Novel potential treatable traits in asthma: Where is the research taking us?

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Asthma is a complex, heterogeneous disease in which the underlying mechanisms are not fully understood. Patients are often grouped into phenotypes (based on clinical, biologic, and physiologic characteristics) and endotypes (based on distinct genetic or molecular mechanisms). Recently, patients with asthma have been broadly split into 2 phenotypes based on their levels of type 2 inflammation: type 2 and non–type 2 asthma. However, this approach is likely oversimplified, and our understanding of the non–type 2 mechanisms in asthma remains extremely limited. A better understanding of asthma phenotypes and endotypes may assist in development of drugs for new therapeutic targets in asthma. One approach is to identify "treatable traits," which are specific patient characteristics related to phenotypes and endotypes that can be targeted by therapies. This review will focus on emerging treatable traits in asthma and aim to describe novel patient subgroups and endotypes that may represent the next step in the search for new therapeutic approaches. (J Allergy Clin Immunol Global 2022;1:27-36.)

Key words: *Asthma, treatable, trait, phenotype, inflammation, physiologic, infection-mediated, airway remodeling*

Abbreviations used

BAL:	Bronchoalveolar lavage
CFTR:	Cystic fibrosis transmembrane conductance regulator
CT:	Computed tomography
EGPA:	Eosinophilic granulomatosis with polyangiitis
ER:	Endoplasmic reticulum
FLAP:	5-Lipoxygenase activating protein
HDAC:	Histone deacetylase
HES:	Hypereosinophilic syndrome
ISG:	Interferon-stimulated gene
JAK:	Janus kinase
LXA_4:	Lipid mediator lipoxin A_4
NET:	Neutrophil extracellular trap
NK:	Natural killer
RV:	Rhinovirus
TRM:	Tissue-resident memory
TSLP:	Thymic stromal lymphopoietin

Asthma is a complex, heterogeneous disease with variable clinical manifestations. Patients with common clinical, biologic, and physiologic characteristics (phenotypes) are grouped together to guide diagnosis, therapy, and management of asthma. However, patients within a given phenotype can show heterogeneity of disease severity and response to therapy, prompting the need for more specific disease classifications. Recently, the term *endotype* has been introduced to define patients with asthma by distinct genetic or molecular mechanisms underlying asthma pathology.[1-3] Approaches based on endotypes and phenotypes have been proposed to optimally manage patients with asthma.

Classifying patients into phenotypes and endotypes can direct treatment toward targeting specific pathophysiologic pathways that may be dysregulated in a given phenotype or endotype. For example, asthma has been broadly split into 2 distinct phenotypes according to the degree of type 2 inflammation: type 2 and non–type 2 asthma.[1,2,4] Of these 2 phenotypes, type 2 asthma is the better understood and more easily identifiable in patients: eosinophilic inflammation and IgE synthesis both play a key role.[1,4] Non–type 2 asthma is less easily defined and may comprise several subpopulations (distinct phenotypes and endotypes) of patients with non–type 2 asthma.[4] However, because of the heterogeneity found in asthma, there are also likely to be patients whose asthma is driven by both type 2 and non–type 2 inflammatory mechanisms. Specific mechanisms may contribute to severe asthma in certain patients who do not respond to therapies targeting type 2 asthma alone.[5] A greater understanding of the phenotypes and endotypes involved in asthma pathology will help to identify patients who are more to likely benefit from established or novel or emerging targeted therapies.

The fact that patients with asthma can present with many clinical phenotypes justifies the need for a precision medicine strategy based on the presence of what have recently come to be known as "treatable traits."[6,7] A treatable trait is a therapeutic

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target identified by phenotype or endotype recognition through validated biomarkers; it is not necessarily specific to 1 disease and can change over time.[6,7] Agusti et al[6] have proposed treatable traits of chronic airway disease based on 3 domains: pulmonary (eg, airflow limitation, eosinophilic airway inflammation, airway bacterial colonization), extrapulmonary (eg, obesity, obstructive sleep apnea, cardiovascular disease), and treatable behavior/lifestyle risk factors (eg, smoking, symptom perception, adherence to treatment). The introduction of biologics directed at patients with eosinophilic and allergic asthma strongly suggests that identifying therapeutic targets contributing to pathophysiologic characteristics will significantly improve asthma control.[8] The identification and treatment of eosinophilic and allergic asthma may serve as a template for what could be achieved when targeting other treatable traits. However, not all patients with a given phenotype, such as late-onset eosinophilic asthma, will derive the same benefit from a targeted biologic, perhaps because multiple factors are at play. These treatable traits may be present across different phenotypes and endotypes of chronic airway disease, representing additional opportunities for targeted therapy. Furthermore, there is evidence that focusing on treatable traits leads to significant improvements in health-related quality of life and asthma control.[9]

There are numerous reviews that have covered asthma phenotypes and endotypes previously.[2,4,10-13] This review will focus on those treatable traits in asthma that are more recently discovered and those that represent a treatment gap in current asthma care. These include inflammatory traits (T_H17 cells and neutrophilic inflammation, T cells and natural killer [NK] cells, IL-6–high asthma, IL-6 transsignaling, and type 2–ultrahigh asthma), physiologic traits (airway mucus hypersecretion, chronic airway remodeling, nasal polyposis and comorbid asthma, leaky airway epithelial barrier, and endoplasmic reticulum [ER] stress), and infection-mediated traits (viral and bacterial infections) (Fig 1). Some traits may be less common or fall outside the typical type 2 versus non–type 2 categorization of asthma but are often associated with more severe disease, and although research is in its infancy, they may provide insight into our limited knowledge of the clinical features of treatable asthma pathology.

INFLAMMATORY TRAITS

T_H1 cells, T_H17 cells, and neutrophilic asthma

Although significant advances have been made for patients with type 2 asthma, non–type 2 asthma remains poorly understood. It is difficult to estimate the prevalence of non–type 2 asthma on account of the downregulation of type 2 biomarkers in patients treated with corticosteroids, which may result in patients with type 2 asthma being wrongly identified as having non–type 2 asthma.[14] Patients with non–type 2 asthma tend to have a poor response to corticosteroid treatment and often display relatively higher neutrophil blood counts than patients with type 2 asthma do.[1]

T_H1 and T_H17 are key cell types in non–type 2 asthma. T_H1 cells secrete the proinflammatory cytokines IFN-γ and TNF-α, which are implicated in neutrophilic airway inflammation.[15] IFN-γ and TNF-α are also known to induce corticosteroid resistance in human airway smooth muscle,[16] and IFN-γ is recognized as a driver of severe steroid-resistant asthma.[17] T_H17 cells also drive a distinct pathway in non–type 2 asthma that leads to IL-17 release and neutrophilic inflammation. Once activated, neutrophils act to eliminate pathogens via phagocytosis, degranulation, or formation of neutrophil extracellular traps (NETs).[18] NETs, which are composed of extracellular DNA, histones, and granular proteins, have been found in high levels in the airways of patients with neutrophilic and severe asthma.[19,20] The accumulation of NETs in patients' airways may aggravate their asthma further, contributing to a more severe disease phenotype.[19]

Neutrophilic asthma can be identified by the presence of sputum neutrophilia.[18,21] There are currently no specific therapies for neutrophilic asthma, which is exacerbated by the fact that patients with neutrophilic asthma tend to have a poor response to corticosteroid treatment.[22]

A number of novel, small molecule drugs are in early stages of development for the treatment of neutrophilic asthma. 5-Lipoxygenase activating protein (FLAP) inhibitors have the potential to reduce neutrophilic inflammation for patients with a high neutrophil count and airway obstructions. However, in a placebo-controlled trial in patients with moderate-to-severe asthma (N = 14), GSK2190915, a potent FLAP antagonist, failed to decrease sputum neutrophil numbers over 2 weeks. Further clinical trials in patients with neutrophilic asthma are required to assess efficacy.[23]

Macrolides may be used to reduce asthma exacerbations in patients with neutrophilic asthma. In a clinical trial of patients with severe asthma, low-dose azithromycin reduced asthma exacerbations in a subgroup of patients with neutrophilic asthma. However, whether the benefits occurred owing to azithromycin's antimicrobial or anti-inflammatory properties is unclear.[24] It should be noted that treatment with macrolides is associated with long-term microbial resistance and increased risk of adverse events.

Other potential therapies are in the preliminary stages of being studied for their effects on IL-17 and neutrophilic inflammation. BITS7201A, an antibody that neutralizes IL-17 and IL-13, was well tolerated in healthy volunteers and participants with mild atopic asthma in a phase 1 trial.[25] However, phase 2 trials have not started. A trial with adalimumab (anti–TNF-α) was conducted in healthy volunteers. A neutrophilic response was induced by using an inhaled endotoxin, which increased neutrophil counts in sputum, suggesting that anti–TNF-α could inhibit neutrophils. The authors suggest that the endotoxin model could be used for the early prediction of anti–TNF-α therapeutics in patients with asthma. However, clinical trials with anti–TNF-α have been unsuccessful in patients with asthma[26-28]; a large phase 2 study with golimumab was discontinued because of an unfavorable safety profile, with serious adverse effects (sepsis, cellulitis) and malignancies occurring more frequently in the golimumab group than in the placebo group.[27]

Therapies that target thymic stromal lymphopoietin (TSLP) may have the potential to treat neutrophilic asthma. TSLP is an upstream cytokine mediator that initiates type 2 signaling pathways and may drive neutrophilic inflammation through T_H17 cells and IL-17.[29,30] In the phase 3 NAVIGATOR trial, tezepelumab (an anti-TSLP therapy) was effective in both eosinophilic and noneosinophilic subgroups. Although the noneosinophilic subgroup may have included patients with neutrophilia, this population were not assessed specifically[31]; however, a phase 2 trial (CASCADE) measured the change in neutrophil, eosinophil, T-cell and mast cells counts in response to tezepelumab treatment in patients with differing levels of type 2 inflammation. The trial has been completed, but results are yet to be published.[32]

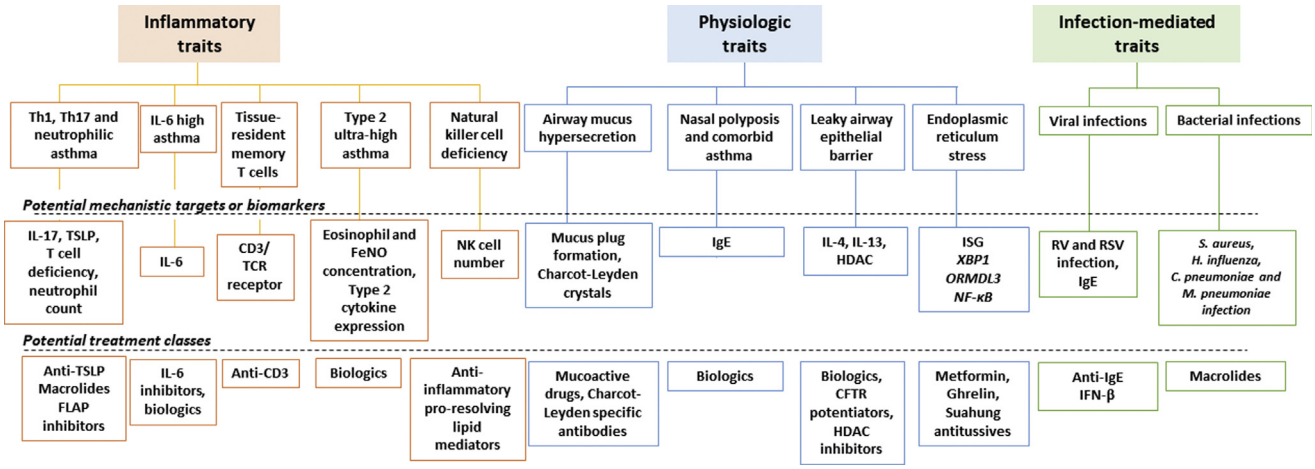

FIG 1. Novel treatable traits in asthma. An overview of the inflammatory, physiologic, and infection-mediated treatable traits for asthma, their potential mechanistic targets, and potential treatment classes. *FENO,* Fractional exhaled nitric oxide; *ISG*, interferon-stimulated gene; *TCR*, T-cell receptor.

Tezepelumab has now been approved for the treatment of severe asthma.[33] Another anti-TSLP therapy, CSJ117 (an inhaled antibody fragment), has shown positive results in a 12-week phase 1 trial in patients with mild asthma.[34]

Other therapies that target neutrophil chemotaxis and/or signaling cascade, such as IL-17A or CXC chemokine receptor 2, have not demonstrated efficacy in clinical studies so far. A phase 2 study demonstrated that a mAb blocking the IL-17 receptor, brodalumab, had no treatment effect in patients with moderate-to-severe asthma.[35] However, it is important to note that the study did not select for a T_H17 cell–high population. Placebo-controlled trials have demonstrated that CXC chemokine receptor 2 antagonists reduce blood neutrophil counts in patients with severe neutrophilic asthma; however, there was no associated improvement in terms of asthma control, lung function, or reduced exacerbation rates in those studies.[36,37] This suggests that a reduction in blood neutrophil counts may not be correlated with a reduction in airway neutrophil numbers or airway inflammation,[38,39] limiting the accuracy of this biomarker for monitoring or predicting response to therapy. The aforementioned results call into question the role of circulating neutrophils in asthma and the extent to which non–type 2 asthma is driven by neutrophilic inflammation. Although there is a notable body of evidence implicating neutrophils in non–type 2 asthma, clinical data to support the efficacy of targeted antineutrophil therapies in non–type 2 asthma are lacking.[36,37] Therefore, there is a need for further clinical trials to be carried out in patients with neutrophilic or T_H17 cell–high asthma.

TRM T cells

Memory T cells are antigen-specific T cells that remain after an infection has been eliminated. Lung tissue-resident memory (TRM) cells are a subset of these cells that do not recirculate; they patrol the mucosal barriers of the lung and play a crucial role in mounting optimal responses during reinfections. After reactivation, TRM cells rapidly secrete effector cytokines. Although lung TRM cells can protect against respiratory infection,[40] it has been observed that in murine models of asthma lung, T_H2 TRM cells can cause chronic airway inflammation via the release of cytokines that recruit eosinophils and also maintain "allergic memory" in the lung.[40,41] Additionally, in a study that clustered patients with asthma on the basis of the cell composition of their bronchoalveolar lavage (BAL) fluid, a distinct patient group dominated by IFN-γ–producing T cells, including $CD4^+$ and $CD8^+$ TRM cells, was identified.[42] Therefore, targeting TRM cells could be a conceivable therapy, potentially via the T-cell receptor-CD3 complex. A preclinical study in mice demonstrated that anti-CD3 treatment specifically inhibited eosinophilic lung inflammation driven by T_H2 TRM cells.[43] There are currently no clinical trials of anti-CD3 in patients with asthma, although anti-CD3 is in development for the treatment of autoimmune disorders.[44]

$CD8^+$ T-cell deficiency

A recent study has shown that individuals with non–type 2 asthma exhibit a deficiency in airway cytotoxic $CD8^+$ T cells associated with obesity-driven inflammation.[45] This has led the authors to speculate that deficiency in cytotoxic $CD8^+$ T cells and an impaired immune response to viral infections could be a mechanism of exacerbations in non–type 2 asthma. Additionally, it is possible that obesity-related systemic inflammation could cause cytotoxic T-cell dysfunction, possibly via T-cell exhaustion.[45] So far, there have been no studies investigating therapies that target $CD8^+$ T-cell immunity in asthma.

NK cell deficiency

There is evidence that decreased NK cell abundance and cytotoxicity may play a role in persistent airway inflammation in patients with asthma.[46] In a study investigating BAL fluid cell samples taken from patients enrolled in the 3-year longitudinal Severe Asthma Research Programme-3 study, patients with asthma had fewer NK cells in their BAL fluid than healthy participants did.[46] In addition, compared with healthy participants, patients with severe asthma had decreased ratios of NK cells to T_H cells and neutrophils.[46] There was also evidence that the NK cells present in patients with asthma are less effective at killing target cells than the NK cells in healthy participants are.[46]

These data suggest that in some patients with severe asthma, the number and efficacy of NK cells may be reduced, leading to an impaired anti-inflammatory response that is only worsened by corticosteroid treatment. This may provide a plausible mechanism for the poor response of some patients with non–type 2 asthma to corticosteroid treatment.

Therapies that preserve NK cell effector mechanisms, such as anti-inflammatory proresolving lipid mediator lipoxin A_4 (LXA_4) may be beneficial for the treatment of the aforementioned individuals.[47] In an *in vitro* study, peripheral blood and lung NK cells from healthy participants were exposed to LXA_4, leading to increased NK cell–mediated apoptosis of eosinophils. This highlights LXA_4 as a potential anti-inflammatory and treatment for severe asthma caused by NK cell deficiency.[47]

IL-6–high asthma and obesity

IL-6 is a proinflammatory cytokine, and studies suggest that it plays an active role in the pathogenesis of asthma.[48-50] IL-6 is a biomarker of obesity-related systemic inflammation and metabolic dysfunction, and a distinct subgroup of patients with obesity and severe asthma has previously been described.[3,51] Comorbid asthma and obesity are frequently characterized by late-onset of disease, female predominance, and non–type 2 inflammation.[52,53] Better asthma control, lung function, and asthma-related quality of life can sometimes be improved following aggressive weight loss[54]; however, it should be noted that the impact of obesity on asthma pathology does not appear to be isolated to the physiologic impact of increased body mass on chest wall function. This was demonstrated in 2 separate studies that evaluated the impact of IL-6 systemic inflammation on asthma exacerbation rates and lung function measurements. Peters et al reported that patients with metabolic dysfunction and elevations in plasma IL-6 demonstrated more frequent asthma exacerbations and lower lung function than did IL-6–low patients, independent from body mass index.[50] Specifically, nonobese patients with high plasma IL-6 levels had more severe asthma when compared with the levels in nonobese patients without metabolic dysfunction and low levels of IL-6. These findings suggest that IL-6 and metabolic dysfunction may worsen asthma severity, even in nonobese patients.

Therapeutics targeting IL-6 may be promising for patients with IL-6–high asthma. However, in a small proof-of-concept clinical trial, the IL-6 inhibitor tocilizumab was unable to prevent allergen-induced bronchoconstriction in adult patients with mild asthma.[55] There is the potential for combination of IL-6 inhibition with other therapies. A preclinical study in a BAL fluid mouse model for asthma has demonstrated that a combination of IL-6 and TNF inhibition prevented the increase of eosinophilic and neutrophilic infiltrate, so it may therefore be effective in reducing inflammatory response in the lungs.[56,57] There is currently an ongoing phase 2 trial assessing the efficacy and safety of the IL-6 inhibitor FB704A in adults with severe asthma. The results are yet to be published.[58]

IL-6 transsignaling

IL-6 transsignaling (an alternative mechanism to classic IL-6 signaling) is seen in certain cells that do not express high levels of membrane IL-6 receptor, and it has also been implicated in exacerbation-prone asthma.[59] IL-6 transsignaling is mediated by a soluble IL-6 receptor that is likely produced by neutrophils at the site of inflammation in patients with asthma.[59,60] A novel subset of patients with asthma whose asthma is driven by IL-6 transsignaling pathway activation in the lung epithelium and is associated with a high exacerbation rate and type 2–independent eosinophilia has been described.[59] Further research into the prevalence and impact of this emerging mechanism of inflammation in patients with asthma is warranted.

Taken together with the data on IL-6–high asthma, these data are important, as they demonstrate that IL-6 may be a plausible underlying mechanism in some populations with non–type 2, severe asthma and may provide direction for further research.[56]

Type 2–ultrahigh asthma

It has become increasingly apparent that type 2 inflammation exists on a spectrum of severity. Patients with mild-to-moderate asthma may demonstrate airway measures of type 2 inflammation that are higher than those in healthy control subjects, but these measures are frequently extinguished by inhaled or systemic corticosteroids.[61] In contrast, many patients with severe asthma have airway measures of type 2 inflammation that are resistant to corticosteroid treatment.[62] Corticosteroid resistance is linked to various mechanisms, including respiratory infections and obesity,[63] but it could also be due to a type 2–ultrahigh phenotype.[45] In a network analysis of sputum cell transcriptome expression data on patients with asthma, a subgroup of type 2–high patients with uniformly higher expression of type 2 measures was identified. Compared with patients with standard type 2 asthma, patients with type 2–ultrahigh asthma had characteristics that included a high sputum eosinophil count (median 7.3% vs 2% in patients with type 2 asthma) and high fractional exhaled nitric oxide concentrations (median 52 ppb vs 41 ppb in patients with type 2 asthma); in addition, they were generally older and had more severe airflow obstruction.[45]

Other conditions characterized by an exceptionally high eosinophil count include hypereosinophilic syndrome (HES), which is an idiopathic group of disorders characterized by blood and/or tissue eosinophilia,[64] and eosinophilic granulomatosis with polyangiitis (EGPA), which is a systemic vasculitis occurring in people with asthma.[65] Both disorders are typically characterized by eosinophil levels higher than 1500 cells/μL.[64,66]

IL-5 is produced by T_H2 cells and is a potent activator of eosinophils.[67] In a phase 3 study with patients with HES, mepolizumab, which is an anti–IL-5 agent, markedly reduced mean blood eosinophil counts from 1460 cells/μL to 170 cells/μL after week 2.[64] Mepolizumab additionally reduced peripheral eosinophil count[68] and significantly extended the remission period in patients with EGPA.[69] Benralizumab, a biologic targeting the IL-5 receptor, is also in development for treatment of EGPA and HES.[70,71] Given that mepolizumab and benralizumab are approved for the treatment of severe asthma and the existence of evidence that the higher the blood eosinophil level, the higher the expected impact of treatment,[72,73] anti–IL-5 biologics have clear potential for treating type 2–ultrahigh asthma.

Janus kinase (JAK) inhibitors are another possible treatment: preclinical data demonstrate that JAK inhibition may reduce airway inflammation and hyperreactivity in asthma,[74] and JAK inhibitors reduce BAL eosinophilia *in vivo*.[74,75] JAK inhibitors are in the early stages of development in patients with asthma.[76]

PHYSIOLOGIC TRAITS

Airway mucus hypersecretion

Mucus hypersecretion is a widely recognized hallmark of asthma and plays a key role in pathogenesis of the disease. In small peripheral airways, mucus hypersecretion may lead to plugging of the airway lumen and airway obstruction. Mucus plugging has been well documented in fatal asthma and is believed to play a major role in cause of death. Recent research has demonstrated that it is also common in chronic severe asthma.[77] Multidetector computed tomography (CT) lung scans from 146 patients with asthma and 22 healthy participants demonstrated that mucus plugs were more common in patients with severe asthma than in healthy participants.[78] Mucus plugs were visually observed on a CT scan, and a mucus score from 0 to 20 was assigned. High mucus scores (a score of 4-20 based on the median score of the "plugged" group) were strongly correlated with airway eosinophilia and other markers of type 2 inflammation,[77] and patients with particularly high mucus scores did not respond to bronchodilator or systemic corticosteroid treatment.[78]

Detection of mucus plugs in the lung by using multidetector CT lung scans could potentially serve as a biomarker of disease severity in the airways of patients with asthma. Detection of mucus plugs could also be an indicative outcome for clinical trials to determine whether mucolytics or inhibitors of type 2 inflammation can reduce mucus plug formation to improve airflow in chronic severe asthma.

A separate study has also indicated that Charcot-Leyden crystals, an indicator of eosinophilic inflammation often found in patients with asthma, are highly abundant in airway mucus.[79] The formation of such Charcot-Leyden crystals actively promotes key features of asthma, such as airway inflammation, goblet cell metaplasia, bronchial hyperreactivity, and IgE synthesis.[79] Charcot-Leyden crystal–specific antibodies were able to dissolve the crystal formations, *in vitro* and *in vivo*.[79]

Mucus plugs and Charcot-Leyden crystals are a tractable treatment target in patients with severe asthma. Targeted treatment with mucoactive drugs may improve airflow in patients with chronic severe asthma, especially in the subset of patients with high mucus scores who did not respond to traditional therapies.[77,78] Similarly, specific antibodies could potentially be used to dissolve Charcot-Leyden crystal formations and reduce the associated airway inflammation.[79]

Chronic airway remodeling

Airway remodeling in asthma is recognized as structural changes in the airways, including thickening of the airway epithelium, hypertrophy and hyperplasia of the airway smooth muscle cells, thickening and fibrosis of the subepithelial basement membrane, hypertrophy of the bronchial glands, goblet cell hyperplasia, and loss of lung elastic recoil.[80,81] These changes can lead to persistent airflow limitation and are a leading cause of reduced lung function. Both type 2 and non–type 2 asthma can lead to airway remodeling, which usually worsens over time and with disease severity.

The inflammatory cytokines IL-4, IL-5, and IL-13, produced by activated T_H2 cells[2] and type 2 innate lymphoid cells,[82] promote eosinophil recruitment. Elevated eosinophil levels contribute to airway remodeling and airway hyperresponsiveness by causing chronic inflammation and damage to the airways. Airway remodeling has been linked with early-onset asthma and disease severity, and it has also been reported in very young children with asthma. It is therefore likely that airway remodeling can also occur in parallel to chronic inflammation, rather than as a direct consequence of sustained inflammation, through a distinct mechanism (or mechanisms) that may not respond to therapies targeting inflammation alone.

IgE is also involved in the pathogenesis of airway remodeling and plays a key role in the development of many asthma-related symptoms.[2,83] TSLP has direct effects on fibroblasts, which may contribute to airway remodeling in asthma through increased deposition of collagen or other pathways.[84,85] Furthermore, TSLP expression in the bronchial epithelium and airway smooth muscle is upregulated in patients with asthma and promotes mast cell synthetic function.[85]

Airway remodeling can be assessed by obtaining surgical lung specimens, or by sampling airway tissues through flexible bronchoscopy. However, these methods require specialist expertise, so tools have been developed to bypass this. Indirect analysis of blood, urine, and sputum remodeling markers can be carried out, although whether the variations in these markers results in significant consequences in the airway walls is not always clear. Other techniques such as CT, endobronchial ultrasound, and lung function measurement can also be used as screening tools.[86]

At present, there are no therapies that have demonstrated long-term disease modification in asthma. However, there are biologics targeting IL-5, IL-4/IL-13, and IgE that have been shown to have an effect on airway remodeling. The anti-IgE biologic omalizumab has been shown to reduce reticular basement membrane thickness and decrease levels of proteins specifically related to airway remodeling.[87] A computational model based on bronchial biopsy samples from adults with eosinophilic asthma (N = 25) treated with either benralizumab (an anti–IL-5 receptor biologic) or placebo demonstrated that benralizumab significantly reduced airway smooth muscle mass and number of eosinophils versus placebo. Additional studies into the effects of benralizumab and mepolizumab (an anti–IL-5 biologic) on airway remodeling are currently under way. Although biologics may be a potential treatment for airway remodeling in asthma, it is important to note that not all patients will respond to these therapies, and the data are limited.[88] There have been few studies assessing airway hyperresponsiveness, which may be key for airway remodeling in asthma. Bronchial thermoplasty is another potential therapy that may combat airway remodeling. It has been shown to reduce airway smooth muscle mass and reticular basement membrane thickness in patients with severe asthma, although its mode of action remains unclear.[89]

The therapies described earlier in this review have shown potential to exhibit an effect on airway remodeling in patients with asthma, but further study into their long-term effects is required. The development of treatments to prevent or reverse airway remodeling would address a key unmet need in current asthma care.

Nasal polyposis and comorbid asthma

Late-onset asthma, which is often nonallergic and severe, has been shown to be highly correlated with nasal polyposis (also known as chronic rhinosinusitis with nasal polyps). Patients with nasal polyposis often have severe asthma and a high disease burden, including an increased risk of hospitalization. They may also be more likely to have aspirin-exacerbated respiratory

disease, eosinophilic granulomatosis with polyangiitis, or allergic fungal sinusitis with or without concomitant allergic bronchopulmonary aspergillosis.[90-94] Patients with both nasal polyposis and asthma often present with distinct biomarkers, which suggests a common underlying mechanism.[90,95] For example, patients with eosinophilic nasal polyposis and comorbid asthma often have higher IgE levels,[96] providing a plausible target for nasal polyposis therapies. In 2 phase 3 studies, add-on omalizumab (anti-IgE) was shown to improve nasal polyposis scores and nasal congestion scores in patients with nasal polyposis[97]; accordingly, omalizumab has recently received approval as an add-on treatment of nasal polyps in adult patients with an inadequate response to nasal corticosteroids. Similarly, dupilumab (anti–IL-4/IL-13) has also been approved for use in patients with severe refractory nasal polyposis due to shared inflammatory pathways involving IL-4/IL-13 found in both asthma and nasal polyposis. IL-5 may also represent a shared inflammatory target: the phase 3 clinical trial SYNAPSE investigating mepolizumab (anti–IL-5) demonstrated that mepolizumab reduced nasal polyp size, sinonasal symptoms, the need for endoscopic surgery, and the need for systemic corticosteroid use in adults with severe nasal polyposis. In 2021, mepolizumab was approved for the treatment of nasal polyposis in the United States. The OSTRO study investigating the anti–IL-5 receptor benralizumab for nasal polyposis has also been completed, with results similar to those of the SYNAPSE study.[98]

Leaky airway epithelial barrier

Repeated injury and repair of the airway epithelium following exposure to inflammation and environmental factors can cause damage to tight junctions of the airway epithelium. This leads to increased airway epithelial permeability and contributes to chronic mucosal airway inflammation by facilitating paracellular transport of pathogens and allergens.[99] It is observed in patients with asthma, allergic rhinitis, and nasal polyposis.[100-103]

In a study of primary human bronchial epithelial cells from patients with and without asthma, the bronchial epithelial cells of patients with asthma had an increased expression of histone deacetylases (HDACs). HDACs suppress the transcription of key genes involved in epithelial integrity and tight junction formation. In these patients, IL-4 and IL-13 appeared to upregulate HDAC activity, suggesting that type 2 inflammation may drive barrier leakiness. Inhibition of HDACs in bronchial epithelial cells from patients with asthma increased the synthesis of tight junction molecules to the levels seen in healthy participants, improving barrier integrity.[99] HDAC activity may be just 1 of many mechanisms involved: altered ion transport channels and shifts in the homeostasis of sphingolipids, angiopoietins, and prostaglandins have all been proposed as potential mechanisms driving increased airway epithelial permeability.[104]

Recently, ionocytes were discovered; they are novel airway epithelial cells that highly express cystic fibrosis transmembrane conductance regulator (CFTR), a transmembrane protein that regulates anion transport.[105] CFTR has been demonstrated to regulate tight junction assembly and epithelial differentiation[106]; therefore, ionocytes may play a crucial role in regulating epithelial barrier function.[100]

Despite breakthroughs in understanding of the pathology of airway epithelial permeability, this pathology has not been studied extensively, and potential solutions for airway epithelial barrier dysfunction have not reached clinical practice. Therapies may include HDAC inhibitors or CFTR potentiators (currently used to treat cystic fibrosis, and under investigation for the treatment of chronic obstructive pulmonary disease)[107]; however, the preservation or reconstitution of airway barrier function warrants extensive studies, and it may be some time before therapeutic strategies are realized.

ER stress

ER stress involves the disruption of protein folding in the ER, leading to the accumulation of misfolded proteins. It is likely to impair the immune and inflammatory response commonly seen in asthma; this is unsurprising given the variety of cell types and high levels of secreted proteins involved in the inflammatory process in asthma.[108] Furthermore, many environmental factors that induce ER stress in the lung are known triggers of asthma, including air pollutants, cigarette smoke, allergens, and pathogens. Importantly, ER stress has been linked to both type 2 and non–type 2 inflammation.[5,109,110] Genes and proteins associated with ER stress include interferon-stimulated genes (ISGs), X-box binding protein 1, the ER-resident transmembrane protein ORMDL3, and the transcription factor nuclear factor-κB.[5,109,110] ISG expression was elevated in patients with asthma and associated with reduced lung function and ER stress.[5]

Although further research is necessary, both ER stress and ISG expression are potential therapeutic targets that do not fall within the type 2 or non–type 2 endotype. Additionally, the potential role of ER stress in corticosteroid resistance has recently begun to emerge, as it mediates the activation of the P13K, MAPK, and nuclear factor-κB pathways, which are involved in corticosteroid-resistant asthma.[108,111] A number of compounds have been observed to treat ER stress-based asthma in preclinical studies; however, the research has been limited. Suhuang antitussive capsule is a traditional Chinese patent drug shown to inhibit ER stress in the lungs of rats with induced cough-variant asthma. Treatment with ghrelin, a peptide hormone released by the stomach, has been observed to inhibit ER stress in a murine ovalbumin-induced asthmatic mouse model by stimulating the Akt signaling pathway, thereby reducing inflammatory responses.[110,112] Metformin has also been shown to protect against ER stress in mice with cigarette smoke–induced lung inflammation, and it may therefore have potential for the treatment of asthma.[113] Further studies are required to establish the potential of these therapies to treat ER stress-based asthma.

INFECTION-MEDIATED TRAITS

Viral infections

Viral infections such as rhinovirus (RV) and respiratory syncytial virus have been associated with early-onset asthma development,[114-116] and they are among the leading causes of acute asthma exacerbations.[117] This is supported by early reports of a reduction in asthma exacerbations during the COVID-19 pandemic, as social distancing and hygiene measures reduced viral spread through populations.[118,119] Although the mechanisms driving viral-exacerbated asthma likely vary depending on the infection and presence of NK cells,[120] there may be a subgroup of patients who are more susceptible to virus-induced exacerbations; these patients experience more exacerbations, perhaps

on account of interactions between the IgE-mediated allergen response and the viral infection.[117,121] In a study of 183 patients with asthma who were 6 to 17 years old, an increase in both total IgE levels and allergen-specific IgE levels was associated with an increase in the severity of RV-triggered asthma exacerbations.[122] Separately, 2 parallel studies demonstrated that adults with both asthma and high levels of total serum IgE had worse lower respiratory tract symptoms, lower lung function, and increased eosinophil levels compared with healthy participants 2 to 3 days after RV infection. The same studies demonstrated that anti-IgE treatment with omalizumab improved lung function and asthma control during the first 4 days of infection in adult patients with asthma versus in those who received placebo.[123] Other studies have indicated that omalizumab has a positive impact on RV-induced exacerbations in children. In 1 study, omalizumab was shown to reduce seasonal exacerbations in children, adolescents, and young adults during the autumn (a time associated with viral infection and increased allergen levels).[124] In a more recent study, when compared with standard asthma care, add-on omalizumab was associated with a decrease in duration of RV infections, viral shedding, and the risk of RV illnesses in children with allergic asthma.[125] These results further support the existence of an association between allergic IgE-mediated asthma and viral-exacerbated asthma in some patients, who may therefore be at increased risk of exacerbations than their counterparts without allergy.

There is also potential to treat viral-induced asthma by boosting antiviral immunity. Studies have shown that patients with asthma are susceptible to viral infection due to deficiencies in interferon production.[126-128] In a randomized study of 147 patients with asthma, treatment with IFN-β ameliorated airway response to viral infection and enhanced morning peak expiratory flow recovery. These studies suggest a possible therapeutic benefit of IFN-β for targeting virus-induced asthma, and they support the need for further investigation.[129]

Bacterial infections

The microbiome, both pulmonary and gastrointestinal, is likely to play a crucial role in modulating immune responses in asthma.[130] Bacterial colonization also appears to play a role in the induction and exacerbation of asthma in both children and adults. In asthma, *Staphylococcus aureus* activates the sensitization phase of the allergic response via the release of enterotoxins and serine protease–like proteins, which are able to induce B-cell IgE class switching and production of polyclonal IgE.[131] *S aureus* enterotoxins can also act as superantigens that activate large numbers of T cells and B cells and ultimately trigger release of inflammatory mediators.[131] Nontypeable *Haemophilus influenzae* is thought to play an important role in the progression of neutrophilic asthma and promote the occurrence of corticosteroid resistance.[132] In addition, infection or colonization of the airway with atypical bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* is also implicated in asthma pathogenesis.[133,134] A study is currently investigating the bronchial microbiome in patients with neutrophilic and nonneutrophilic asthma, which may provide further insights. Interestingly, it appears that key components of the innate immune system that are associated predominantly with the prevention of infection may also play a role in the control of pulmonary inflammation in asthma. Surfactant protein A, for example, has been found at lower levels in patients with asthma (particularly those who are obese) than in healthy participants.[135] Recent studies using animal models[136,137] and primary epithelial cells taken from patients with asthma suggest that surfactant protein A regulates IL-13–induced inflammation and promotes eosinophilic clearance. It appears that in at least some patients with asthma, these functions may be impaired.

Macrolide antibiotics, such as azithromycin, are active against gram-positive bacteria such as *Staphylococcus*, *Streptococcus*, and *Diplococcus* and are thought of as a potential therapy for bacterial infection–mediated asthma. They also have broad anti-inflammatory and immunomodulatory effects.[138,139] There is evidence that macrolides may reduce severe asthma exacerbations and symptoms[140]; so far however, whether the antimicrobial properties of macrolides are necessary for their therapeutic efficacy has not been established. Further insights may be gained from an ongoing study assessing the effects of azithromycin on the lung bacteria of patients with asthma and determining whether these effects translate to an improvement in asthma symptoms.

Prebiotics, which are foods that promote the growth of the gut's beneficial bacteria, have also been studied for their effects in preventing allergic disease in pregnant women and children, and they have been found to reduce the risk of asthma and wheezing compared with placebo.[141]

The current clinical evidence does not support the use of therapies targeting the microbiome as effective treatment for asthma, and additional trials are required to understand the effects of these therapies.[142]

SUMMARY

Given the growing evidence of asthma populations that do not neatly fit into type 2 or non–type 2 phenotypes, acknowledging treatable traits in patients with asthma may help identify new treatment targets and potential asthma therapies, particularly for patients who might currently lack effective therapies, such as those with non–type 2 asthma. Improving our understanding of lesser-known treatable traits in asthma, even if the research is still in its infancy, may expand our knowledge of treatable asthma pathology and be a vital step in improving asthma care.

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