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Eosinophils and tissue remodeling: relevance to airway disease

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The ability of human tissue to reorganize and restore its existing structure underlies tissue homeostasis in the healthy airways, but in disease can persist without normal resolution, leading to an altered airway structure. Eosinophils play a cardinal role in airway remodeling both in health and disease, driving epithelial homeostasis and extracellular matrix turnover. Physiological consequences associated with eosinophil-driven remodeling include impaired lung function and reduced bronchodilator reversibility in asthma, and obstructed airflow in chronic rhinosinusitis with nasal polyps (CRSwNP). Given the contribution of airway remodeling to the development and persistence of symptoms in airways disease, targeting remodeling is an important therapeutic consideration. Indeed, there is early evidence that eosinophil attenuation may reduce remodeling and disease progression in asthma. This review provides an overview of tissue remodeling in both health and airway disease with a particular focus on eosinophilic asthma and CRSwNP, as well as the role of eosinophils in these processes and the implications for therapeutic interventions. Areas for future research are also noted, to help improve our understanding of the homeostatic and pathological roles of eosinophils in tissue remodeling, which should aid the development of targeted and effective treatments for eosinophilic diseases of the airways.

Keywords

Airway remodeling, eosinophil, asthma, chronic rhinosinusitis with nasal polyps

Abbreviations

DNA, deoxyribonucleic acid; CCR3, C-C chemokine receptor 3; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; ECM, extracellular matrix; ECP, eosinophil cationic protein; EPO/EPX; eosinophil peroxidase; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GM-CF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; ILC2, type 2 innate lymphoid cell; MBP, major basic protein; MMP, matrix metalloproteinase; RGD, arginyl-glycyl-aspartic acid; RNase, ribonuclease; TGF, transforming growth factor; uPA, urokinase-type plasminogen activator.

Introduction

Human tissue has an inherent ability to reorganize or restore its existing structure, so-called tissue remodeling, which enables normal development and growth and mediates responses to injury or inflammation. Increasing evidence demonstrates that both the upper and lower airways can respond to injury by repairing and replacing damaged tissue, through processes including extracellular matrix (ECM) deposition and degradation and epithelial cell migration.[1] While in healthy tissue this remodeling process contributes to damage repair and growth, airway disease can occur where the same process is exaggerated and persists without normal resolution.[1,2] As the structural changes associated with airway remodeling develop during the course of disease, airway function often declines and the response to standard therapy becomes poor.[2]

Eosinophils are known historically as end-stage effectors in the inflammatory response to infection and in eosinophilic diseases such as eosinophilic asthma.[3] Now, as proposed over ten years ago by Lee and colleagues with the Local Immunity And/or Remodeling/Repair hypothesis,[4] eosinophils are also recognized as essential contributors to tissue homeostasis, repair and remodeling.[5] Here, we review evidence for the role of eosinophils in tissue repair and remodeling in health and in airway disease. We focus on data from studies in severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), two of the most studied eosinophilic airway diseases for which biologic treatments have been approved. Data from patients with these conditions, which are associated with substantial morbidity and in some cases an unmet treatment need, have provided valuable insights into the role of eosinophils in human airways, validating earlier murine model data.[6-11]

The biology of repair and remodeling

Healthy airways

During normal airway tissue development and growth, or in response to injury and/or inflammation, various structural adaptations contribute to repair and regeneration.[12] Tissue repair is driven by epithelial cell migration to the site of damage and deposition of a provisional matrix comprising ECM glycoproteins including fibronectin and vitronectin, as well as basement membrane components such as laminin and collagen IV (**Figure 1**).[13,14] In addition, underlying mesenchymal cells secrete ECM proteins and cytokines that contribute to airway repair and stimulate epithelial cell functions.[15] The spreading, migration, and proliferation of epithelial cells during epithelial repair requires the participation of integrins, which signal through matrix metalloproteinase (MMP)-dependent activation of transforming growth factor (TGF)-β, a multipotent epithelial and mesenchymal cell growth factor.[16-18] Following airway injury epithelial cells are also regulated by WNT/β-catinin signaling pathways, which play critical roles in the function and behavior of these cells during tissue regeneration.[19-21] Resolution of inflammation and tissue repair in healthy tissue requires the clearance of activated immune cells and production of lipid pro-resolving mediators that contribute to normal tissue restoration.[22]

Airway disease

Pathological airway remodeling is primarily considered a consequence of chronic injury and/or inflammation that leads to persistently altered airway wall structure and function.[23] Some studies (reviewed by Fehrenbach, *et al*.) also report that airway features of remodeling in symptomatic children may be evident before a clinical diagnosis of asthma is made, and it is appreciated that mechanical stress, in the absence of inflammation, may promote tissue remodeling.[12] Primarily, the remodeling changes arise from dysregulated repair and regeneration pathways, leading to an exaggerated wound repair response culminating in the accumulation of (myo)fibroblasts and increased ECM deposition (**Figure 1**).[12,24,25] In asthma, ECM deposition is increased in the reticular basement membrane region, lamina propria, and submucosa, with deposited proteins including collagen I, III and V, the adhesion proteins fibronectin and tenascin, plus proteoglycans, which play roles in the interaction between fibrils and collagen fibrinogenesis considered to be important in the functional consequences of the remodeling process.[26-29] Epithelial-mesenchymal transition, the transformation of epithelial cells into fibroblast-like mesenchymal cells due to loss of epithelial polarity and expression of mesenchymal proteins,[30-34] contributes to accumulation of fibroblast-like cells. Moreover, fibroblast transformation into myofibroblasts further increases ECM deposition.[35,36]

TGF-β mediates epithelial-mesenchymal transition[32] and stimulates fibroblasts to synthesize collagens type I and III, fibronectin and proteoglycans.[37] TGF-β is activated by integrins, reactive oxygen species, and mechanical stress, and stimulates downstream Smad2/3 and Smad4 signaling that mediate gene expression.[38] Increased levels of TGF-β are also associated with increased osteopontin, an ECM protein released by eosinophils that is implicated in the modulation of inflammation and fibrosis in diseased airways.[39-44]

The role of eosinophils in airway repair and remodeling

Eosinophil biology and its relevance for repair and remodeling

Eosinophils are highly complex cells with a wide range of surface molecules and receptors. Key cell membrane receptors that define the unique biology of eosinophils include C-C chemokine receptor 3 (CCR3), which binds eotaxins, the lectin (carbohydrate-binding protein) Siglec-8, which can trigger eosinophil cell death when engaged, and the interleukin-5 alpha receptor (IL-5Rα).[45,46] Eosinophils also express receptors for multiple other cytokines and growth factors, including IL-4, IL-13, IL-33, thymic stromal lymphopoietin, and TGF-β.[46] They also express integrin adhesion molecules, through which they can interact with endothelial and airway cells.[47]

Eosinophils are equipped to modify their immediate tissue environment; they contain large specific cytoplasmic granules, which possess a crystalloid structure and can be released into target tissues upon activation (**Figure 1**).[48] Granules are released by cytolysis or piecemeal degranulation, during which granule proteins are packaged into secretory vesicles that deliver specific proteins to the extracellular space while leaving intracellular granules intact.[49-51] Eosinophil granules contain four cationic proteins: major basic protein 1 (MBP1; [MBP and PRG2]), eosinophil cationic protein (ECP; [RNase3]), eosinophil-derived neurotoxin (EDN; [RNase2]) and eosinophil peroxidase (EPX; [EPO]).[48] Eosinophil granules also store numerous cytokines, enzymes, and growth factors that promote airway remodeling and include the major mediator of airway remodeling, TGF-β, and MMPs. **Figure 2** provides an overview of the eosinophil proteins involved in airway remodeling.[32,39-44,52-75] Activated eosinophils also form extracellular DNA traps (eosinophil extracellular traps [EETs]) and Charcot–Leyden crystals (CLCs)/galectin-10.[76,77] In patients with asthma, EETs negatively correlate with lung function and may have a hand in airway epithelial damage,[78,79] whilst CLCs/galectin-10 have been implicated in mucus production and the tenacity of mucus plug formation.[80] In patients with CRSwNP, EETs and CLCs have been strongly associated with disease severity and their presence could negatively impact olfaction.[81]

Eosinophil recruitment to sites of remodeling in healthy tissue

Under normal physiological conditions, human eosinophils typically reside in the bone marrow, lung, thymus, adipose tissue, and gastrointestinal tract and are thought to spend ~1 day in the circulation, with longer periods at their physiological sites of action, where they assist in normal tissue processes.[82] In health, the eosinophil-specific chemoattractant eotaxin-1 (CCL11), produced by local epithelial cells, endothelial cells, and fibroblasts, contributes to eosinophil recruitment to the airways.[83-85]

Eosinophil maturation is regulated by granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5.[86] GM-CSF is also thought to play a role in priming, activation and survival of tissue eosinophils,[49] whilst IL-3 and IL-5 may promote trafficking of eosinophils, under normal conditions.[87] Importantly, IL-5 supports eosinophil generation from CD34-positive bone marrow progenitors, enhancing their sensitivity to eotaxin-1, and sustaining their survival.[88-91] Although the role of type 2 innate lymphoid cells (ILC2s) in airway homeostasis is yet to be fully elucidated, in other healthy tissues they play a cardinal role in maintaining circulating IL-5 levels and, thereby, normal eosinophil levels in circulation and tissues.[92-94] ILC2 cells are also responsible for eosinophil tissue recruitment in tumor regulation.[95]

Eosinophils potentially contribute to epithelial remodeling by inhibiting cell surface plasmin generation by bronchial epithelial cells, through the local release of TGF-β.[96] Therefore, the accumulation of eosinophils in bronchial walls may directly promote fibrin deposition and bronchial tissue repair/remodeling through this network.[96] Additionally, eosinophils produce key factors contributing to coagulation (tissue factor, thrombin) and fibrinolysis (plasminogen), which are required for wound healing and epithelial remodeling.[97] Fibrinogen, another coagulation and fibrinolysis factor, may be a chemoattractant for eosinophils[98] and is a specific trigger for cytolytic eosinophil degranulation.[99] Notably, eosinophils are frequently present at sites of high epithelial-mesenchymal turnover, during which new layers of differentiated epithelium are created from the mesenchymal unit; eosinophils are engaged by chemokines, growth factors, ECM proteoglycans and morphogenetic ligands, secreted by mesenchymal cells.[9]

Eosinophils in pathophysiological airway remodeling

Eosinophil recruitment and activation is exaggerated in both lower and upper airway disease.[100-102] There is evidence directly linking the presence of eosinophils to disease-related airway remodeling. This is discussed below, specifically in asthma and CRSwNP.

Asthma

Airway remodeling in asthma is caused by changes in the cellular and extracellular matrix, which lead to narrowed airways due to thickened airway walls; this is a key pathologic feature of asthma.[26] Eosinophilic inflammation in the airway wall (and in induced sputum) has been related to the extent of reticular basement membrane thickening in asthma and eosinophilic bronchitis.[103,104] Furthermore, airway eosinophils in patients with asthma display hyperadhesiveness towards provisional ECM, interacting with ECM components via expression of specific integrins (CD11c, CD11b, beta 5 integrins) and toll-like receptors.[105-

[107] Eosinophils are one of the major sources of airway TGF-β in asthma,[108] with TGF-β expression localized to eosinophils in the bronchi of patients with severe asthma.[70,109] Aside from eosinophils, TGF-β is also produced by other immune cells in addition to epithelial cells, endothelial cells, vascular and airway smooth muscle cells, and fibroblasts.[110] As described in the previous section, TGF-β promotes myofibroblast transformation, and facilitates the transcription of osteopontin.[111,112] This in turn further potentiates airway remodeling,[43] since myofibroblasts have increased synthetic capability for collagen and ECM proteins.[113,114] Osteopontin initiates the migration, adhesion, and proliferation of fibroblasts through cytokine signaling and macrophage activation.[115] TGF-β can also promote epithelial detachment and epithelial-mesenchymal transition,[32] which combined with impaired repair processes could in turn lead to increased ECM deposition. Eosinophil localization to the airway smooth muscle bundle has also been demonstrated in endobronchial biopsies from patients with severe, difficult-to-treat asthma.[104] In contrast, there is no evidence of elevated eosinophil counts in the airway smooth muscle of patients with asthma requiring Global Initiative for Asthma Step 1–4 treatment, patients with eosinophilic bronchitis, or healthy controls.[104]

Co-culture of airway smooth muscle cells and pulmonary fibroblasts with peripheral blood eosinophils from patients with asthma (especially those with severe non-allergic eosinophilic asthma) alters the gene expression of ECM proteins, MMPs, tissue inhibitors of MMPs, and TGF-β, versus healthy controls, indicating relevant interactions between activated eosinophils and the structural airways in the remodeling process.[116] Furthermore, bronchial biopsies from patients with asthma show increased eosinophil accumulation, which is associated with poor epithelial integrity,[117,118] and increased basement membrane thickness.[103,119,120] Notably, in these studies, eosinophil accumulation was associated with a decline in lung function. The presence of intraepithelial eosinophils in asthma is associated with endogenous airway hyperresponsiveness and IL-5 gene expression;[121] high eosinophil numbers in the bronchial submucosa are a marker of an altered mucus-repair phenotype and epithelial damage.[118] Taken together, these results support eosinophil localization in areas of airway remodeling. This notion is strengthened by the findings of Drake et al., who showed that eosinophils co-localized to airway epithelial sensory nerves in endobronchial biopsies from patients with eosinophilic asthma.[122] Eosinophils contributed to substantial structural remodeling in these patients (demonstrated by increased epithelial nerve density); they also increased epithelial innervation and neuronally-mediated airway responsiveness in a transgenic mouse model.

Exaggerated eosinophil recruitment and activation has other indirect effects, which include epithelial cell damage; this triggers repair pathway activation and epithelial-to-mesenchymal transition, which underpins airway remodeling.[123-125] Secondary effects of this response

include increased exacerbation frequency and severity due to progressive airway remodeling, which stems from epithelial cell mechano-stimulation during bronchoconstriction.[23,126] Frequent and repeated exacerbations themselves may also result in structural airway remodeling.[127-130] In addition, repeated bronchoconstriction induces goblet cell proliferation, subepithelial thickening, and mucus secretion, which together can lead to further airway obstruction.[23]

CRSwNP

Chronic rhinosinusitis (CRS) is characterized by inflammation of the paranasal sinuses; common symptoms include nasal congestion, excess mucus, hyposmia or anosmia, and facial pain.[131] Data on upper airway remodeling in CRSwNP are limited versus asthma; however, there are similarities between the remodeling changes observed in both diseases. For example, as with asthma, there is evidence in CRSwNP for extensive epithelial cell disruption,[132] basal cell hyperplasia,[133] goblet cell hyperplasia and mucin hypersecretion.[134] There is also excess production of ECM components, with increased collagen and fibronectin, elevated numbers of ECM-producing myofibroblasts, and inflammation facilitated by eosinophil-derived CLCs, as well as an increase in extracellular matrix remodeling endopeptidases (MMP-1 and MMP-2, MMP-9, and MMP-7).[135-138] In addition, immunohistochemistry has demonstrated the sinonasal epithelium can transition to a mesenchymal phenotype, which correlates with airway fibrosis and inflammation.[139]

Elevated tissue eosinophil counts in CRSwNP, which may be facilitated by delayed eosinophil apoptosis,[140] have been associated with enhanced epithelial-mesenchymal signaling, with recent evidence suggesting that TGF-β-mediated epithelial-mesenchymal transition may promote nasal polypogenesis.[141] Furthermore, there is significant correlation between the number of epithelial eosinophils and the extent of epithelial damage, sub-basement membrane collagen deposition and the level of epithelial to mesenchymal transition in patients with CRSwNP.[142,143] At the site of epithelial barrier defects, extracellular eosinophilic traps can form in patients with CRSwNP, likely as a protective response against pathogenic bacteria.[76] Furthermore, there is a strong correlation between expression of the eosinophil protein galectin-10 and CRSwNP severity.[144] Some studies have demonstrated correlations between basement membrane thickening and elevated levels of tissue eosinophils in CRSwNP.[139,142] Features of remodeling in CRS have also been associated with tissue eosinophilia and eosinophil activation.[145]

Tissue edema in nasal polyps has been linked to an imbalance between coagulation factor expression and fibrinolytic activity, leading to increased fibrin accumulation, with the resultant fibrin scaffold trapping plasma proteins to enhance edema.[146] Eosinophils are

involved in this process through the release of tissue factor[147] (which enhances initiation of the clotting cascade) and MBP/EPX basic proteins. These inhibit thrombomodulin, a potent anticoagulant, thereby impairing fibrin breakdown.[148] Tissue plasminogen activator (tPA), which usually plays a role in fibrin degradation, is decreased in CRSwNP.[149] While the fibrinolytic urokinase-type plasminogen activator (uPA) is increased in CRSwNP (especially in inflammatory cells) and correlates with ECP, excessive uPA expression might interfere with the normal TGF-β–activated feedback mechanism of uPA in CRSwNP, resulting in nasal polyp edema.[150]

The role of IL-5 in pathophysiological airway remodeling

Through its well-known effects on eosinophils, IL-5 is likely to contribute to airway remodeling. Via binding to IL-5Rα, IL-5 promotes the maturation, activation, proliferation and migration of eosinophils as well as their survival within the airways.[151] IL-5 also supports eosinophil generation from CD34-positive bone marrow progenitors, enhancing their sensitivity to eotaxin-1, and sustaining their survival.[88-91] However, functional IL-5Rα is also expressed on basophils, mast cells, plasma cells, and bronchial epithelial cells as well as airway fibroblasts, with effects on the latter two functional cells being of particular relevance to tissue remodeling.[152-155] The enhanced airway collagen synthesis observed in asthma may be driven by the direct activating effect of IL-5 on fibroblasts, with functional IL-5R upregulated in asthmatic lung fibroblasts versus healthy controls.[155] IL-5 is also associated with increased levels of airway collagen in allergen sensitivity (which is increased in asthma).[156] In addition, the downregulation of epithelial tight junction genes by IL-5 may be a factor that increases the susceptibility of epithelium to eosinophilic damage.[152] As further evidence of the importance of eosinophils and IL-5 to asthma-related airway remodeling, anti-IL-5 biologic therapy is associated with reduced airway eosinophil counts and decreased airway remodeling and proximal airway wall thickness (assessed by ECM deposition and thoracic computed tomography [CT] scanning, respectively), in patients with eosinophilic asthma.[157] In patients with asthma, nasal polyposis, and a confirmed diagnosis of aspirin-exacerbated respiratory disease, IL-5 inhibition with mepolizumab leads to decreased inflammatory eicosanoid production and upregulation of epithelial cell transcripts involved in tight junction pathways and cilium organization,[153] potentially impacting the strength of the epithelial barrier and evidencing the local detrimental effect of IL-5 exposure on epithelial function and integrity (a possible contributor to the susceptibility of epithelial cells to eosinophil-directed damage). Consistent with the importance of eosinophils and IL-5 to the abnormal tissue remodeling that underlies nasal polyp formation, levels of IL-5 and ECP (an

eosinophil activation marker) in resected polyp tissue have both been identified as independent predictors of further nasal polyp recurrence.[158] Together, these data support a central role for IL-5 in pathological airway remodeling.

Physiological consequences of eosinophil-driven airway remodeling

The airway changes described in this review are pathological features of eosinophilic airway disease and contribute to the clinical manifestations seen in patients (**Figure 3**).[159-164] In severe eosinophilic asthma, the structural effects of chronic eosinophil-driven airway remodeling (goblet cell hyperplasia, decreased epithelial cell and cartilage integrity, subepithelial collagen deposition with increased thickness of the reticular basement membrane in the bronchial mucosa, increased airway smooth muscle cell mass, mucus plug persistence, and angiogenesis of the airways) have been postulated to explain the persistent airflow obstruction seen in some patients.[119,165-172] While it is acknowledged that bronchial wall thickness measurements using computed tomography (CT) scanning can be influenced by reversible factors such as edema, airway secretions, and inflammatory cell infiltration,[120,173] quantitative CT imaging studies, in some cases supported by endobronchial biopsies, have demonstrated proximal airway wall thickness/wall area and structural changes to predict airflow limitation and lung function impairment (measured by reduced forced expiratory volume in 1 second [FEV_1], postbronchodilator percent predicted FEV_1, FEV_1/forced vital capacity [FVC], and forced expiratory $flow_{25–75\%}$), in patients with asthma.[174-176] Several cross-sectional studies in patients with asthma have demonstrated increased odds of worse lung function[177,178] and worse airflow obstruction over time[179] in patients with eosinophilic inflammation. In addition, epidemiologic data have linked elevated blood eosinophils to worse lung function outcomes, irrespective of the diagnosis of asthma.[180,181] Finally, higher blood eosinophil counts in children with untreated asthma are predictive of lower growth in FEV_1 and FVC during adolescence.[182] Interestingly, lung computational models have demonstrated that a) small airway narrowing is associated with clinically relevant deterioration in both asthma control and quality of life, and b) biologics targeting type 2 inflammation could reverse small airway narrowing, suggesting that early intervention could potentially modify the disease course.[183] Altogether these data show that as a result of airway remodeling, patients may experience irreversible airway obstruction leading to worsening of lung function, airway thickening, air trapping and potentially reduced response to bronchodilators.

In CRSwNP, excess mucus can be explained by goblet cell hyperplasia and mucin hypersecretion,[134] downstream consequences of upper airway remodeling. Furthermore, extracellular connective tissue matrix degradation is likely to be an important pathological component in CRSwNP, contributing to the loosening of tissue architecture, tissue expansion, and pseudocyst formation.[1]

Therapeutic implications of eosinophil-driven airway remodeling

Given the substantial contribution of airway remodeling to symptom development and persistence in patients with airway diseases, targeting the remodeling component of the disease is an important therapeutic consideration. Currently, the only available treatment that directly targets airway remodeling is bronchial thermoplasty, a bronchoscopy procedure that reduces airway smooth muscle cell mass through the local delivery of controlled radiofrequency energy. While histopathological effects are distinct in different disease endotypes/phenotypes, bronchial thermoplasty helps control asthma in patients with severe disease, thus demonstrating the therapeutic value in targeting several components of bronchial remodeling in this population.[184-188]

There is evidence that suppressing eosinophilic inflammation may reduce airway remodeling and disease progression among patients with airway disease. For example, in vitro blocking of eosinophil arginyl-glycyl-aspartic acid (RGD)-binding integrins significantly reduces eosinophil adhesion to airway smooth muscle cells, resulting in reduced eosinophil-mediated TGF-β1, WNT-5a, and ECM protein gene expression and reduced proliferation in airway smooth muscle cells.[189] In animal model studies, eosinophil-deficient mice showed attenuation of airway remodeling,[7,190] with similar results demonstrated in IL-5 knockout mice.[8] In humans with asthma, reduced eosinophil numbers are significantly associated with greater improvements in airway hyperresponsiveness, when tested with methacholine treatment.[191] Of note, in patients with asthma and rhinitis, house dust mite sublingual immunotherapy in addition to pharmacotherapy reduced eosinophilic airway inflammation while improving symptoms and pulmonary function.[192] Finally, in a Phase II study of patients with eosinophilic asthma, the eosinophil-depleting drug dexpramipexole improved lung function and reduced airway eosinophil granule proteins cognate with the magnitude of reduction in blood eosinophils.[193] Together, these studies demonstrate that eosinophils are a critical factor driving airway remodeling in asthma and may be an important therapeutic target.

Biologic intervention

Biologics currently used in the treatment of severe asthma and CRSwNP have the potential to reverse or reduce the impact of airway remodeling through their effects on eosinophils. While work to determine whether these agents can reduce or reverse remodeling is still in its infancy, there are some key studies that support their role in reversing airway remodeling (**Table 1**).[153,157,194-211] Several asthma studies show that the humanized monoclonal antibody mepolizumab, which targets IL-5 (the primary cytokine responsible for differentiation, activation and survival of eosinophils; also of relevance to airway remodeling through its

direct non-eosinophilic effects on structural airway cells),[12,212] reduces airway eosinophil numbers and ECM/inflammatory mediator expression as well as reducing airway wall thickness and wall area and lowering rates of FEV_1 decline.[153,157,200,202,208] In addition, the anti-IL-5Rα antibody, benralizumab, can reduce eosinophil counts and numbers of tissue myofibroblasts, as well as improve hyperinflation, airway dysfunction and peripheral resistance in patients with asthma.[197,206,207] The anti-IL-4/IL-13 antibody, dupilumab, improves epidermal remodeling and inflammation in lesional and healthy skin among patients with severe atopic dermatitis (detected by dynamic optical coherence tomography), suggesting that broader targeting of type-2 inflammatory cytokines may have anti-remodeling effects.[205] However, dupilumab did not modify airway tissue eosinophil numbers in a recent randomized, placebo-controlled study in patients with persistent asthma (NCT02573233; https://clinicaltrials.gov/ct2/show/results/NCT02573233) and there are no published studies demonstrating an effect in modifying airway remodeling in asthma.[198] Finally, the monoclonal antibody tezepelumab, which blocks thymic stromal lymphopoietin, partially reduces airway tissue eosinophil numbers in asthma, but evidence to date does not support a significant impact on airway remodeling changes, although there was evidence of reduced airway hyperresponsiveness and reduced mucus plugging.[199,209,213] Studies in patients with CRSwNP have demonstrated reductions in polyp size following treatment with omalizumab, mepolizumab, benralizumab or dupilumab,[194-196,201,203,210,214,215] suggesting an effect of anti-immunoglobulin E (IgE), anti-type 2 cytokine, and eosinophil-targeting biologics on nasal/sinus mucosa remodeling. In contrast, near-complete elimination of eosinophils in nasal polyp tissue was achieved with dexpramipexole in CRSwNP, without any reduction in polyp size.[204] However, dexpramipexole has been shown in asthma to reduce airway eosinophil granule proteins cognate with the magnitude of reduction in blood eosinophils, and to improve lung function,[193] a physiological feature that was also evident in the dexpramipexole EXHALE trial.[216] This suggests that the failure of dexpramipexole to improve symptoms in CRSwNP is not a failure of the drug but that modifying eosinophilic inflammation alone in CRSwNPS may be insufficient to deliver clinical benefit. Notably, in the SYNAPSE study, which demonstrated significant reductions in polyp size with mepolizumab treatment overall, 49.5% of patients did not experience a ≥1-point improvement in total endoscopic nasal polyp score.[203] This indicates there is heterogeneity in response to targeting IL-5 in patients with severe, recurrent nasal polyps requiring further surgery. A post hoc analysis of SYNAPSE found no clear differences in baseline clinical characteristics between patients considered to be mepolizumab responders versus non-responders, highlighting a need for further investigation of the underlying endophenotypic characteristics that may predict treatment response.[217] With further research, the effects of biologic therapies on airway remodeling may provide specific clues as to the underlying mechanisms

of this process. In addition, CRSwNP pathobiology may change at different stages of the disease, with potential differences in the factors that drive nasal polyp formation versus those that maintain the edematous polyp state. Accordingly, further work is needed to fully explore and understand the impact of eosinophil-targeting therapies on remodeling in airway disease and whether alterations in eosinophil activation (rather than eosinophil numbers) or the effects of IL-5 inhibition that extend beyond eosinophils themselves, are mechanisms contributing to clinical impact.

Future directions and unanswered questions

While our understanding of the role of eosinophils in airway remodeling in health and disease is improving, there are still many unanswered questions. A key objective will be to further understand the relationship between reductions in tissue eosinophil numbers, eosinophil activation status, and airway remodeling in airway diseases, as well as evaluating the relevance of the eosinophil-independent local effects of IL-5 on airway structural biology. Fully characterizing the differences between eosinophils involved in homeostasis and those involved in disease, observed in both mouse and human studies,[218,219] will also be important. To this end, data on the phenotype and function of airway-resident eosinophils versus those in other tissues will be useful. Assessing genetic and inflammatory interactions and overcoming technical barriers to performing single cell sequencing of eosinophils (for example, eosinophil RNAses) will be integral to addressing this. In particular, studies using mass cytometry techniques such as cytometry by time of flight and tissue imaging mass cytometry can produce multidimensional data to help characterize subgroups of eosinophils with different expression profiles (and identify their presence in different disease phenotypes), in addition to establishing eosinophil-stromal cell interactions in the tissue microenvironment.[102,220,221] There is also a need to understand airway changes during clinical remission, particularly remission induced by eosinophil-targeting biologics. Furthermore, the inclusion of endpoints more relevant to airway remodeling in clinical trials will help determine whether currently available eosinophil-targeting therapies can reduce the clinical effects of remodeling. Indeed, it will be important to determine whether airway remodeling becomes irreversible and, if so, what the contributors to and markers of irreversible remodeling are. Further characterization of the molecular signaling pathways involved in eosinophil migration and activation that initiate airway remodeling will also be useful in identifying novel molecular targets for therapy. For example, Rac1 has recently been identified as a target that has the potential to simultaneously reduce airway smooth muscle hyperplasia, airway hyperresponsiveness, and inflammation.[222]

Although data on eosinophil-driven remodeling in CRSwNP are beginning to emerge, they are sparser than in asthma. As such, further information on the etiologic role of eosinophils and downstream signaling pathways in the pathophysiology of tissue remodeling in patients with CRSwNP is needed. It will be important to further determine what effect the reduction of eosinophil levels has on tissue remodeling and whether any of the effects of anti-IL-5 biologic therapy are related to inhibitory effects on structural cells expressing the IL-5 receptor, additional to those resulting from modification of local tissue eosinophilic inflammation.

Conclusion

There is growing evidence that tissue remodeling contributes to both upper and lower airway disease. While evidence for remodeling in upper airway disease does not yet fully correspond with that seen in the lower airways, there are aspects consistent to both, such as epithelial cell disruption and excess ECM production. Furthermore, there is now evidence that eosinophil localization is important in upper airway remodeling, a notion already established in the lower airways. Our knowledge of eosinophils in tissue homeostasis and remodeling in health and eosinophil-mediated diseases is improving and has highlighted further therapeutic possibilities. Nonetheless, there is a need to further characterize the roles of eosinophils in the tissue remodeling that contributes to eosinophil-mediated disease, to help develop therapeutic interventions that attenuate and even reverse the effects of remodeling and thereby improve clinical outcomes and symptoms. Such evidence is needed to understand whether disease modification and prevention of disease progression are realistic outcomes of targeted therapy, especially in asthma, as the ability to fundamentally alter the biology underlying exaggerated airway remodeling processes is a key goal of disease modifying asthma therapy.

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Author contributions

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Figures and Tables

Table 1 Effects of eosinophil-targeting therapies on tissue remodeling

Treatment	Study	Number of patients	Patient characteristics	Treatment arms/ schedule	Method of measuring remodeling/ endpoints of interest	Results summary (study drug vs placebo/ no study drug)
Asthma						
Mepolizumab	• Biopsy study[200]	24	• Mild atopic asthma • Treated only with β_2 agonists	• Mepolizumab 750 mg IV or placebo	• Thickness and density of markers of airway remodeling: tenascin, lumican and procollagen III in the reticular basement membrane	• Significantly decreased expression of tenascin, lumican and procollagen III in bronchial reticular basement membrane • Reduced percentage and number of eosinophils expressing TGF-β
	• Randomized, double-blind, placebo-controlled, parallel-group study[157]	61	• Refractory eosinophilic asthma • History of recurrent severe exacerbations	• Mepolizumab 750 mg IV or placebo every 4 weeks for 12 infusions	• CT assessment of airway wall geometry	• Reduced eosinophil counts in bronchial biopsy specimens (2.1-fold), bronchoalveolar-lavage specimens (8.2-fold) and bronchial-wash specimens (16.0-fold) • Significantly reduced airway wall area (between-group difference in change from baseline: 1.1 mm^2) and total wall area (between-group difference in change from baseline: 1.5 mm^2)
	• Real-world, longitudinal analysis[202]	318	• Severe asthma	• Mepolizumab 100 mg SC vs	• Lung function decline	• Significant reduction in FEV_1 decline (0.6

				no mepolizumab		vs –11.1% predicted/year)
	• Single-visit study[153]	36	• Aspirin-exacerbated respiratory disease with asthma and nasal polyposis	• Mepolizumab 100 mg SC for ≥3 months vs matched controls not receiving mepolizumab	• Circulating granulocytes, nasal scraping transcripts, eosinophilic cationic protein, tryptase and antibody levels, and urinary and nasal eicosanoid levels	• Decreased production of inflammatory eicosanoids • Upregulated tight junction proteins (likely due to decreased IL-5 signaling on tissue mast cells, eosinophils and epithelial cells)
	• Longitudinal study[208]	15	• Severe eosinophilic asthma	• 1 year of mepolizumab treatment, pre- vs post-treatment	• Chest high-resolution CT and endobronchial ultrasound	• Significant reduction in bronchial wall thickness (1.30 vs 1.26 mm) and its layers (0.186–0.2 vs 0.015–0.88 mm) Reduction in bronchial wall area, significant in patients with longer asthma duration and lower baseline FEV_1 (70.08 vs 62.27%)
Benralizumab	• Biopsy study[197]	25	• Eosinophilic asthma	• Single benralizumab 1 mg/kg IV infusion or placebo, benralizumab 100 mg or 20 mg SC every 4 weeks for 3 months or placebo[223]	• Airway smooth muscle mass in bronchial biopsies (using α-smooth muscle actin immuno-staining)	• Significant reduction in eosinophil count in airway lamina propria (between-group difference in % reduction: 88%) • Non-significant reduction in airway smooth muscle mass (between-group difference in change from baseline: -2.6%)

						• Non-significant reduction in number of tissue myofibroblasts (between-group difference in change from baseline: -21.7)
	• Multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study[207]	233 (40 in the plethysmo-graphy substudy)	• Severe eosinophilic asthma	• Benralizumab 30 mg SC or placebo on Days 0, 28 and 56	• Whole-body plethysmo-graphy assessment of lung capacity parameters	• Early non-statistically significant improvements in whole-body plethysmography assessment of hyperinflation (change from baseline at Day 84 in residual volume: -415 vs -208 mL; inspiratory capacity: 119 mL vs -268 mL)
	• Single-dose study[206]	29	• Poorly controlled asthma (as defined by GINA	• Benralizumab 30 mg on Day 0 and Day 28, pre- vs post-treatment	• Airway dysfunction (VDP) and peripheral resistance ($R_{5–19Hz}$)	• Significantly improved mean VDP on Day 28 • Significantly improved $R_{5–19Hz}$ on Day 28
	• Randomized, Phase II study[198]	42	• Persistent asthma	• Dupilumab 300 mg SC (with a 600 mg loading dose) or placebo every 2 weeks for 12 weeks	• Eosinophil, mast cell and lymphocyte levels in the bronchial mucosa	• Non-significant change from baseline in eosinophil count in the bronchial mucosa (-6.04 vs 5.80 cells/mm^2 at Week 12)
Tezepelumab	• Double-blind, randomized, placebo-controlled, parallel-group, Phase II study[199]	99	• Uncontrolled, moderate-to-severe asthma	• Tezepelumab 210 mg or placebo every 4 weeks for 28 weeks (extended up to	• Reticular basement membrane thickness and epithelial integrity	• Reduced airway submucosal eosinophils (89% vs 25% at end of treatment)

				52 weeks if necessary due to COVID-19-related disruption)	(proportions of denuded, damaged, and intact epithelium)	• No significant impact on reticular basement membrane thickness (between-group difference in change from baseline: -0.16 µm at end of treatment) or epithelial integrity (between-group difference in change from baseline: -2.20% at end of treatment) • Significantly reduced airway hyperresponsiveness in an exploratory analysis (between-group difference in PD_{15} of mannitol: 138.8 mg at end of treatment)
	• Double-blind, randomized, placebo-controlled, Phase II study[209]	40	• Asthma and airway hyperresponsiveness	• Tezepelumab 700 mg or placebo intravenously every 4 weeks for 12 weeks	• Change in airway hyperresponsiveness and inflammation	• Non-significant increase in change in PD15 from baseline to Week 12 (1.9 vs 1.0) • Significantly reduced airway tissue (74% reduction vs 28% increase from baseline) and bronchoalveolar lavage eosinophils (75% vs 7% reduction from baseline)
CRSwNP						
Omalizumab	• Two double-blind, randomized, placebo-controlled studies[138]	138 and 127	• CRSwNP inadequately controlled with	• Omalizumab 75–600 mg subcutaneously or placebo	• Total endoscopic NP score	• Significantly improved total endoscopic NP score

			intranasal corticosteroids	every 2 or 4 weeks, for 24 weeks		(-1.08 vs +0.06 and -0.90 vs -0.31)
Omalizumab	• Prospective, real-world study in tertiary care centre[211]	22	• Difficult-to-treat CRSwNP	• Omalizumab subcutaneous injections every 4 weeks for 24 weeks, pre- vs post-treatment	• Total endoscopic NP score	• Significantly improved total endoscopic NP score (1.00)
Mepolizumab	• Double-blind, randomized, placebo-controlled study[201]	30	• CRS with primary or recurrent NP who had failed standard of care treatment	• Two single IV injections (28 days apart) of mepolizumab 750 mg or placebo	• Total endoscopic NP score • Blood eosinophil counts	• Significantly improved total endoscopic NP score (between-group difference: -1.30 at Week 8) • Significant reduction in blood eosinophil count
	• Double-blind, randomized, placebo-controlled, Phase III study[196,203]	407	• Recurrent, refractory, severe, bilateral CRSwNP	• Mepolizumab 100 mg SC or placebo plus standard of care every 4 weeks for 52 weeks	• Total endoscopic NP score based on centrally read endoscopies • Baseline blood eosinophil count	• Significantly improved total endoscopic NP score (between-group difference: -0.73) • Significant reductions in blood eosinophil counts (between-group ratio: 0.19) • More patients with baseline blood eosinophil counts ≥150 or ≥300 cells/μL had ≥1-point improvement from baseline in total endoscopic NP score (49.5% vs 28.1% and 50.4% vs 28.1%) and ≥3-point improvement from baseline in nasal obstruction VAS score (59.1% vs

						34.1% and 59.0% vs 32.4%) with mepolizumab vs placebo at Week 52
Benralizumab	• Randomized, placebo-controlled, Phase III study[195]	413	• Severe CRSwNP	• Benralizumab 30 mg or placebo every 4 weeks for the first 3 doses and every 8 weeks thereafter	• Total endoscopic NP score • Blood eosinophil counts	• Significant improvement in total endoscopic NP score (between-group difference: -0.570 at Week 20) • Some evidence (non-significant) of differential effects of blood eosinophil counts on total endoscopic scores (data not shown)
	• Double-blind, randomized, placebo-controlled, Phase II study[210]	24	• Severe NP	• Benralizumab 30 mg or placebo	• Total endoscopic NP score and CT scan • Blood eosinophil count	• Significantly improved total endoscopic NP score (-0.9 at Week 20) and CT polyp score (-4.2 at Week 20) vs baseline • Significant reduction (97%) in blood eosinophil count vs baseline • Blood eosinophil count/positive allergen skin prick test ratio significantly predicts reductions in total endoscopic NP score and CT scan polyp score
Dupilumab	• Two double-blind, randomized, placebo-controlled, Phase III studies[194]	276	• Severe uncontrolled CRSwNP	• Dupilumab 300 mg every 2 weeks or placebo for 24 weeks (SINUS-24)	• Total endoscopic NP score • Blood eosinophil count	• Significantly improved total endoscopic NP score (treatment difference: -1.89 at Week 24, -1.80 at Week 52)

				• Dupilumab 300 mg every 2 weeks for 52 weeks, placebo for 52 weeks, or dupilumab every 2 weeks for 24 weeks followed by every 4 weeks for the remaining 28 weeks		• Transient, non-significant increase in blood eosinophil count with dupilumab (change from baseline: 0.02 to 0.15 giga/L at Week 24)
Dexpramipexole	• Prospective, open-label study[204]	16	• CRSwNP	• Dexprami-pexole 150 mg twice daily, pre- vs post-treatment	• Total endoscopic NP score • Blood eosinophil count • Eosinophil levels in nasal polyp biopsies	• No significant change in total endoscopic NP score (0.07 at Month 6) • Significant reduction (94%) in blood eosinophil count • Significant reduction (97%) in nasal polyp eosinophilia

CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; IL-5, interleukin-5; IV, intravenous; PD15, 15^{th} percentile lung density; SC, subcutaneous; TGF-β, transforming growth factor-β; VAS, visual analogue scale; VDP, ventilation defect percentage.

Figure 1 Airway remodeling in health and disease[12-14,24,25,48]

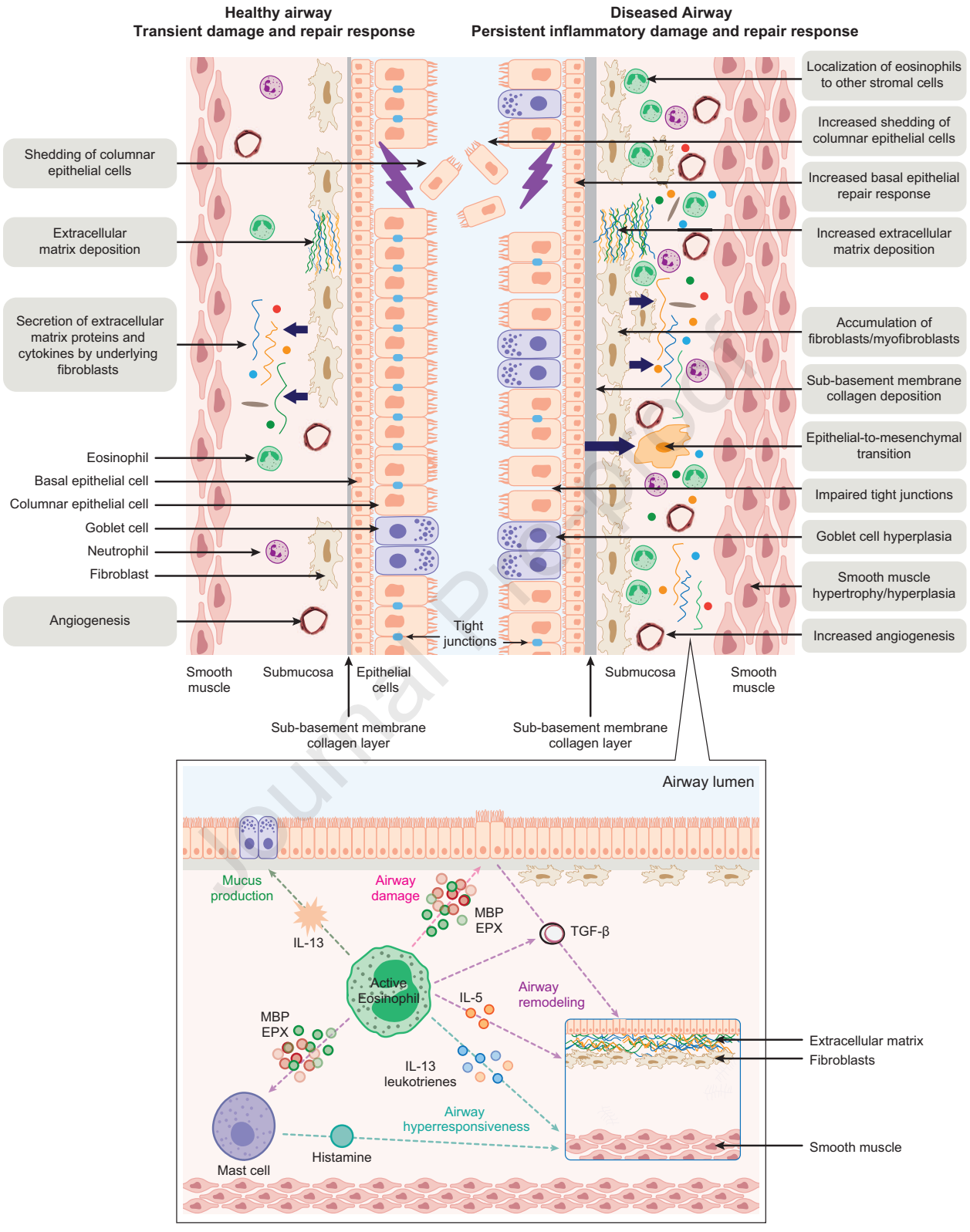
In airway disease, the transient tissue injury and subsequent tissue repair/regeneration seen in the healthy airway (left hand side) are exaggerated, leading to persistent inflammation and repair (right-hand side).
Callout panel adapted from Vatrella et al. 2022[14] (CC BY), and depicts the role of eosinophils in mediating airway damage, airway remodeling, airway hyperresponsiveness, and mucus production in type 2 asthma.
EPX, eosinophil peroxidase; IL-13, interleukin-13; MBP, major basic protein.

Figure 2 Eosinophil proteins and their roles in airway remodeling[32-34,39-44,53-75,224-233]

bFGF, basic fibroblast growth factor; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; FEV_1, forced expiratory volume in 1 second; Gal-3, galectin 3 gene; HB-EGF, heparin-binding epithelial growth factor-like growth factor; Ig, immunoglobulin; IL, interleukin; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor.

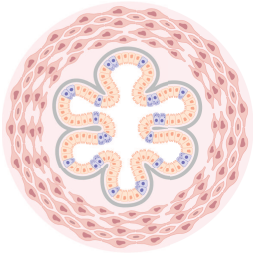
Figure 3 Physiological consequences of eosinophil-driven remodeling[33,34,159,160,162-164,206]

The left-hand side of the figure shows schematic cross sections of the airways in patients with asthma and the right-hand side of the figure shows schematic cross sections of the nasal mucosa in patients with CRSwNP. These schematic cross sections illustrate the impact of eosinophilic tissue inflammation in the lower and upper airways and the consequences of this in asthma and CRSwNP.
CRSwNP, chronic rhinosinusitis with nasal polyps.


Healthy airway
Transient damage and repair response
Diseased Airway
Persistent inflammatory damage and repair response
Shedding of columnar epithelial cells
Extracellular matrix deposition
Secretion of extracellular matrix proteins and cytokines by underlying fibroblasts
Eosinophil
Basal epithelial cell
Columnar epithelial cell
Goblet cell
Neutrophil
Fibroblast
Angiogenesis
Localization of eosinophils to other stromal cells
Increased shedding of columnar epithelial cells
Increased basal epithelial repair response
Increased extracellular matrix deposition
Accumulation of fibroblasts/myofibroblasts
Sub-basement membrane collagen deposition
Epithelial-to-mesenchymal transition
Impaired tight junctions
Goblet cell hyperplasia
Smooth muscle hypertrophy/hyperplasia
Increased angiogenesis
Tight junctions
Smooth muscle
Submucosa
Epithelial cells
Sub-basement membrane collagen layer
Submucosa
Smooth muscle
Sub-basement membrane collagen layer
Airway lumen
Mucus production
IL-13
Airway damage
MBP
EPX
TGF-β
Active Eosinophil
IL-5
Airway remodeling
MBP
EPX
IL-13
leukotrienes
Airway hyperresponsiveness
Histamine
Mast cell
Extracellular matrix
Fibroblasts
Smooth muscle

		
TGF-β	• Increased levels associated with increased levels of osteopontin, an extracellular matrix protein released by eosinophils that is implicated in the modulation of inflammation and fibrosis in diseased airways	• Induces epithelial-mesenchymal transition in primary airway epithelial cells • Promotes differentiation of fibroblasts to myofibroblasts and triggers their proliferation • Induces the expression of MMPs and TIMPs • Regulates subepithelial fibrosis by signaling through the Smad7 pathway • Induces the transcription and translation of mucin in bronchial epithelial cells • Epithelial/submucosal expression correlates with basement membrane thickness and fibroblast numbers • Induces hypertrophy and increased contractility of airway smooth muscle in vitro • Increased levels associated with increased levels of osteopontin
MMP-9 and TIMP-1		• Sputum MMP-9 and TIMP-1 concentrations are higher in patients with asthma compared with controls; the MMP-9/TIMP-1 ratio is lower in patients with asthma and chronic bronchitis, and positively correlates with FEV_1
VEGF, bFGF and angiogenin		• Bronchial biopsies from patients with asthma exhibit greater immunoreactivity to VEGF, bFGF and angiogenin; immunoreactivity to these factors positively correlates with vascular area
Specific granule proteins		• Damaged airway epithelium produces TGF-β • ECP induces fibroblast migration and inhibits fibroblast-mediated proteoglycan degradation • EDN stimulates MMP-9 in nasal epithelial cells
IL-17		• Fibroblasts isolated from bronchial biopsies produce more IL-6 and IL-11 (profibrotic cytokines) when stimulated by IL-17 • Promotion of airway smooth muscle cell migration • Cross-talk with TGF-β resulting in epithelial-to-mesenchymal transition • Stimulation of inactive fibrocyte maturation to fibroblasts, which deposit collagen within extracellular matrix
IL-13		• In vitro, IL-13 induces human bronchial epithelial cells to release TGF-β • Changes in goblet cell density
HB-EGF	• Recombinant HB-EGF promotes migration of airway smooth muscle cells in vitro	• Recombinant HB-EGF promotes migration of airway smooth muscle cells in vitro
NGF		• NGF causes migration of vascular smooth muscle cells and fibroblasts, and proliferation of epithelial cells and airway smooth muscle cells
Tissue factor	• Reduces airway hyperresponsiveness, airway inflammation and airway remodeling in asthmatic mice	
Thrombin		• Induces secretion of PDGF in nasal and bronchial epithelial cells, sufficient for stimulating proliferation of fibroblast and bronchial smooth muscle cells • Stimulates VEGF production from airway epithelial cells
Galectin	• Galectin 3 inhibition significantly lowered collagen deposition in an allergic lung inflammation mouse model • In a chronic asthmatic mouse model, Gal-3 gene treatment reduced lung collagen • Galectin 3 deficiency associated with decreased airway remodeling following allergen sensitization in mice • Recombinant galectin 10 crystals promote type 2 immunity and mimic features of asthma in naive mice • Anti-galectin 10 antibodies reversed the effects of CLCs and house dust mite challenge in a humanized mouse model, reducing airway inflammation, goblet cell metaplasia, bronchial hyperreactivity and IgE synthesis	• Galectin 1 mRNA concentrations are lower in sputum from children with versus without asthma; in vitro knockdown of Galectin 1 promotes proliferation, migration and phenotypic switching in human airway smooth muscle cells • Galectin 3 predicts remodeling-associated anti-IgE treatment responses in bronchial biopsy samples from patients with severe asthma • Galectin 3 stimulation associated with in vitro MMP-9 release from peripheral blood neutrophils from patients with asthma • Sputum galectin 10 concentrations are higher in patients with asthma compared with healthy individuals; levels significantly correlate with sputum eosinophil counts • High versus low baseline galectin 10 levels do not predict greater improvements in FEV_1 following 32 weeks of anti-IL-5 treatment

INCREASED AIRWAY SMOOTH MUSCLE CELL MASS



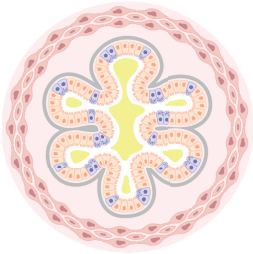
Asthma

- Increased asthma severity
- Airway narrowing
- Airway hyperresponsiveness
- Impaired lung function

Key

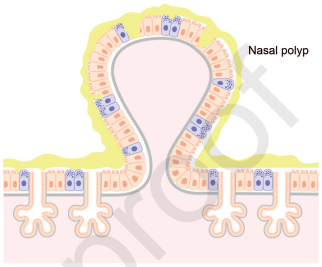
- Airway epithelial cell
- Goblet cell
- Eosinophil
- Neutrophil
- Th2 cell
- B cell
- Dendritic cell
- Macrophage
- Allergen
- Inhaled irritant
- Respiratory virus
- Collagen

GOBLET CELL AND MUCUS GLAND HYPERPLASIA



Asthma

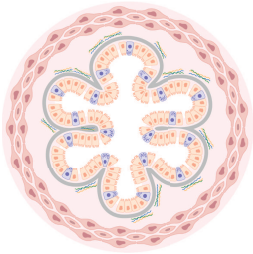
- Mucus plugs
- Narrowing of the airway
- Ventilation defect
- Reduced lung function
- Reduced asthma control



CRSwNP

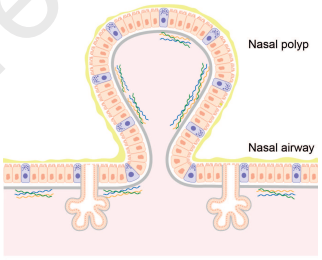
- Excess mucus

SUB-EPITHELIAL FIBROSIS (COLLAGEN DEPOSITION)



Asthma

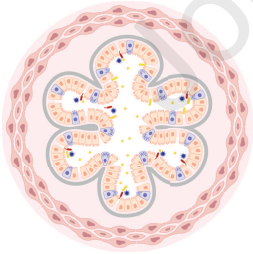
- Increased asthma severity
- Poor lung function with impaired reversibility
- Persistent symptom expression



CRSwNP

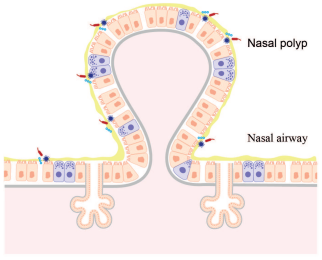
- Polyp formation
- Persistent symptom expression

IMPAIRED TIGHT JUNCTIONS



Asthma

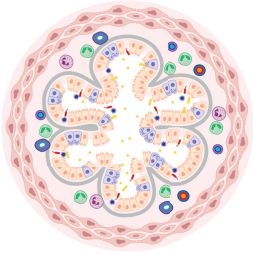
- Sensitization to aeroallergens
- Increased susceptibility to respiratory virus



CRSwNP

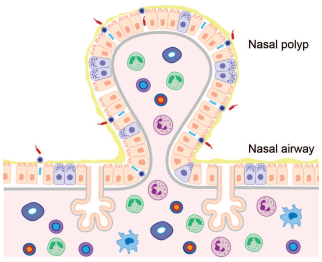
- Increased susceptibility to respiratory virus

DECREASED EPITHELIAL INTEGRITY



Asthma

- Airway hyperresponsiveness
- Perpetuating eosinophilic inflammation
- Persistent repair response with epithelial mesenchymal signaling



CRSwNP

- Perpetuating eosinophilic inflammation
- Persistent repair response with epithelial mesenchymal signaling