro, IL-4 and IL-13-activated ASMC increase collagen contraction that is inhibited by PGE2 [366], and IL-13 increases human ASMC proliferation [505]. A possible mechanism for IL-13-enhanced ASMC proliferation is via the augmentation of surface CystLT receptors on ASMC and their interaction with LTD_4 [506]. Both CysLT and non-CysLT amounts are higher in BALF in subjects with asthma symptoms compared to controls [507], and both IL-13 and IL4 induce LT and their receptors [508], which are powerful bronchochonstrictor agents and further promote leukocyte inflammation [220]. Furthermore, IL-13 increases the production of the complement component C3 (C3) by BEC, which cleaved product, C3a causes ASMC contraction in asthma [509, 510]. Both IL-13 and IL-4 enhance histamine- and LTD_4-induced human ASMC contraction and Ca^{2+} mobilization, in vitro [511], while IL-13, but not IL-4, reduces β-adrenoceptor-induced relaxation of ASMC via MAP kinase signaling [503, 512]. Finally, in vivo, IL-13 likely increases bronchoconstriction and CCL2 production in asthmatic subjects due to ASMC activation by IL-13-induced adenosine [375, 513].

In mice, lack of IL-5 leads to reduced peribronchial smooth muscle thickness after chronic administration of allergen [514]. In passively sensitized human airways, anti-IL5 therapies reduced histamine-induced AHR [515]. However, these effects of IL-5 on the smooth muscle are likely mostly due to the deletion or reduced IL-5-induced activation of eosinophils, mast cells, and basophils.

The receptor for IL-9 is expressed on ASMC, and it activates ASMC to release pro-eosinophilic and neutrophilic chemokine, CCL11, and IL-8 via ERK and STAT3 signaling [516–518]. To our knowledge, besides IL-9 effects on ASMC to release pro-inflammatory cytokines/chemokines, there is no evidence of IL-9 affecting ASMC migration, proliferation, or contractility, and thus having direct consequences on airway smooth muscle thickening or AHR.

T17 Adaptive Immunity

In vivo and in vitro, IL-17A enhances the effects of IL-13 on AHR [433], and Th17 transfer or IL-17A overexpression in an airway allergen challenge mouse model, increased methacholine-induced AHR [519]. Unlike IL-13 and IL-4, neither IL-17A nor IL-5 enhances histamine- and LTD_4-induced human ASMC contraction and Ca^{2+} mobilization, in vitro [511]. However, there is evidence that IL-17A can directly activate ASMC. ASMC express the receptor for IL-17A [520], IL-17A stimulates the production of IL-8 by human ASMC [521], and IL-17A synergizes with OSM to induce human ASMC-release of IL-6 and CCL2 [522]. In addition, T17 cytokines increase both ASMC proliferation [523] and the production of IL-17-induced growth-related oncogene (GRO) by ASMC, which promotes ASMC migration [524]. Kudo et al. have shown that in vivo, lack of Th17, but not IL-17A-producing γδ T cells, is associated with lack of AHR after allergen challenge in mouse [525]. In that same study, in vitro, IL-17A acted directly on ASMC to enhance methacholine-induced contraction of mouse tracheal rings and human bronchi through nuclear factor κ light-chain enhancer of activated B cells (NF-κB), ras homolog gene family, member A (RhoA) and Rho-associated coiled-coil containing protein kinase 2 (ROCK2) signaling cascade [525]. IL-17A-induced ASMC contractility was later confirmed by other studies [526, 527].

T1 Adaptive Immunity (IFN-γ)

In a mouse model, IFN-γ-producing CD4+ T cells are responsible for increased AHR following a chronic low-level allergen challenge [528]. Yet, in vitro, IFN-γ inhibits SMC activities, including ASMC proliferation and chemotaxis [529–531]. IFN-γ blocks spontaneous release of VEGF by ASMC and reduces T2- and TGF-β-augmented VEGF production [532]. While the role of IFN-γ on ASMC contractility has not been reported, it has been described that IFN-γ reduced normal human intestinal SMC contractility, motility and proliferation [533]. Therefore, because most of the in vitro studies identify an inhibitory function for IFN-γ on SMC, it is possible that the role observed on AHR in vivo, in the study by Kumar et al., did not occur via ASMC.

B Cells

In asthma, serum IgE level is associated with AHR [534]. ASMC express both a functional high-affinity receptor for IgE (FcεRI) [535] and the low-affinity IgE receptor (FcεRII; CD23) that are upregulated by IL-4, TNF-α, IL-1β, and GM-CSF [536, 537]. In ASMC, IgE triggers the production of IL-8 and eotaxin, two chemokines that recruit neutrophils and eosinophils, respectively; and following FcεRI upregulation on ASMC, IgE induces the release of T1 and T2 chemokines via MAPK, Akt, and STAT3, and intracellular calcium mobilization [535, 537]. Furthermore, IgE increases ASMC proliferation and their deposition of fibronectin and collagen through MAPK and STAT3 [538, 539]. It has also been reported that IgE-sensitized ASMC produces IL-13, which can activate ASMC in an autocrine way to augment AHR [512].

Human ASMC may also express FcγRI (CD64) and FcγRIIb (CD32), the latter of which possesses an immunoreceptor tyrosine-based inhibitory motif (ITIM) and its interaction with heat aggregated-IgG (ligand for CD32) leads to inhibition of IL-1-induced production of IL-6 and IL-8 [540]. Interestingly, activation in vitro of a SMC issued from a guinea pig, with the complex IgG/antigen leads to SMC contraction [541]. However, to our knowledge, studies on the potential role of a complex IgG/antigen on ASMC in asthma remain inexistent.

Interestingly, B cells, particularly regulatory IL-10+ B cells, appear to have a beneficial regulatory effect on AHR and airway collagen deposition as examined in allergen-challenged mouse models [542].

The role of the adaptive immune response on airway smooth muscle activation, as described above, is summarized in Fig. 3.

Adaptive Immunity and Mucus Production

Airway mucus is produced by BEC and submucosal glands and forms a gel layer on the epithelial surface to protect against external agents. Mucous gel is cleared from the lower airways as a result of its transportation by epithelial ciliated cells toward the oral cavity. Impaired mucus clearance causes mucus plug formation and airway obstruction [543]. Mucus is mostly composed of water, lipids, and proteins such as mucins [544]. MUC5AC and MUC5B are the main secreted mucin proteins in the airways, and they define the biophysical characteristics of the mucous layer [544]. MUC5AC is mostly secreted from airway epithelial goblet cells, while MUC5B is produced by mucous cells in the submucosal glands [545]. In asthma, the ratio MUC5AC:MUC5B is increased relative to that in healthy individuals, notably because of the significant increase in the number of goblet cells and MUC5AC production [546–548].

T2 Adaptive Immunity and IL-9

Compared to T2-low asthma, T2-high asthma is associated with an enhanced MUC5AC:MUC5B expression ratio [497]. IL-13, IL-4, and IL-9 can induce mucus production by human BEC in vitro [549–551], and murine studies have shown that IL-9, IL-4, and IL-13 have a role in goblet cell hyperplasia and mucin gene expression, including MUC5AC and MUC2 [552]. IL-9 induces mucus production in epithelial cells during injury repair [551]. However, while transgenic mice expressing IL-4 or IL-9 in the lung display increased expression of MUC5AC and levels of mucus glycoconjugates [553, 554], IL-4 or IL-9 deficient mice still produce mucus hyperplasia in vivo [407, 555]. In fact, although IL-4 and IL-9 can directly activate BEC to produce mucus, these cytokines may also do so indirectly via IL-13 in vivo [498]. For instance, the production of IL-9 in the lung can induce T2 cytokine production, including IL-13 which thereafter stimulates mucin expression in BEC [407, 549]. Therefore, IL-13 is usually seen as the major T2 cytokine to induce mucus production by BEC in asthma. IL-13 is sufficient to induce mucus

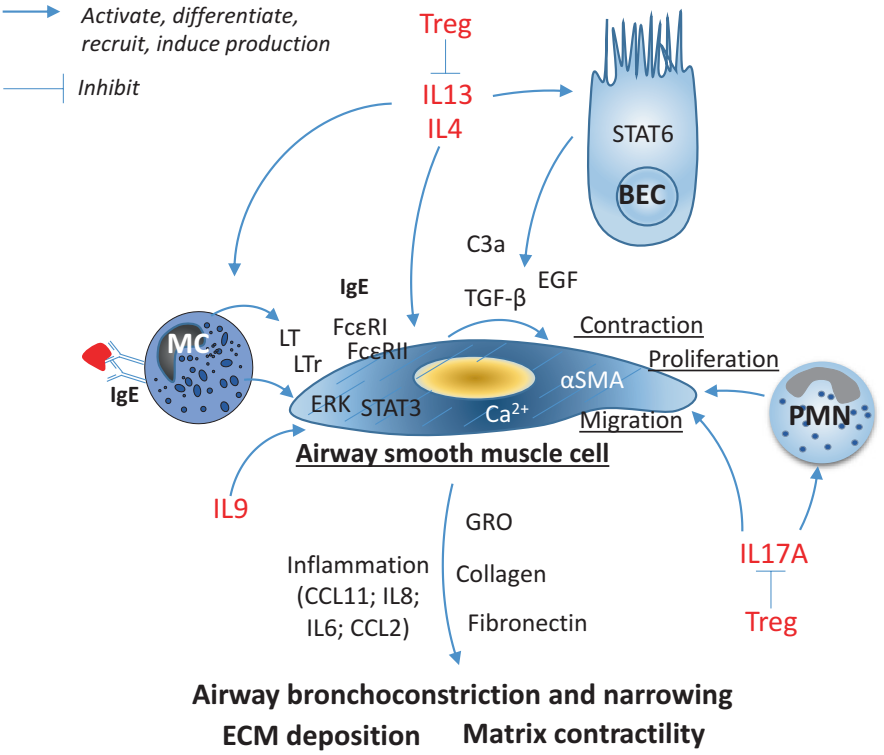

Fig. 3 Adaptive immunity in airway smooth muscle cell activation. Increased airway smooth muscle mass is a pathological feature of asthma and is a major cause for airway hyperresponsiveness, bronchoconstriction, and narrowing. In vivo, IL13 induces airway hyperresponsiveness (AHR) by direct effects on the airway smooth muscle cells (ASMC) or indirectly via activation of the STAT6 pathway in bronchial epithelial cells (BEC). In vitro, IL-13 increases ASMC proliferation directly or indirectly via the upregulation of the leukotriene receptors (LTr) on the ASMC surface. IL4 and IL13 enhance ASMC-induced collagen contraction, an event inhibited by PGE2. In addition, IL13-activated BEC augment the presence of TGF-β, EGF and C3a that lead to ASMC hypertrophy, production of alpha-smooth muscle actin (αSMA), contraction, and migration. In vitro, also, both IL13 and IL4 enhance human ASMC contraction and Ca^{2+} mobilization by the mast cell (MC) products, histamine, and LT, while cross-linking of surface MC high-affinity receptor for IgE (FcεRI) with the complex IgE/antigen induces the release of numerous activators of ASMC, including histamine, LT, and TGF-β. The receptor for IL9 is expressed on ASMC and IL9 activates ASMC to release pro-eosinophilic and neutrophilic chemokine, CCL11, and IL-8 via ERK and STAT3 signaling. ASMC also express the receptor for IL-17A. In vitro, IL17A promotes ASMC migration, proliferation, contraction, and it stimulates ASMC production of IL8, IL6, CCL2 and growth-related oncogene (GRO). In addition, downstream IL17A and the presence of the chemokine IL8, activated neutrophils enhance ASMC proliferation through the release of exosomes. ASMC express both FcεRI and the low-affinity IgE receptor (FcεRII) that are upregulated by IL-4. Via these receptors, IgE triggers intracellular calcium mobilization, and the production of IL-8, CCL11, T1, and T2 chemokines via MAPK, Akt, and STAT3. Finally, IgE increases ASMC proliferation and their deposition of fibronectin and collagen through MAPK and STAT3. T-regulatory lymphocytes (Treg) inhibit the adaptive T2 and T17 immune responses

production in naïve mice [353, 499], and in an inducible transgenic mouse model, overexpression of lung IL-13 induced mucus cell metaplasia [353]. Conversely, a neutralizing anti-IL-13 significantly reduces mucus production in an allergen challenge mouse model [364], and in many other studies using mouse models, blockage of IL-13 signaling demonstrates that IL-13 is essential for mucus production [499, 556–560]. In vitro, IL-13 increases the ratio of goblet cells:ciliated BEC [561] and BEC proliferation in an EGFR/EGFR ligand (TGFα or epigen)-dependent manner [562, 563]. Furthermore, IL-13 induces increased mucus secretion by BEC through enhanced expression of a Ca^{2+} activating chloride channel, CLCA1 [564], and STAT6 signaling [504]. Importantly, demonstration of direct induction of mucus production in BEC and globlet cell hyperplasia by IL-13 were also reached using human BEC cultured at air-liquid interface (ALI) [565–569], a model that recapitulates the characteristics of the bronchial epithelium in vivo. Additionally, long-term activation of human BEC in ALI cultures with IL-13 increases MUC5AC production [570].

In addition to augmenting mucus production by BEC, IL-13, and IL-4 have broader effects on BEC and the bronchial epithelium. For instance, IL-13 can damage the epithelial barrier by inducing apoptosis in human epithelial cells [382] and by impairing tight junctions [571, 572]. IL-13 and IL-4 also increase fibrosis via BEC by enhancing their production of TGF-β2, leading to myofibroblasts activation to produce α-SMA and ECM [378, 379, 570]. Note that these effects from the T2 cytokines on TGF-β2 in BEC are attenuated by IFN-γ [378]. Additionally, one of the main T2-response genes in BEC, periostin, is an ECM protein and a component of subepithelial fibrosis in bronchial asthma [573–575]. Periostin is used as a T2-high asthma biomarker [576, 577] and it predicts lung function decline in asthma [578]. Periostin plays a role in the recruitment of inflammatory cells (eosinophils, neutrophils, macrophages) and, thus, indirectly, lung fibrosis [579–581]. BEC-derived periostin also functions directly on BEC themselves as well as fibroblasts to activate MMP, TGF-β, and consequently type 1 collagen production [582]. In addition, periostin binds type 1 collagen and fibronectin and can then participate in the stiffness of the ECM mass [583].

T17 Adaptive Immunity

In vivo, IL-17A enhances the effects of IL-13 on mucus production [433]. Lung epithelial cells express both the IL-17 and IL-22 receptors [584, 585]. Interestingly, comparable to IL-13, IL-17A increases the expression of MUC5AC by nasal epithelial cells and promotes goblet cell hyperplasia [586]. Conversely, in a study, where all three types of cytokines, T2 (IL-13), T1 (IFN-γ), and T17 (IL-17A), were used on nasal epithelial cells cultured at ALI, it was shown that both IFN-γ and IL-13 increased the number of goblet cells and expression of MUC5AC, but IL-17A only augmented MUC5B production [587]. Conversely, a previous study had demonstrated that IL-17A increased the expression of both mucin genes, MUC5B and MUC5AC, in differentiated human BEC in vitro, partially via an autocrine role of IL-6 and JAK2 signaling [588]. To support that study, Pezzulo et al. more recently

reported goblet cell hyperplasia in IL-17-activated human BEC cultured at ALI [569].

Besides IL-17A's role in mucus production, IL-17A has other potential detrimental functions on the epithelium that would lead to profibrotic events. For instance, IL-17A promotes epithelial-mesenchymal transition (EMT) of mouse alveolar epithelial cells and their production of collagen in a TGF-β-dependent manner [421]. In addition, through PIK3CA, IL-17 inhibits autophagy in alveolar epithelial cells, which may cause collagen accumulation, and epithelium death and amplify IL-1β/IL-17-induced lung pathology in a vicious circle [421, 589–591].

Thus, there is evidence of the direct role of IL-17A on BEC to produce gel-forming mucin proteins and to amplify airway fibrosis.

B Cells

Human AEC express CD23 and FcεRI, which activation by IgE leads to the production of ET-1 and the release of 15-hydroxyeicosatetraenoic acid (15-HETE), respectively [592, 593]. Downstream the stimulation of BEC by IgE, ET-1 can activate ASMC and increase bronchoconstriction, whereas arachidonic acid-derived 15-HETE that is typically upregulated by T2 cytokines [594], has anti-inflammatory properties [595, 596] and is associated with airway fibrosis in asthma [597]. 15-HETE reduces AHR to methacholine [598] and, in vitro, 15-HETE reduces the production of MUC5AC in a bronchial epithelial cell line [599]. This latter study, however, disagrees with a previous study where 15-HETE enhanced MUC5AC expression in IL-13-activated primary AEC [600]. Therefore, it is possible that IgE induces mucus production by BEC via 15-HETE, yet the role of IgE on BEC remains ill-defined.

The role of the adaptive immune response on airway mucus production as described above is summarized in Fig. 4.

Adaptive Immunity and Fibrin Clots and Angiogenesis

Fibrin Clots

Fibrin clotting is the end-product of the coagulation cascade, and it requires the activity of numerous proteins that are part of this cascade. Exaggerated pro-coagulation activity or impaired fibrin degradation in the airways has been observed in asthma, particularly in severe asthma, and is associated with the number of inflammatory cells [601–606]. Pro-coagulation factors are increased in the airways after SBP-Ag in patients with asthma and they correlate with eosinophil inflammation [607, 608]. In an allergen challenge rat model, the amount of the pro-fibrin accumulation protein, plasminogen activator inhibitor 1 (PAI-1), is augmented in blood and the airways [609], confirming a pro-coagulation activity after allergen challenge. In vitro, OSM increases the level of fibrinogen while IL-4, IL-13, and IL-10 decrease it [610]. In nasal epithelial cells, the anti-fibrin deposition protein, tissue plasminogen activator (tPA) level is decreased by IL-13 and IFN-γ with an additive effect when IL-13 and IFN-γ are used together, indicating that T1 and T2

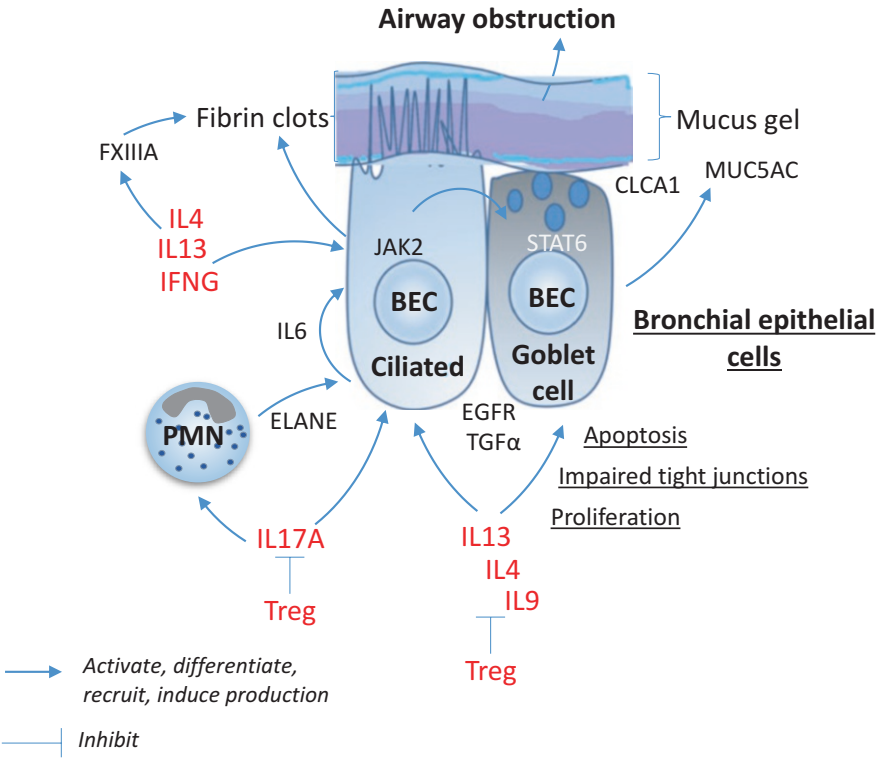

Fig. 4 Adaptive immunity and airway mucus production. Loss of ciliated mucosal bronchial epithelial cells (BEC) and bronchial epithelial goblet cells hyperplasia with mucus accumulation in the airways are features of asthma and airway obstruction. In asthma, increased goblet cells:ciliated cells ratio leads to increase production of gel-forming mucus proteins (e.g., MUC5AC) and lack of mucus gel clearance because of deficiency of cilia movement. IL13, IL4, and IL9 increase mucus production by BEC, in vitro. Yet, in vivo, IL4 and IL9 may also augment MUC5AC production by BEC indirectly by increasing IL13, which remains the essential T2 cytokine directly enhancing mucus production by BEC. IL13 and IL4 also impair BEC tight junctions and increase apoptosis as well as proliferation via an EGF receptor (EGFR) manner and the EGFR ligand, TGFα. Furthermore, IL-13 increases mucus secretion by BEC through enhanced expression of a Ca^{2+} activating chloride channel, CLCA1 and STAT6 signaling. Comparable to IL13, IL17A can increase the expression of MUC5AC by epithelial cells and promotes goblet cells hyperplasia, partially via IL6 and JAK2. IL17A also acts indirectly on mucus production and goblet cell hyperplasia via the production of ELANE by neutrophils (PMN). T-regulatory lymphocytes (Treg) inhibit the adaptive T2 and T17 immune responses. Both T1 (IFNG) and T2 (IL13) cytokines engage epithelial cells into a pro-fibrin deposition function that may further plug the airways with mucus, while T2 cytokines induce the production of the pro-fibrin clot transglutaminase, FXIIIA by antigen-presenting cells

cytokines engage epithelial cells into a pro-fibrin deposition function [611, 612]. In another in vitro model, IFN-γ increases the receptor for TNF-α, which leads to TNF-α-induced production of the pro-fibrin deposition protein, tissue factor, by

epithelial cells [613]. In addition to acting on pro- and anti-fibrin formation protein level changes, other proteins such as the transglutaminases have a key role in cross-linking fibrin to form clots. The coagulation factor XIII (FXIIIA) is such a transglutaminase that covalently cross-links fibrin at the end of the coagulation cascade. FXIIIA is produced by the airway cells and correlates with T2 inflammation, markers of DC, and airway obstruction in asthma [614–617]. Finally, the cytokines IL-13, IL-4, and IL-10 enhance the production of FXIII-A by APC [618–620] and thus can enhance fibrin clot formation by raising FXIIIA activity in the airways.

Angiogenesis

Angiogenesis is the process leading to formation of new blood vessels, which is enhanced in the airway walls [63], and it is recognized as an important event part of airway inflammation and remodeling in asthma [31, 621–624]. In inflammatory diseases, angiogenesis may contribute to tissue growth [625], as well as microvascular permeability and edema formation [626]. There is evidence that the increased number and size of blood vessels in asthma contribute to the thickening of the airway wall and narrowing of the airway lumen during ASMC contraction [627]. Several important factors are involved in angiogenesis, including FGF, TGF-α, IL-8, TGF-β, and angiogenin, but VEGF signaling is a critical rate-limiting step of angiogenesis during normal or pathological conditions by promoting the growth of vascular endothelial cells (reviewed in Ref. [628]). In mice, VEGF generated by lung epithelial cells increases airway T2 inflammation, mucus production, angiogenesis, edema, and vascular remodeling [629]. VEGF also induces vascular leakage and enhances thrombin activity in asthmatic airways, explaining its functions on inflammation and fibrin deposition in tissues [630, 631]. In asthma, airway walls display VEGF-dependent increased vascularity [626, 632–635]. The expression level of VEGF and its receptors are increased in the airways [633] and associate with vascularity and reduced pulmonary function [636]. In addition, VEGF level is enhanced in sputum samples and BAL fluids and is associated with airway vascular permeability and asthma severity [637, 638]. In vitro, in addition to TNF-α and IL1-β, the T2 cytokines, IL-4, and IL-13 are inducers of VEGF in ASMC, which is attenuated by IFN-γ [532, 639, 640]. Furthermore, TGF-β1 in presence of IL-4 and IL-13 increases VEGF in bronchial fibroblasts [639–641]; and in mouse, in vivo, overexpression of IL-13 promotes VEGF accumulation in BAL fluids after hyperoxia [642]. These data demonstrate a close interaction between T2 inflammation and VEGF with the potential to lead to airway remodeling. Besides the T2 cytokines, IL17F, another member of the T17 family, augments CD40L-induced VEGF and angiogenin production in PBMC-derived fibroblasts [434]. Finally, as indicated above in the paragraph on mast cells, VEGF can be released from mast cells following the cross-linking of IgE with its cell surface high-affinity receptor, FcεRI [643].

Conclusions

Adaptive immunity plays a critical role in host defense and pathogen elimination. Inappropriate activation of this immune response is a fundamental mechanism leading to airway inflammation in asthma, with eosinophilia as a hallmark of the cellular response. Increased mucus generation, fibroblast activation with matrix protein generation, and new vessel formation are likely the results of inflammatory mediators associated with the response, and collectively they lead to structural airway changes known as airway remodeling which contribute to disease severity and lack of response to therapy. Recent advances in asthma therapeutics have ushered in new biologics aimed at various steps in the inflammatory cascade. These therapies have been approved based on their ability to reduce asthma exacerbations and, in some cases, improve lung functions and quality of life; however, there are no available therapies to date that have been shown to reverse the underlying mechanism of asthma, leading to disease "remission." Beneficial outcomes relative to controlling lung remodeling using biologic therapies targeting one or several specific cytokine/chemokine pathway(s) may first require precisely endotype patients with asthma vis-à-vis their dominant adaptive immune response(s) during asthma exacerbation.

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