Understanding the key issues in the treatment of uncontrolled persistent asthma with type 2 inflammation

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Abstract

Asthma is a complex respiratory disease that varies in severity and response to treatment. Several asthma phenotypes with unique clinical and inflammatory characteristics have been identified. Endotypes, based on distinct molecular profiles, help to further elucidate the heterogeneity within asthma. Type 2 inflammation, involving both the innate (type 2 innate lymphoid cell) and adaptive (T-helper type 2 cells) immune systems, underpins the complex pathophysiology of chronic inflammation in asthma, as well as the presence of comorbid disease (e.g. chronic rhinosinusitis with nasal polyps, allergic rhinitis and atopic dermatitis). Type 2 inflammation is characterised by upregulation of the type 2 cytokines interleukin (IL)-4, IL-5 and IL-13, IgE-mediated release of immune mediators and dysfunction of epithelial or epidermal barriers. Targeting these key proximal type 2 cytokines has shown efficacy in recent studies adopting a personalised approach to treatment using targeted biologics. Elevated levels of biomarkers downstream of type 2 cytokines, including fractional exhaled nitric oxide, serum IgE and blood and sputum eosinophils, have been linked to mechanisms involved in type 2 inflammation. They have the potential to aid diagnosis, and to predict and monitor response to treatment. The objective of this review is to summarise the current understanding of the biology of type 2 inflammation in asthma, examine its influence on type 2 inflammatory comorbidities, and discuss how type 2 inflammatory biomarkers can be harnessed to further personalise treatments in the age of biologic medicines.

Introduction

Asthma is associated with significant heterogeneity. Several different asthma phenotypes with unique clinical and inflammatory profiles have now been identified. The 2020 Global Initiative for Asthma (GINA) guidelines recommend assessment of inflammatory phenotypes in patients with severe asthma because these profiles can help describe the physical manifestation of airway inflammation and may also help predict responsiveness to tailored treatments [1, 2]. Table 1 presents an example of current asthma phenotypes as they relate to inflammatory type (type 2-high or type 2-low) and phenotypic characteristics. Hallmarks of type 2 pathway activation include IgE production, eosinophilia and elevated type 2 biomarkers such as fraction of exhaled nitric oxide (F_{eNO}). Endotypes help to further elucidate the heterogeneity within asthma by identifying subtypes of the condition based on distinct functional or pathophysiological characteristics [12–14]. Unlike phenotypes, which may change over time or in response to treatment, endotype subgroups remain relatively stable because they are defined by inherent genetic and molecular mechanisms [15].

TABLE 1 Type 2 inflammation and phenotypic characteristics of asthma [3–5]

Type 2-high asthma IL-4, IL-5, IL-13	Type 2-low asthma
Blood eosinophilia (⩾150 cells·µL^{-1} [6])	Low blood eosinophil counts (<150 cells·µL^{-1})
Elevated tissue eosinophilia	Sputum neutrophilia (>40% of total cells [6–8])
Elevated serum IgE (surpassing the normal range of 1.5–114 kU·L$^{-1\#}$ [9, 10])	Obesity associated
Elevated F_{eNO} (>19.5 ppb [11])	Poor response to corticosteroids
Upper airway comorbidities, including AR and CRSsNP/CRSwNP	
Other type 2 comorbidities, including EoE and AD	
Responsive to corticosteroids	

IL: interleukin; Ig: immunoglobulin; F_{eNO}: fraction of exhaled nitric oxide; AR: allergic rhinitis; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; EoE: eosinophilic oesophagitis; AD: atopic dermatitis. [#]: value within the normal range does not exclude atopy [10].

Asthma and associated type 2 inflammation are observed in 50–70% of patients with asthma, and are driven by both the innate (type 2 innate lymphoid (ILC2) cells) and adaptive (T-helper cell type 2 (Th2) cells) immune systems, characterised by the release of cytokines such as interleukin (IL)-4, IL-5 and IL-13, key pathophysiological characteristics of asthma [3, 13]. IL-4 and IL-13 are involved in mucus production and goblet cell hyperplasia, airway smooth muscle contractility and proliferation, fibrosis, basement membrane thickening, barrier dysfunction, eosinophil trafficking into the lungs and IgE production [16]. IL-5 promotes eosinophil maturation, activation and trafficking [16]. IgE then promotes the degranulation of mast cells and basophils, and the development of allergic reactions in asthma. Elevations in inflammatory cells and biomarkers downstream of type 2 cytokines, including F_{eNO}, serum IgE and blood and sputum eosinophils, have been linked to mechanisms involved in type 2 inflammation [17].

Targeting specific cytokines within the type 2 inflammatory pathway reduces the pathophysiology of asthma and other type 2 inflammatory comorbidities [13]. A number of targeted biologics have been evaluated as potential treatments, including monoclonal antibodies to IL-4, IL-5, IgE and IL-13; in the process, insights have been provided into the molecular mechanisms of these atopic diseases [18–20]. Current GINA guidelines recommend blockade of the IL-4 receptor (IL-4R) (thus inhibiting signalling of both IL-4 and IL-13) in patients with severe type 2/eosinophilic asthma, inhibition of IgE in patients with severe allergic asthma, and inhibition of IL-5/blockade of the IL-5 receptor (IL-5R) in patients with severe eosinophilic asthma (figure 1) [2, 21]. Biomarkers that reflect type 2 cytokine involvement are currently being used for personalised treatment or patient selection in clinical trials of a number of these targeted biologics [13].

This review discusses our current understanding of the biology of type 2 inflammation in asthma, its influence on type 2 inflammatory comorbidities and how type 2 inflammatory biomarkers can be harnessed to further personalise treatments in the age of biologic medicines.

The impact of type 2 cytokines on the pathophysiological features of asthma

Type 2 inflammatory airway disease can be associated with debilitating symptoms, greater requirement for corticosteroid medication, suboptimal disease control and poor quality of life. The characteristic pathological features of type 2 asthma, as outlined above, include cytokine-induced eosinophilic airway inflammation, mucus plugging, goblet cell hyperplasia, changes in epithelial barrier and airway smooth muscle function, and remodelling of the airway wall (table 2) [16, 23]. In this section, we discuss each of the features in turn, highlighting the key drivers and cytokines involved.

Inflammatory response

The interplay between innate and adaptive cells and mediators in type 2 inflammation underpins asthma pathophysiology (figure 2) [3, 16, 24]. Type 2 immune responses in the airway are mediated mainly by eosinophils, mast cells, basophils, Th2 cells, ILC2s and IgE-producing B-cells. Upstream events in the airway epithelium involving secretion of master regulators or alarmins such as IL-33, IL-25 or thymic stromal lymphopoietin (TSLP) regulate maturation of CD4^{+} T-cells to induce a Th2 adaptive immune response. Th2 cells migrate to the airway epithelium, where, together with ILC2 cells, they generate a variety of type 2 cytokines (IL-4, IL-5 and IL-13) that aid in eosinophil recruitment and B-cell class switching [13, 24]. These cytokines play key roles in the disease pathophysiology and drive a variety of downstream events, including activation of airway epithelial cells, chemoattraction of effector cells,
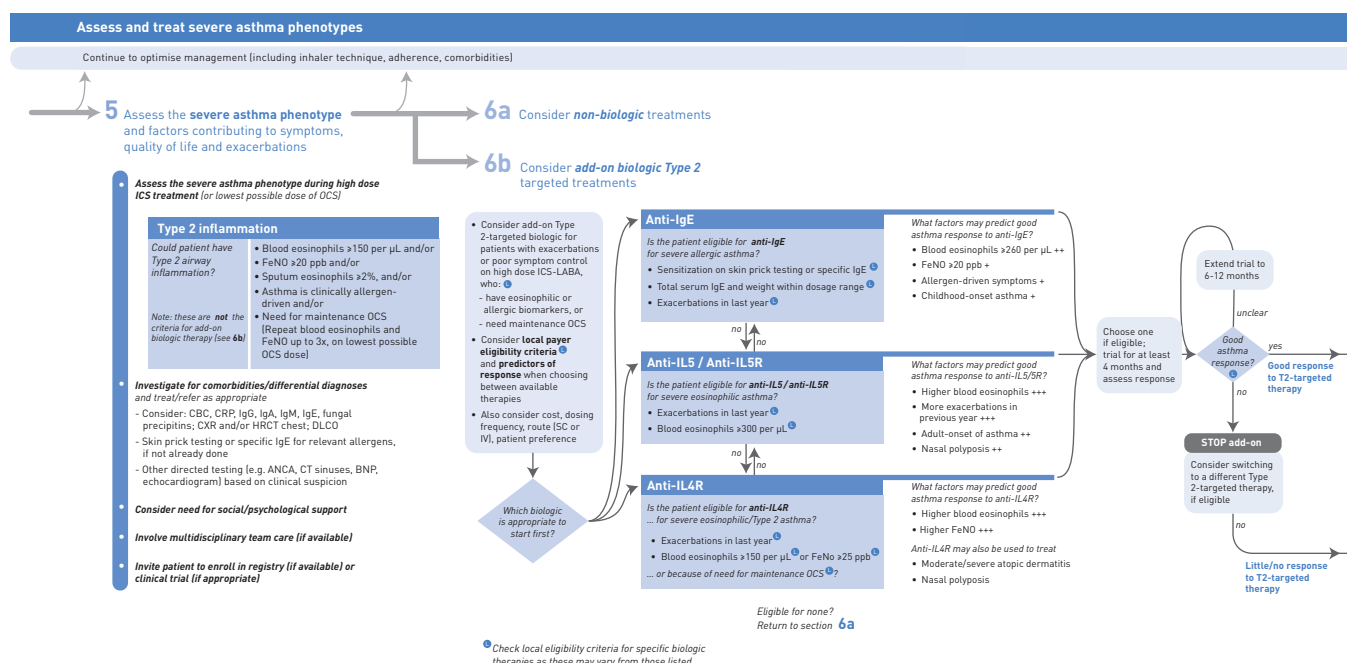
FIGURE 1 GINA guidelines for the assessment of adult and adolescent patients with difficult-to-treat asthma including biologic treatment options. ©2020 Global Initiative for Asthma, reprinted with permission (www.ginasthma.org). ANCA: antineutrophil cytoplasmic antibody; BNP: B-type natriuretic peptide; CBC: complete blood count; CRP: C-reactive protein; CT: computerised tomography; CXR: chest X-ray; DLCO: diffusing capacity of the lung for carbon monoxide; FeNO: fractional exhaled nitric oxide; HRCT: high-resolution computerised tomography; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; IV: intravenous; LABA: long-acting β2-agonist; OCS: oral corticosteroids; SC: subcutaneous.

regulation of airway smooth muscle and remodelling of the epithelial matrix. These responses, in turn, predispose towards hyperresponsiveness, airflow obstruction and exacerbations. In addition to the adaptive response to external stimuli, IL-25, IL-33 and TSLP can directly activate ILC2s to secrete IL-5, IL-13 and IL-9, the latter contributing to the further activation and survival of ILC2s [25, 26]. *In vitro* studies have shown that IL-4 and IL-13 can induce B-cell switching and IgE production, leading to the sensitisation of mast cells and basophils and consequent release of pro-inflammatory mediators such as type 2 cytokines (IL-4, IL-5 and IL-13), histamine, leukotrienes and prostaglandin D_2 upon allergen exposure [16]. The overlapping functions of IL-4 and IL-13 may be due to receptor and cytokine expression patterns, because both cytokines signal through two potentially heterodimeric receptors with a shared receptor moiety, the IL-4Rα chain [27].

The central clinical role of IL-4 and IL-13 in type 2 inflammation is recognised in the current GINA guidelines, which recommend blockade of IL-4Rα, the shared receptor component for IL-4 and IL-13, in the treatment of patients with severe type 2 asthma (as well as atopic dermatitis (AD) or chronic rhinosinusitis with nasal polyps (CRSwNP). By contrast, anti-IgE and anti-IL-5/anti-IL-5R antibodies are used as targeted therapies against components of type 2 inflammation and they are restricted to use in patients with severe allergic asthma and eosinophilic asthma, respectively (figure 1) [2, 21].

Epithelial barrier function and epithelium-derived cytokines

Epithelial barrier dysfunction in response to chronic airway injury is a pathophysiological feature shared across type 2 inflammatory airway diseases. Disruption of the epithelial barrier allows environmental agents (*e.g.* airway viruses, allergens, bacteria and fungi) to penetrate the epithelium and activate innate and adaptive immune responses, resulting in histological changes and functional abnormalities in the airway mucosal epithelium. The release of epithelium-derived cytokines such as TSLP, IL-25 and IL-33 from bronchial and nasal epithelial cells contributes to the overall pathophysiology of asthma, and the damage to barrier function increases mucosal permeability to foreign substances [28]. Epithelium-derived cytokines recruit dendritic cells and promote their maturation; they in turn activate T-cells *via* antigen presentation and co-stimulation [29]. They also act as chemoattractants for eosinophils and neutrophils, and secretion of TSLP, IL-25 and IL-33 can further stimulate the production of key type 2 cytokines (*i.e.* IL-4,

TABLE 2 Key cytokines that directly promote pathological features of asthma in murine models of asthma [22]

Feature	Cytokines
Eosinophilia	IL-4, IL-5, IL-13
Goblet cell metaplasia	IL-4, IL-13
Airway hyperresponsiveness	IL-4, IL-13, IL-17A
IgE production	IL-4, IL-13
Mastocytosis	IL-3, IL-9
Alternative macrophage activation	IL-4, IL-13
Smooth muscle remodelling	IL-4, IL-13
Th2 induction and maintenance	IL-4, IL-9, IL-17E, IL-25, IL-33, TSLP
Sub-epithelial fibrosis	IL-4, IL-13, TGF-β

IL: interleukin; Th2: T-helper cell type 2; TSLP: thymic stromal lymphopoietin; TGF: transforming growth factor.

IL-5 and IL-13) in inflammatory cells of the innate (ILC2s) and adaptive (Th2 cells) arms of the immune system [3, 30]. These cytokines contribute to epithelial barrier disruption, increasing epithelial permeability [31, 32]. Additionally, release of IL-13 by ILC2s stimulates epithelial cells to increase IL-33 production, resulting in a positive feed-forward loop [33]. Exposure of human bronchial epithelial cells to IL-4 and IL-13 *in vitro* substantially impairs the airway epithelial cell junctional complex structure and function in a Janus kinase-dependent manner. This suggests that Th2-cytokine-dependent barrier disruption may underlie the observed defects in barrier function seen in allergic asthma [31]. Disruption of bronchial epithelial tight junction barrier proteins by IL-13 in *in vivo* studies highlights another essential mechanism of asthma pathogenesis [32].
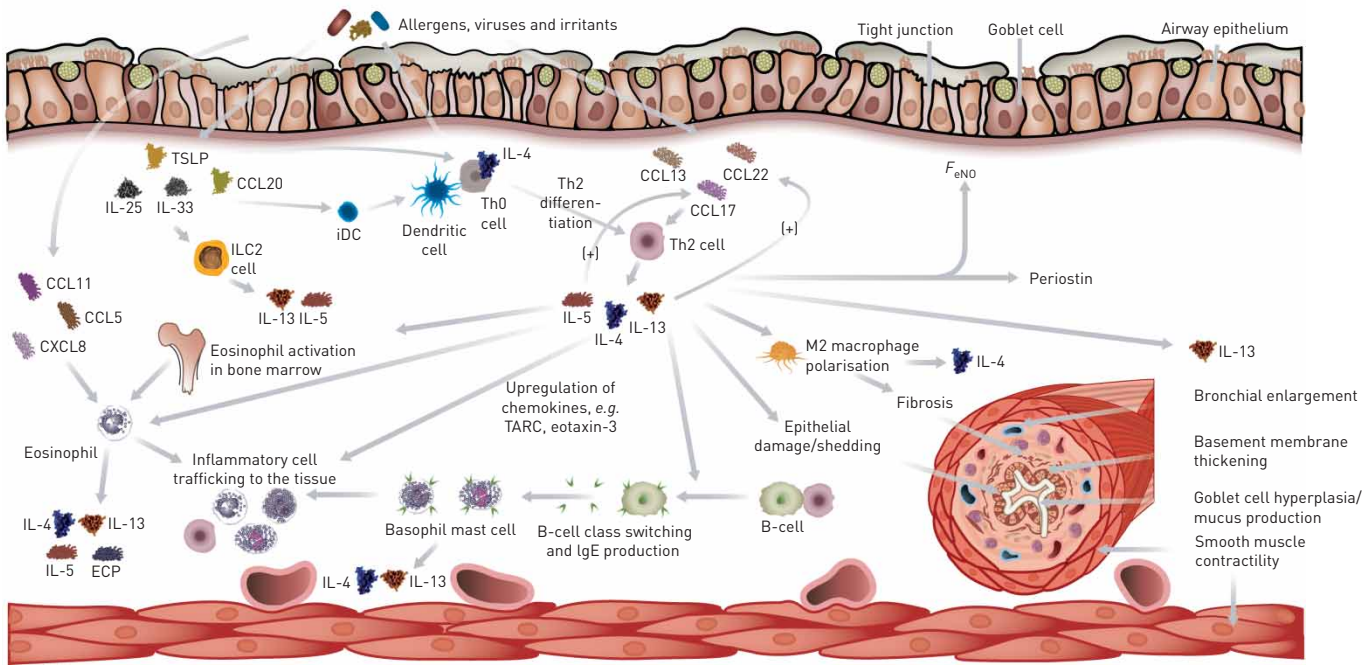

FIGURE 2 The interplay between innate and adaptive cells and mediators in type 2 inflammation underpins asthma pathophysiology. Disruption of the epithelium allows penetration by allergens, viruses or bacteria, activating innate and adaptive immune responses. Presentation of antigens by dendritic cells activates naïve T-helper cells (T-helper cell type 0 (Th0) cells) to differentiate into T-helper cell type 2 (Th2) cells, which in turn produce interleukin (IL)-4, leading to further differentiation of Th0 cells. Cytokines released by Th2 cells lead to eosinophil activation and trafficking of inflammatory cells, B-cell class switching and changes to the airway, including basement membrane thickening, bronchial enlargement, goblet cell hyperplasia and fibrosis. CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; ECP: eosinophil cationic protein; F_{eNO}: fraction of exhaled nitric oxide; iDC: interstitial dendritic cell; ILC2: type 2 innate lymphoid cell; TARC: thymus and activation-regulated chemokine; TSLP: thymic stromal lymphopoietin.

Similar results have also been observed with other pro-inflammatory cytokines (including tumor necrosis factor-α and interferon-γ) that disrupt the tight junction of human airway epithelium and promote inflammatory cytokine release [34]. Epithelial barrier fragility is also strongly associated with the release of epithelial cytokines, TSLP, IL-25 and IL-33, due to the activation of airway epithelial cells, dendritic cells and ILC2s [28].

Mucus secretion

The role of mucus plugging of the airways in the pathophysiology of asthma has long been recognised [35]. The principal cause of death from asthma is asphyxiation from profound airflow obstruction, which likely includes intraluminal airway obstruction by widespread mucus plugs [36]. Excess mucus production contributes to airflow obstruction [37], and the subsequent formation of mucus plugs is associated with decreased lung function. This pathobiology is commonly observed in patients with severe airflow obstruction.

Mucus metaplasia (*i.e.* increased surface epithelial mucin production) and an increased number of bronchial microvessels are components of airway remodelling in asthma and are a predisposition to mucus dysfunction [38]. These changes occur in patients with airway inflammation and are characterised by infiltration of the airway wall and luminal mucus with CD4+ T-cells, eosinophils and ILC2s that secrete Th2 cytokines [39].

In a mouse model, IL-13 signalling affects goblet cell count following an allergic stimulus and plays a significant role in the generation and persistence of airway inflammation, remodelling and dysfunction [40]. IL-13 also increases production of the glycoprotein mucin 5AC (MUC5AC), which is associated with a more adherent type of mucus, over MUC5B. Changes in mucus composition and organisation are likely to be major contributors to airway obstruction, morbidity and mortality in asthma [36].

Smooth muscle function and airway remodelling

Airway remodelling is a collective term that represents the multiple pathological changes that occur in the airway epithelium and submucosa and lead to permanent structural changes of the airway in patients with asthma [3]. IL-4 and IL-13 cause changes in the airway mucosa that may predispose patients with asthma to exacerbations by narrowing the baseline airway calibre and altering structural elements that then exaggerate responses to inhaled triggers (figure 3) [3, 16, 41]. IL-5 has also been implicated in epithelial desquamation and airway remodelling [42]. Ongoing inflammation and airway remodelling in asthma also contribute to a self-perpetuating cycle of exacerbations in the exacerbation-prone phenotype [43].

Airway smooth muscle cells express receptors for cytokines derived from CD4+ T-cells. These cytokines, particularly IL-13, can act directly on airway smooth muscle cells, leading to changes in contractile and relaxant responses, proliferation and the ability of smooth muscle cells to generate chemokines such as eotaxin and thymus and activation-regulated chemokine (TARC), thus potentiating mitogenic effects [44, 45].

IL-13 facilitates calcium influx (a mechanism that mediates airway smooth muscle contraction) in response to contraction to histamine in human airway smooth muscle cells [44]. IL-13 signalling also affects histological responses and is a key mediator of the tissue fibrosis caused by type 2 inflammation [46, 47]. The fibrogenic effects of IL-13 can be mediated by transforming growth factor-β (TGF-β), and IL-13 selectively stimulates TGF-β production in Clara cell 10-kDa (CC10)–IL-13 transgenic mice. TGF-β antagonists (soluble TGFβR-Fc) decrease IL-13-induced lung collagen production in mice [46]. There is also evidence that IL-13 induces sub-epithelial fibrosis through direct effects on fibroblast proliferation and collagen production, both dependent on [48] and independent of [49] TGF-β. IL-13 also increases fibroblast invasiveness in human airway fibroblasts in patients with asthma [47, 50].

Eosinophils are thought to also play an important role in the airway remodelling process. Epithelial-derived cytokines, including chemokine ligands CXCL8, CXCL5 and CCL11, promote the infiltration of eosinophils into the airway tissue [29]. Eosinophils secrete numerous pro-fibrotic molecules, such as eosinophil cationic protein and TGF-β1, which are key drivers of airway remodelling and pro-inflammatory cytokines (*e.g.* IL-5) perpetuating the tissue inflammation. *In vitro* studies have also demonstrated that eosinophils interact with both mast cells and epithelial cells, inducing epithelial secretion of inflammatory cytokines and stimulating mast cells to produce fibrogenic factors as well as tumor necrosis factor-α, which further stimulates TGF-β1 release from eosinophils [51, 52].
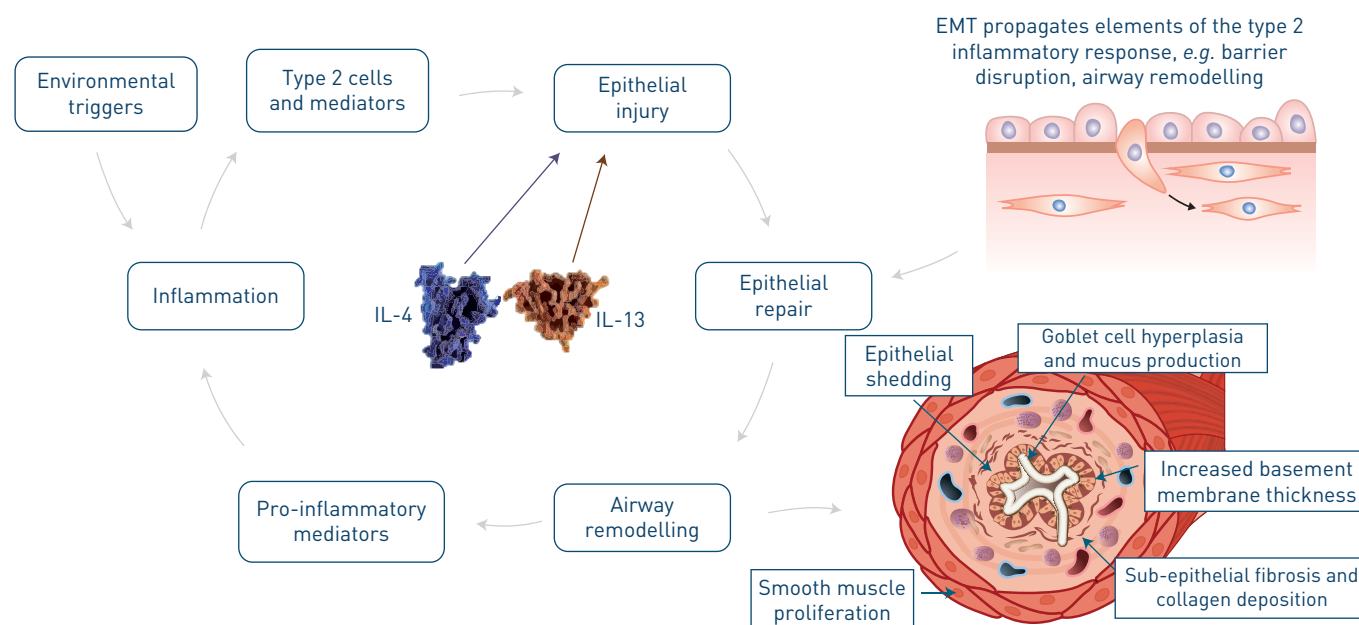
FIGURE 3 Interleukin (IL)-4 and IL-13 are central to airway remodelling. Environmental triggers begin the process of inflammation in the airway with stimulation of type 2 inflammatory cells and mediators, including IL-4 and IL-13, which damage the epithelium. Repair is propagated from the epithelial–mesenchymal transition (EMT), leading to barrier disruption and remodelling of the airway. This remodelling results in epithelial shedding, increased thickness of the basement membrane, fibrosis and collagen deposition, smooth muscle proliferation, goblet cell hyperplasia and mucus production. Additionally, remodelling results in increased pro-inflammatory mediators, which further increase inflammation and epithelial damage.

Common pathophysiological features in type 2 inflammatory comorbidities

Comorbid diseases can interface with type 2 inflammation to enhance existing immune processes of tissue injury. Type 2 inflammation is the unifying feature of uncontrolled, persistent asthma and a number of comorbid inflammatory diseases, including CRSwNP, allergic rhinitis (AR), eosinophilic oesophagitis (EoE) and AD, which can manifest as distinct or comorbid diseases with asthma [16]. The prevalence of common comorbidities varies among inflammatory diseases, with up to 50% of patients with chronic rhinosinusitis or CRSwNP, up to 60% with EoE and up to 26% with AD also having comorbid asthma [53–55]. Similarly, >80% of patients with asthma have AR, and up to 40% of patients with AR have comorbid asthma [56, 57].

Similar to the pathogenesis seen in asthma, CRSwNP, AR, EoE and AD are characterised by an upregulation of type 2 cytokines, IgE-mediated release of immune mediators and dysfunction of epithelial or epidermal barriers [58–63].

Recent asthma and CRSwNP guideline updates recognise the importance of type 2 inflammation and the key type 2 cytokines IL-4, IL-5 and IL-13 in the pathophysiology of these diseases [2, 21, 64]. Targeting these key proximal type 2 cytokines represents a promising strategy to achieve therapeutic benefit across multiple diseases. Efficacy results in recent studies that adopted a personalised approach to treatment suggest that type 2 inflammation is broadly relevant across the severe asthma population if key upstream drivers are blocked effectively; these results support the hypothesis that targeting central pathways could benefit multiple allergic diseases [16]. Type 2 biologic treatments recommended by GINA (asthma) and the European Forum for Research and Education in Allergy and Airway Disease (CRSwNP) reflect the key type 2 cells and mediators in this pathway by targeting IgE, IL-5/IL-5R and IL-4R (figure 2) [21, 64].

Chronic rhinosinusitis with nasal polyps

Epithelial barrier dysfunction and mucosal deficits contribute to *Staphylococcus aureus* colonisation of nasal polyps, which then contribute to the development of chronic inflammation in CRSwNP. *S. aureus* enterotoxins skew the cytokine response towards a type 2 phenotype with increased IL-4, IL-5 and IL-13 expression, which initiates and perpetuates the inflammatory response. These factors combine to drive the

influx of a variety of immune cells, including eosinophils, mast cells, ILC2s and lymphocytes, all of which participate in chronic inflammatory response within the nasal polyps [16, 38, 65].

Allergic rhinitis

The inflammatory response in the nasal mucosa in AR includes an early IgE-mediated and a late-phase response that includes recruitment of eosinophils and basophils, and release of type 2 cytokines including IL-4, IL-5 and IL-13 [66]. Chemoattractants, including eotaxin, IL-5 and RANTES (regulated on activation, normal T-cell expressed and secreted), promote the characteristic infiltration by eosinophils, basophils, Th2 lymphocytes and mast cells seen in chronic AR. As our understanding of the basic pathophysiological features of AR evolves, the development of new diagnostic and treatment options may allow more effective modulation of key pathways in the immune system to alter atopic disease processes and associated morbidity [16, 67–69].

Atopic dermatitis

AD is a common skin disease characterised by a disturbed skin barrier, susceptibility to cutaneous infections and intractable pruritus [16]. AD provokes Th2-mediated immune responses to numerous environmental antigens, and evidence for type 2 inflammation is found in both acute and chronic skin lesions [70]. IL-4, IL-5 and IL-13 are implicated in the pathogenesis of AD, with increased levels leading to amplified signalling of type 2 cytokines and chemokines, activation of subsequent pro-inflammatory signalling pathways and effects on epidermal barrier function [16, 62]. Patients with AD also have increased levels of TARC, a chemokine that promotes migration of Th2 cells [71].

What can be learned about underlying type 2 inflammation from measurements of biomarkers?

Accurate diagnosis and treatment of asthma, while complicated by the heterogeneous pathophysiology of the disease, are particularly important given the availability of targeted therapies that may only be effective for specific patient subgroups. The identification of biomarkers linked to mechanisms involved in type 2 airway inflammation also has the potential to aid diagnosis and predict and monitor response to treatment [13, 16, 72, 73]. A number of biomarkers of type 2 inflammation have been shown to have potential utility in distinguishing type 2-high *versus* type 2-low phenotypes and to predict responsiveness to type 2 cytokine-targeted therapy [3]. These type 2-associated biomarkers include F_{eNO}, serum total and allergen-specific IgE and blood or sputum eosinophil levels [17].

Nitric oxide (NO) is derived endogenously from the amino acid L-arginine and can be measured in exhaled breath as F_{eNO} *via* a simple non-invasive procedure that is relatively easy to use in patients with severe airflow obstruction [74]. IL-4 and IL-13 induce NO production from airway epithelia [73]. F_{eNO} is increasingly recognised as a viable biomarker of type 2 inflammation that reflects corticosteroid-responsive airway inflammation in symptomatic patients and persistence of airway inflammation despite use of inhaled corticosteroids [2, 21, 74–78].

Expression of IL-4 and IL-13 significantly increases NO production from airway epithelia [75]. Patients with asthma with a high F_{eNO} phenotype (⩾35 ppb) represent a significant proportion of the asthma population, and this sub-phenotype is typified by increased arginine metabolism, and clinically characterised by greater airflow obstruction and airway reactivity [79].

High F_{eNO} levels in severe asthma have been shown to identify patients with greater airflow limitation and reversibility, higher sputum eosinophils and most emergency department visits and intensive care unit admissions, suggesting that grouping patients with severe asthma by F_{eNO} identifies the most aggressive asthma phenotype [80].

Elevation in serum IgE is a consequence of IL-4-driven immunoglobulin class switching in B-lymphocytes and is a characteristic feature of atopic diseases [16]. Allergen-specific IgE antibodies also contribute to inflammatory processes in asthma. Currently, the main clinical applications of this biomarker are to estimate the optimal dosage of the anti-IgE antibody omalizumab [81] for add-on treatment in severe allergic asthma, and to support screening for allergic bronchopulmonary aspergillosis, a condition that is often accompanied by very high serum total IgE [82].

As discussed, eosinophils are key cellular effectors of type 2 inflammation and play a major role in maintaining long-term inflammation in asthma. Eosinophils can be measured in peripheral blood, lung tissue and airway lumen (sputum) using various techniques; however, invasive procedures such as tissue biopsies and assessment in induced sputum are not available in routine clinical practice except in very few academic centres. Hence, measurement of peripheral blood eosinophils is more widely used in clinical

practice [83]. Clinical studies have demonstrated correlations between blood eosinophil levels and asthma-related outcomes such as risk of severe exacerbations and asthma control levels [84]. Additionally, clinical trials of biologic treatments for asthma have frequently shown that treatment responses are higher in patients with high levels of blood eosinophils at baseline and are therefore at least partially predictive of treatment response [85]. Studies have shown that sputum eosinophil-guided asthma management can reduce the frequency of exacerbations when a cut-off of >3% sputum eosinophils is used and suggest that this measure is a sensitive and reliable biomarker to guide treatment [13]. Eosinophils contribute to immune response modulation, airway hyperresponsiveness and remodelling, and synergistically interact with IL-4, IL-5, IL-13 and other inflammatory mediators to facilitate their accumulation in the lungs [86].

Therapeutic implications

Type 2 cytokines have integral roles in the pathogenesis of asthma, and a number of targeted biologics have been evaluated as potential treatments, including those that target IL-4, IL-5 and IL-13 pathways. Currently available monoclonal antibodies include omalizumab (anti-IgE); mepolizumab, reslizumab and benralizumab (anti-IL-5 pathway); and dupilumab (anti-IL-4/IL-13) (table 3). The major benefit of these new biologic agents has been in achieving disease control, as evidenced by significant reductions in exacerbations observed in clinical studies [18]. The relative efficacy of these agents correlates with target selection and the molecular characteristics of the inhibitor. Anti-IgE and anti-IL-5 agents that target downstream mediators of the type 2 pathway are effective in treating asthma and, although not currently approved, CRSwNP, but not AD. Dual blockade of IL-4 and IL-13 has demonstrated significant efficacy across multiple allergic diseases (asthma, AD, CRSwNP, EoE), confirming the commonality of the IL-4/IL-13 pathway in these atopic diseases [16, 94].

In patients with severe asthma, underlying type 2 airway inflammation may be identified, according to GINA, on the basis of elevated type 2 inflammatory biomarkers (blood and/or sputum eosinophils and/or F_{eNO}) and/or asthma that is clinically allergen driven and/or requires maintenance oral corticosteroids (figure 1) [2, 21, 78].

Biomarkers that reflect the characteristics of the underlying inflammatory process and the presence of type 2 inflammation are currently used to stratify patients in clinical trials for a number of these agents. Accurate classification of a type 2-high asthma phenotype requires a combination of clinical parameters such as allergic phenotype or responsiveness to corticosteroids, as well as type 2 biomarkers, alone or in combination [13].

TABLE 3 Type 2-directed therapies based on monoclonal antibodies: key clinical trials in asthma				
Th2	Drug	Patient characteristics and biomarkers	Main response	Reference
Free IgE	Omalizumab	Severe asthma on ICS+LABA; atopic status; serum IgE 30–700 IU·mL^{-1} (USA, age ⩾12 years), 30–1300 IU·mL^{-1} (USA, age 6–11 years), 30–1500 IU·mL^{-1} (EU)	Reduced asthma exacerbations Reduction in maintenance OCS	[19]
IL-4 receptor IL-13	Dupilumab	Moderate-to-severe-uncontrolled asthma; FEV$_1$ reversibility, persistent symptoms (ACQ5 ⩾1.5); exacerbation in past year	Decrease in asthma exacerbations Improvement in FEV$_1$ and % change in FEV$_1$ Reduction in maintenance OCS	[87, 88]
IL-5	Mepolizumab	Severe asthma on ICS and LABA±OCS; blood eosinophils ⩾150 mm^{-3} at screening or ⩾300 mm^{-3} in past year	Reduced exacerbation rates Reduction in maintenance OCS Improvement in FEV$_1$	[89, 90]
IL-5	Reslizumab	Inadequately controlled, moderate-to-severe eosinophilic asthma (⩾400 cells·µL^{-1} during screening)	Decrease in asthma exacerbations Improvement in FEV$_1$	[91]
IL-5 receptor	Benralizumab	Severe asthma uncontrolled by medium/high-dose ICS+LABA for ⩾1 year; ⩾2 exacerbations in previous year; baseline stratification: eosinophils <300 and ⩾300 cells·µL^{-1}	Decrease in asthma exacerbations Improvement in FEV$_1$ Reduction in maintenance OCS	[92, 93]

Th2: T-helper cell type 2; Ig: immunoglobulin; ICS: inhaled corticosteroids; LABA: long-acting β$_2$-agonist; OCS: oral corticosteroids; IL: interleukin; FEV$_1$: forced expiratory volume in 1 s; ACQ-5: 5-item Asthma Control Questionnaire.

Given the complexity of inflammatory pathways in asthma, there is likely to be considerable overlap in these biomarkers in each of the asthma phenotypes; consequently, there may be more than one dominant biomarker. Panels of type 2 biomarkers may more accurately reflect risks in asthma, and ultimately help physicians to select the most appropriate treatment. Two separate studies have shown that elevated levels of both F_{eNO} and blood eosinophils are associated with greater bronchial hyperresponsiveness and increased exacerbations [95, 96].

Conclusions

Type 2 inflammation encompasses multiple asthma phenotypes and drives the key pathophysiological characteristics of asthma and comorbid conditions. Integrated efforts to improve disease understanding signal a trend towards a more disease biology-based approach, wherein clinical, cellular and molecular aspects of the disease are examined together to better identify correlations between clinical traits and specific disease mechanisms. The use of biomarkers linked to mechanisms involved in type 2 inflammation has the potential to improve diagnosis and treatment selection and provides a rational basis for new and personalised treatments targeting specific type 2 inflammatory pathway cytokines.

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