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Emerging Concepts in Cytokine Regulation of Airway Remodeling in Asthma

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ABSTRACT

Asthma, a chronic respiratory condition that has seen a dramatic rise in prevalence over the past few decades, now affects more than 300 million people globally and imposes a significant burden on healthcare systems. The key pathological features of asthma include inflammation, airway hyperresponsiveness, mucus cell metaplasia, smooth muscle hypertrophy, and subepithelial fibrosis. Cytokines released by lung epithelial cells, stromal cells, and immune cells during asthma are critical to pathological tissue remodeling in asthma. Over the past few decades, researchers have made great strides in understanding key cells involved in asthma and the cytokines that they produce. Epithelial cells as well as many adaptive and innate immune cells are activated by environmental signals to produce cytokines, namely, type 2 cytokines (IL-4, IL-5, IL-13), IFN-γ, IL-17, TGF-β, and multiple IL-6 family members. However, the precise mechanisms through which these cytokines contribute to airway remodeling remain elusive. Additionally, multiple cell types can produce the same cytokines, making it challenging to decipher how specific cell types and cytokines uniquely contribute to asthma pathogenesis. This review highlights recent advances and provides a comprehensive overview of the key cells involved in the production of cytokines and how these cytokines modulate airway remodeling in asthma.

1 | Introduction

Airway obstruction in asthma, along with symptoms like cough, shortness of breath, chest tightness, and wheezing, stems from a combination of dysregulated epithelium, smooth muscle cell constriction, and inflammation in the airways [1, 2]. This constriction can be severe enough to cause life-threatening narrowing or closure of the airways, even without mucous plugging, due to both abnormal smooth muscle contractility and increased smooth muscle mass [3]. The inflammatory response in asthma includes edema across mucosal, submucosal, and adventitial layers; infiltration of eosinophils, neutrophils, and activated helper T lymphocytes; and the unique presence of mast cells within smooth muscle bundles [4]. Furthermore, there is an increase in airway secretions, capillary engorgement, smooth muscle hyperplasia, and collagen deposition beneath the epithelial basement membrane [5–7].

Airway remodeling, which can begin early in life, is now understood as more than just a consequence of inflammation. It involves epithelial damage, ciliary dysfunction, goblet cell hyperplasia, thickening of the reticular basement membrane, increased vascularity, and a rise in subepithelial myofibroblasts, fibrocytes, and smooth muscle mass, the latter being a key predictor of airflow limitation [7, 8]. These changes lead

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to thickened airway walls, narrowed lumens, mucus plugging, and small airway obliteration. Exacerbations significantly affect asthma-related healthcare costs and quality of life and can be fatal even in mild cases [9]. They are triggered by factors such as infections, allergens, environmental pollutants, and comorbidities, all linked to the immune responses of asthmatic patients [9, 10]. Asthma medications were traditionally divided into bronchodilators and anti-inflammatory drugs, but newer treatments like leukotriene modifiers and combination therapies (e.g., inhaled corticosteroids with long-acting β-adrenergic agonists) have combined effects that defy this old classification [11]. Current treatment strategies categorize medications by their role in overall asthma management, distinguishing between quick relief and long-term control, which aids in patient communication. Identifying therapeutic targets among cytokines, cytokine receptors, and associated signaling molecules requires further research, particularly in preclinical models, and clinical trials should explore mechanisms beyond safety and efficacy.

2 | Cytokine Production by Epithelial Cells and Immune Cells in Asthma

Cytokines play a key role in airway inflammation and remodeling, as their receptors are widely expressed in both hematopoietic and non-hematopoietic cells and can instigate multiple signaling pathways on activation [12]. All major cytokines produced during allergic inflammation have defined functions in shaping tissue pathophysiological responses. Figure 1 summarizes the multiple cytokines produced by immune cells and stromal cells during asthma.

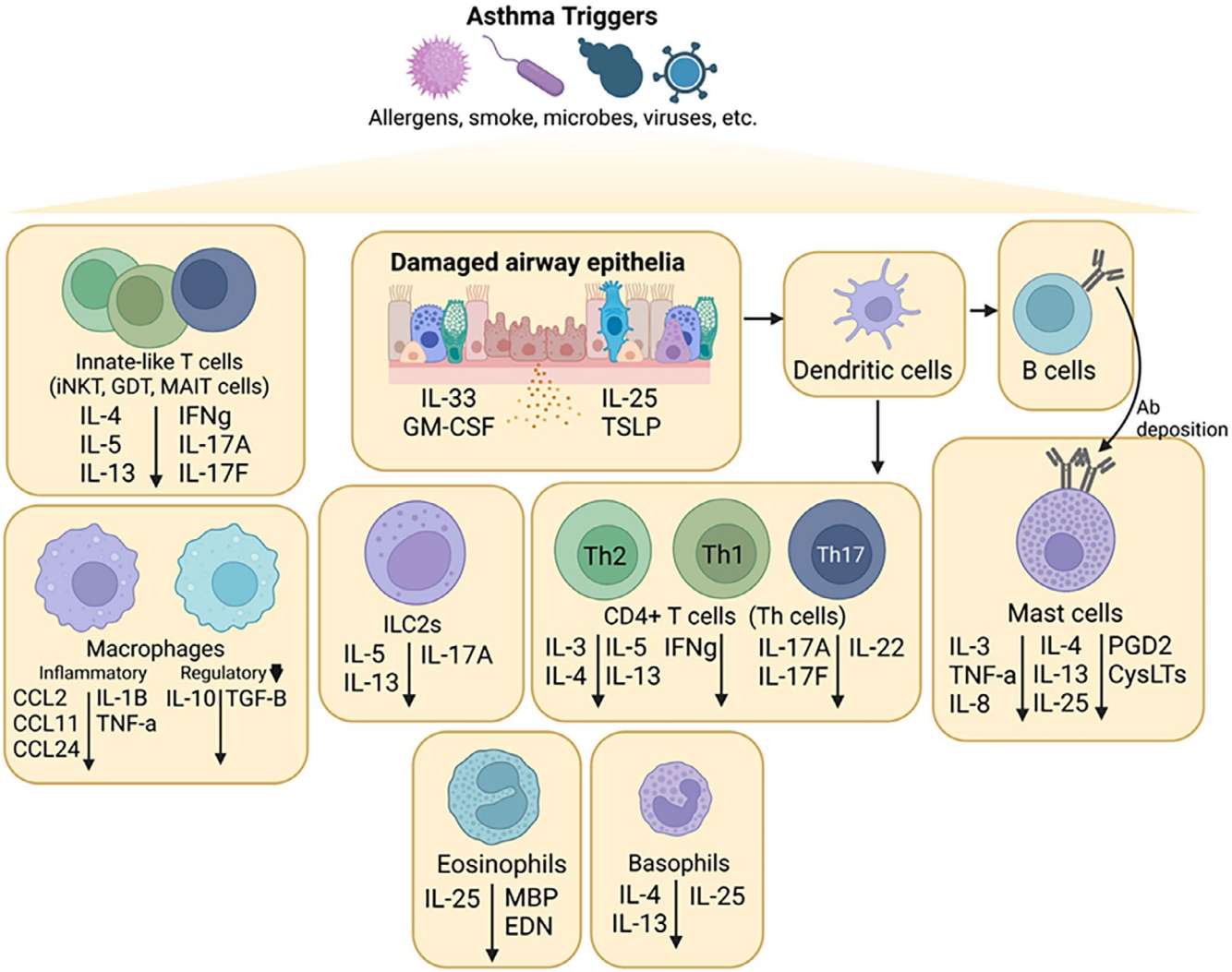

FIGURE 1 | Major cell sources of cytokines during asthma. Asthma triggers, including allergens, smoke, microbes, and viruses, can lead to airway epithelial damage and activation of multiple immune cell types. Altogether, these cells produce cytokines that contribute to major symptoms of asthma, including inflammation, airway hyperresponsiveness, pathogenic airway remodeling, and increased mucus production. ILC2s, type 2 innate lymphoid cells; IL, interleukin; Th1 cells, t helper 1 cells; Th2 cells, t helper 2 cells; Th17 cells, t helper 17 cells; TSLP, thymic stromal lymphopoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; CysLTs, cysteinyl leukotrienes; IFNγ, interferon gamma; TNF-α, tumor necrosis factor alpha; PGD2, prostaglandin D2; MBP, major basic protein; EDN, eosinophil-derived neurotoxin.

2.1 | Airway Epithelia

Immune cells significantly contribute to inflammation and pathologic tissue remodeling in asthma, but a critical first step in developing asthma symptoms is damage to airway epithelia. In asthma, components from the environment, including allergens, microbes, smoke, and air pollution, enter the lung via the trachea and damage epithelial cells in large and small airways [13]. Damaged airway epithelial cells release damage-associated cytokines, also known as alarmins, including IL-25, TSLP, GM-CSF, and IL-33, which cause distinct effects during asthma [13, 14]. Alarmins IL-25 and TSLP promote activation and recruitment of multiple immune cell types that drive type 2 inflammation during asthma, including antigen-presenting cells, B cells, basophils, mast cells, and eosinophils [14, 15]. Similarly, epithelial cell-derived GM-CSF can promote eosinophil survival and recruitment. IL-33 induces immune responses by activating phagocytes and inducing them to release inflammatory factors [14, 16]. Crosstalk between epithelial cells and cytokines from recruited immune cells induces multiple pathologic airway remodeling events, including goblet cell hyperplasia and airway wall thickening [17].

2.2 | Dendritic Cells

Dendritic cells (DCs) are patrolling immune cells that reside in the blood and tissues and act as professional detecting systems for antigens [18]. In allergic asthma, DCs are recruited to the lung and activated by cytokines produced by damaged lung airway epithelial cells [19]. Recruited DCs uptake antigen particles and travel to the lymph nodes, where they present the processed antigen to naive CD4 T helper cells (Th cells) and secrete costimulatory molecules [18]. This DC-Th interaction promotes the differentiation of the naive CD4 Th cells towards antigen-specific T cell subsets. During allergen re-exposure, these antigen-specific T cells can mount a rapid immune response to the allergen, contributing to acute asthmatic symptoms [20]. Dendritic cell-derived cytokines can also drive inflammation, with DC-derived IL-6 found to be important in developing neutrophilic inflammation [21].

Certain subsets of dendritic cells instead generate protective responses during asthma [18]. These DC subsets can arise by stimulation with other factors, such as zymosan or various bacteria, and secrete high levels of the anti-inflammatory cytokine IL-10 [22]. However, the mechanisms of how these DC subsets induce tolerance in asthma and how they can be utilized for therapeutic purposes remain open to further study.

2.3 | B Cells

B cells primarily contribute to asthma symptoms via their release of immunoglobulin E (IgE) antibodies. During asthma, B cells within lymphoid tissue are activated by antigen-specific follicular helper T cells and proliferate [20]. IL-4 produced by type 2 immune cells induces these B cells to switch from producing immunoglobulin M to producing immunoglobulin E (IgE) [23]. B cell-derived antigen-specific IgE binds to FcεRI on the surface of mast cells and basophils, prompting them to rapidly degranulate upon allergen re-exposure [24]. These granules contain histamine and other potent mediators that contribute to AHR and mucus production in asthma.

Other B cell phenotypes may instead play regulatory roles in asthma. Recently, regulatory B cells have been suggested to reduce asthmatic inflammation, though the mechanisms behind their differentiation and functions remain unclear. Certain subsets of regulatory B cells produce immunomodulatory cytokines, including IL-10, TGF-β, and IL-35, which may reduce inflammation by promoting regulatory phenotypes in surrounding lung immune cells [23].

2.4 | Eosinophils

Eosinophils are a subset of immune cells enriched in the lungs during type 2 high asthma. During asthma, eosinophils circulating in the body migrate to the lung tissues due to various chemokines and other migratory factors such as eotaxin, RANTES, and PGD2 [25]. Eosinophil activity can then be mediated by mediators present in the lung environment. IL-5 created by Th2 cells and type 2 innate lymphoid cells (ILC2s) in asthma promotes eosinophil survival, proliferation, and activation via binding to the IL-5 receptor on eosinophils [26]. Additionally, binding of eotaxin-1 to the CCR3 receptor on eosinophils potently induces eosinophil degranulation. Released eosinophilic granules contain many potent bronchoconstrictors, including leukotriene C4 [27], which strongly induces airway constriction [28].

Eosinophils also contribute to asthmatic inflammation through the release of inflammatory mediators and cytokines that activate and recruit other immune cells. For instance, eosinophils recruit and activate plasmacytoid dendritic cells by releasing eosinophil-derived neurotoxin, which drives the development of Th2 responses [16]. Eosinophils are also major producers of IL-25 in asthma [14]. IL-25 secreted by eosinophils contributes to the recruitment of immune cells that induce Th2-like immune responses, including ILC2s, basophils, and mast cells [14]. Eosinophils also secrete major basic protein, which activates other effector cells such as mast cells and basophils. Activation of these effector cells leads to the release of histamine, TNF, and proteases that drive inflammation, tissue remodeling, and airway hyperresponsiveness (AHR) [29].

2.5 | Basophils

Basophils are a type of circulating innate immune cell that migrate into the lung during asthma. They can secrete a host of factors that induce inflammatory responses and AHR [30]. The factors that dictate basophil recruitment to the lung during asthma are unknown, but the chemokines CCL11 and CCL2 have been implicated via their binding to basophil CCR3 and CCR2 receptors [31]. Epithelial cell-derived TSLP may also play a role in promoting basophil activation and migration to the lung by upregulating basophil expression of the CCR3 ligand [32].

Basophils are capable of amplifying inflammatory responses and pathologic airway remodeling during asthma by secreting type 2 cytokines IL-4 and IL-13 [33]. The role of basophil-derived IL-4 is especially important in driving early type 2 inflammatory responses during asthma exacerbations, as it both controls early eosinophil recruitment into the lung and contributes to ILC2 activation [32]. Basophils are also potent sources of IL-25 during asthma, which promotes the development of type 2 immune responses [14].

2.6 | Mast Cells

Mast cells are major effector immune cells of asthma and contribute to airway inflammation, pathologic epithelial remodeling, and airway hyperresponsiveness. They can be primed for rapid activation by B cell-derived antibodies. During atopic asthma, antigen-specific antibodies from B cells attach to Fc receptors on mast cells. Upon repeated exposure to a specific antigen, these antibody-bound receptors crosslink with each other, leading to rapid mast cell degranulation and the release of several mediators [34].

Activated mast cells secrete several factors that directly contribute to asthma pathology. In the acute phase of the allergic asthma response, mast cells release pre-stored granules containing histamine and enzymes such as tryptase and chymase [34]. These mediators lead to rapid contraction of airway smooth muscle as well as mucus secretion [34]. On activation, mast cells can also rapidly produce eicosanoids such as PGD2 and cysteinyl leukotrienes (CysLTs) [35]. Mast cell-derived PGD2 recruits and stimulates Th2 cells and eosinophils, increasing type 2 responses [36]. Both PGD2 and CysLTs sensitize ILC2s for activation by upregulating activating receptors on the ILC2 cell surface [16]. In the later phase of the allergic asthma response, mast cells can produce cytokines IL-3, TNF-a, IL-8, and the type 2 immune cytokines IL4, IL-13, as well as IL-25 [16]. These cytokines are capable of recruiting and activating multiple types of immune cells, including eosinophils, basophils, ILC2s, and neutrophils, furthering inflammatory responses [37].

Mast cell mediators also promote pathologic airway remodeling and AHR in asthma. Both PGD2 and CysLTs, as well as several mast cell-produced cytokines, contribute to goblet cell metaplasia and increased mucus production during asthma [35]. TNF-α and TGF-β, released by mast cells, both contribute to airway hyperresponsiveness during asthma by promoting epithelial cell proliferation and effects on fibroblast differentiation and proliferation, respectively [35, 37].

2.7 | Innate Lymphoid Cells (ILCs)

Type 2 and Type 3 innate lymphoid cells (ILC2s and ILC3s) are types of lymphocytes that do not depend on antigen recognition to formulate immune responses and are instead activated by cytokines in their surroundings.

During the asthma response, ILC2s can be activated by epithelial cell-derived alarmins IL-25, IL-33, and TSLP [38]. ILC2s can also be activated by IL-4 produced by several type 2 response-associated immune cells, including basophils, eosinophils, and type 2 helper T cells [16].

Activated ILC2s readily secrete IL-5 and IL-13, driving the development of type 2 inflammatory responses, AHR, and pathologic airway remodeling in asthma [39]. However, recent studies have discovered that ILC2s have a high degree of plasticity and can shift to a mixed ILC2-ILC3 phenotype that produces both IL-13 and IL-17A after induction by IL1B, IL-23, and TGF-β, indicating a potential context-dependent role for ILC2s during asthma [40, 41]. ILC3s, on the other hand, mostly play a role in neutrophil-high asthma, during which they secrete pro-inflammatory IL-17A [41].

2.8 | T Helper Cells

CD4 helper T cells (Th cells) are immune cells that exert long-term, antigen-specific actions in allergic asthma and are often notable sources of key asthma-associated cytokines [42]. Th cells can differentiate into multiple subsets depending on surrounding cytokine signals, and the different subsets uniquely contribute to asthma pathogenesis.

During allergic asthma, T follicular helper cells (Tfh cells) within germinal centers amplify inflammation by inducing allergen-specific B cell differentiation and proliferation. IL-21 produced by Tfh cells is critical in this B cell expansion [43]. Other recent work also indicates that Tfh-produced IL-9 is important in ramping the cascade of B cell responses during asthma [44].

In Type-2 high asthmatic airway inflammation, a subset of Th cells called Th2 cells readily secrete IL-3, IL-4, IL-5, and IL-13 after activation by dendritic cells [45]. In asthma, these cytokines can trigger a cascade of type 2 immune responses. Elevated IL-4 drives Th2 cell differentiation and proliferation, furthering type 2 inflammation by recruitment of other immune cells. IL-5 increases eosinophil recruitment and activation [26]. IL-13 drives several asthma symptoms, including increased airway hypersensitivity, increased airway epithelial cell differentiation to mucus-secreting cells, and increased mucus production [46]. IL-13 also increases airway epithelial cell secretion of the proinflammatory chemokine eotaxin, which furthers recruitment of eosinophils [47] and other type 2 immune cells to the lung. Lastly, Th2 cells are major sources of IL-31 during asthma, which promotes inflammation, smooth muscle cell contraction, and AHR [48–50].

Other subsets of activated helper T cells, such as Th1s and Th17s, instead play a role in subtypes of type 2-low asthma, in which treatment with inhaled corticosteroids is often ineffective [45]. Th1 cells secrete IFNγ and have historically been thought to play a protective role during asthma by antagonizing Th2 responses [51]. However, other studies have found Th1-skewed responses in 50% of patients with corticosteroid-resistant severe asthma [52], raising questions about the generalizability of Th1/Th2 antagonism as a protective factor in asthma. Th17 cells, on the other hand, produce IL-17A, IL-17F, and IL-22, which increase neutrophil recruitment to the lung and aggravate neutrophilic asthma [53]. IL-17A was found to increase

mucus production, goblet cell hyperplasia, and epithelial cell production of neutrophil-attracting chemokines in air-liquid interface cultures of human airway epithelia [54]. IL-17A may also increase contraction in airway smooth muscle cells, which contributes to airway hyperresponsiveness during asthma [55].

2.9 | Innate-Like T Cells

2.9.1 | iNKT and GDT Cells

Invariant natural killer T (iNKT) cells and gamma delta T (GDT) cells are subsets of innate-like T cells enriched in mucosal tissues such as the lung. Unlike traditional T cells, they are able to detect antigens in an MHC-independent manner and can mount rapid responses even in the absence of prior antigen exposure [56]. Similar to CD4+ T cells, iNKT and GDT cells are capable of driving either type 1/17 or type 2 immune responses depending on their subset. Some subsets of GDT cells are capable of releasing proinflammatory IL-4, IL-5, and IL-13 during type 2-high asthma, promoting eosinophilic inflammation, IgE production, and airway hyperresponsiveness. Other subsets of GDT cells are capable of producing IFNγ as well as IL-17 [57]. Some studies have related GDT IL-17 production to decreased eosinophilic inflammation and decreased AHR [57]. However, the necessity of iNKT and GDT cells in asthma and whether they play a protective versus a pathogenic role is unclear. Conflicts in results between studies may be due to differences in experimental models, subset-specific effects of type 1/17 and type 2 inflammation driving cells, as well as variations between asthma disease severities examined in different studies [58].

2.9.2 | MAIT Cells

Mucosal-associated invariant T cells are another less common T cell subtype enriched in lung mucosa. Though evidence on their role in asthma is unclear, in a severe asthma patient study, patients with more frequent exacerbations were found to have higher levels of IL-17 producing MAIT cells [59]. MAIT cells can secrete IFNγ and are also potent producers of two variants of IL-17, mainly releasing IL-17A during acute infection and IL17F during resolution [60]. MAIT cells have also been implicated in tissue repair [61]. Recent studies found that MAIT cells are able to suppress ILC2-mediated inflammation and goblet cell hyperplasia via MAIT cell production of IFNγ as well as via direct cell-to-cell contacts [61, 62].

2.10 | Macrophages

Macrophages are a type of innate immune cell and contribute to the regulation of asthmatic inflammation via the production of pro-and anti-inflammatory factors. Three major classes of lung macrophages exist: (i) alveolar macrophages, which are local lung tissue macrophages, (ii) interstitial macrophages, which also reside in tissue but may be replenished by circulating monocytes from the bone marrow, and (iii) monocyte-derived/recruited macrophages, in which monocytes are recruited from the bone marrow and differentiate into macrophages in the lung [63]. These macrophage subtypes are located in different areas within the lung and may contribute to localized inflammation and remodeling in asthma differently, as alveolar macrophages are located primarily in alveolar spaces while interstitial and monocyte-derived macrophages usually reside closer to airways [63].

Macrophages can be polarized into different states by surrounding cytokine factors and by engagement of various receptors. In type 2 high asthma, inflammatory lung macrophages were found to be a major source of the chemokine CCL2, which prompts basophil and macrophage recruitment to the lung [63], as well as chemokines CCL11 and CCL24, which prompt eosinophil recruitment and infiltration into the lung. Macrophage secretion of IL-6 was also found to be important in developing type 2 inflammatory responses [21]. Macrophages were also found to be major sources of oncostatin M in LPS and Klebsellia-induced asthma and can translate LPS signals into asthma-related pathologies, which may be particularly relevant in bacterial-associated asthma exacerbations [64].

In severe neutrophilic asthma, inflammatory macrophages potently produce type 1 cytokines IL-1β and TNFα as well as type 17 cytokine IL-17A, which can promote the development of type 1 and type 17 inflammatory responses [63].

Lastly, impaired efferocytosis by macrophages during asthma may also contribute to disrupted inflammatory resolution, as efferocytosis of apoptotic cells induces macrophages to secrete tissue repair-associated cytokines such as IL-10 and TGF-β [63]. Recent work has also highlighted the beneficial role of interstitial macrophages in asthma, in which their secretion of IL-10 helps to induce the expansion of anti-inflammatory regulatory T cells [65].

3 | Cytokine Regulation of Airway Remodeling in Asthma

Key features of pathogenic tissue remodeling in asthma include dysregulated proliferation and differentiation of epithelial cells and fibroblasts, collagen deposition, goblet cell hyperplasia, airway smooth muscle (ASM) cell contractility, and airway contraction [1, 66]. Numerous cytokines and growth factors contribute to these processes, including IFNγ, Th2-associated cytokines (IL-4, IL-5, IL-13), IL-17, IL-6 family cytokines, and TGF-β. A discussion of these cytokines as potent tissue remodeling factors is presented below.

3.1 | Interferon-γ

IFN-γ is a cytokine associated with type 1 inflammatory responses. IFNγ is predominantly produced by immune cells like NK cells, ILCs, Th1 cells, and CTLs, and it activates signaling through the IFNγ receptor (IFNγR), which consists of IFNγR1 and IFNγR2 subunits, expressed widely across cell types [67, 68].

IFN-γ has historically been thought to play a protective role during asthma as it can suppress type 2 immune responses from Th2 cells and ILC2s. In type 2 high asthma, hyperactivation of Th2 cells and ILC2s results in the exacerbation of allergic

responses, characterized by increased production of type 2 cytokines, which in turn accelerate collagen production from fibroblasts [69]. IFN-gamma can suppress Th2 indicators (airway eosinophilia, IL-5, IL-13) by reducing the antigen-presenting capacity and cytokine production of dendritic cells [70]. Interferon-gamma (IFN-γ) can reverse prolonged airway responses and inflammation after allergen challenge in IFN-γ-deficient mice, suggesting its essential role in controlling allergic disease and asthma by returning airway responsiveness and lung CD4(+) cell numbers to baseline levels even when administered post-challenge [71]. It thus stands to reason that IFN-γ may be able to alleviate asthma symptoms, particularly in subsets of type-2 high asthma cases.

However, IFN-γ plays an alternative role in exacerbating asthma severity by increasing airway hyperresponsiveness. Other studies have found IFN-γ high, Th1-skewed responses in patients with corticosteroid-resistant severe asthma [52, 72]. A study by Kobayashi et al. showed that adoptive transfer of IFN-γ producing allergen-specific Th1 cells in a mouse model of asthma induced significant airway hyper-responsiveness (AHR) with neutrophilia [73]. Additionally, administration of IFN-γ alone was able to increase AHR in mice [73]. These effects were proposed to be caused by IFN-γ-driven increases in neurokinin-2 receptor (NK2R) expression and neurokinin A (NKA) production in the lung, including in airway smooth muscle cells [73]. This suggests the IFN-γ/NK2R axis as a contributing factor to worsened AHR in asthma, particularly in patients with Th1-skewed cytokine signatures [73]. IFN-γ can also contribute to AHR by inducing changes to airway epithelia. IFN-γ administration can downregulate secretory leukocyte protease inhibitor (SLPI) production by airway epithelial cells, leading to worsened AHR, though the specific mechanisms behind this effect remain unclear [72]. In another study, combined treatment of IFN-γ and TNF-α revealed multiple genes associated with proinflammatory modulator production and smooth muscle contractility on coexpression analysis [74]. Further, IFN-γ is shown to promote corticosteroid resistance by increasing TNF-α effects on inflammatory cytokines [75]. Next, our group has demonstrated the importance of IL-31RA in IFN-γ-induced airway hyperresponsiveness, with IFN-γ upregulating IL-31RA in ASMC of both humans and mice and the loss of IL-31RA leading to attenuated AHR [49] (Figure 2). IFN-γ is also shown to upregulate IL-31RA in dendritic cells by STAT1 phosphorylation, leading to increased dendritic cell release of proinflammatory mediators [76].

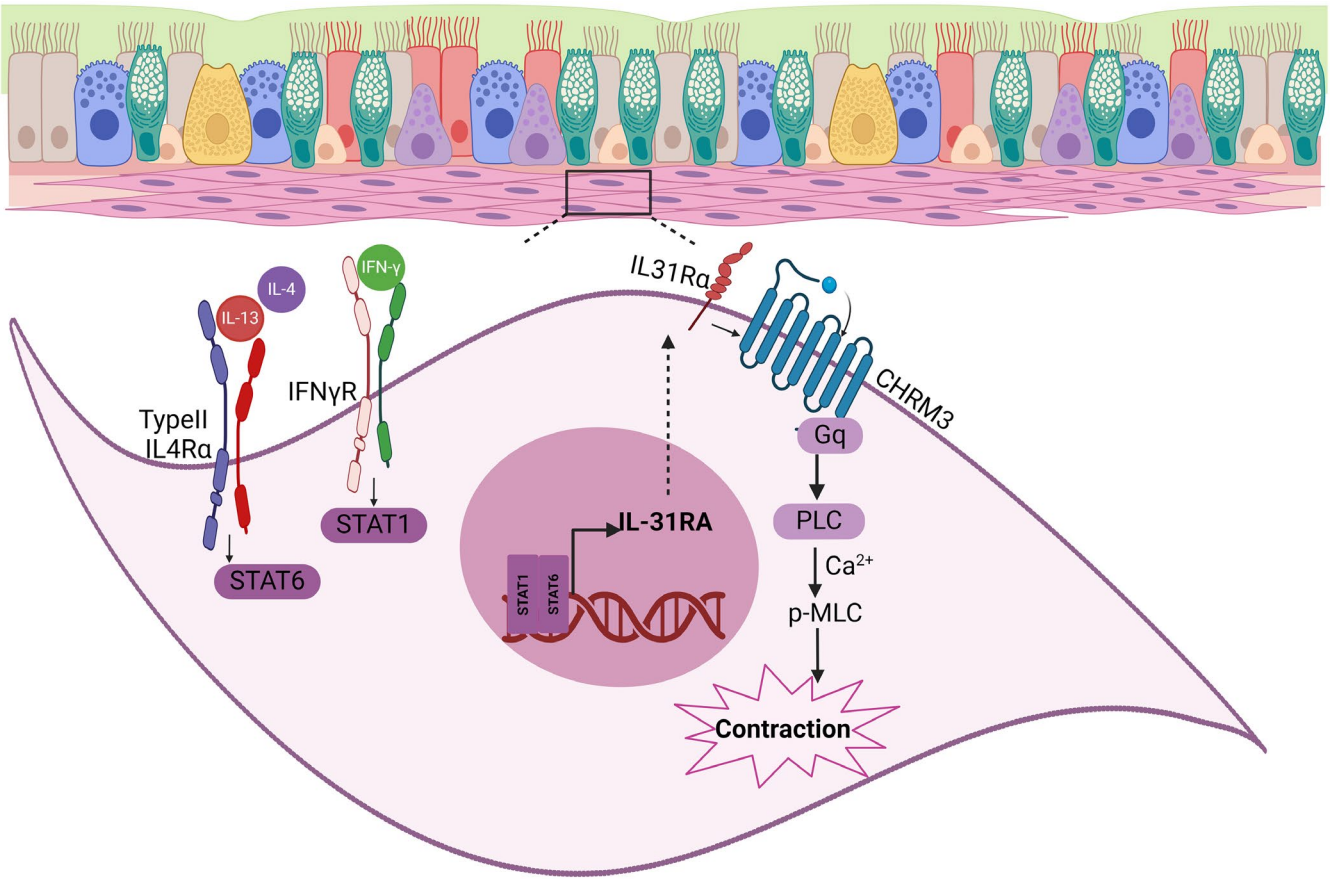

FIGURE 2 | Cytokine regulation of airway smooth muscle cell contraction. Both Th1 and Th2 cytokines upregulate IL-31RA in smooth muscle cells. Independent of IL-31 with no agonist needed, IL-31RA functions as a positive regulator of CHRM3-dependent calcium elevation and smooth muscle cell contraction in asthma. IL-4, interleukin 4; IL-13, interleukin 13; IFNγ, interferon gamma; IL4Rα, interleukin 4 receptor alpha; IL31Rα, interleukin 31 receptor alpha; IFNγR, interferon gamma receptor; STAT1, signal transducer and activator of transcription1; STAT6, signal transducer and activator of transcription 6; CHRM3, cholinergic receptor muscarinic 3; Gq, G alpha-Q protein; PLC, phospholipase c; p-MLC, phosphorylated myosin light chain.

In certain contexts, IFN-γ can also drive asthmatic inflammation, which may be particularly important in severe asthma with dominant Th1 responses [72]. T cell-derived IFN-γ can amplify ASM cell production of the chemokine receptor CXCR3, leading to further recruitment of Th cells [77]. IFN-γ can also work synergistically with the protein LIGHT through their respective receptors, IFNGR and LTBR, to enhance chemokine production by ASM cells. It also demonstrated that IFNGR and LTBR are expressed in ASM tissue from both healthy and asthmatic airways, allowing for the synergistic action of IFN-γ and LIGHT in recruiting immune cells [78].

3.2 | Interleukin-17

Interleukin-17, also known as IL-17A, is a cytokine elevated in steroid-resistant neutrophilic asthma [79]. IL-17A can contribute to pathogenic airway remodeling in asthma by promoting the proliferation of airway smooth muscle cells and fibroblasts [80]. IL-17A uniquely enhances the contractile force generation of airway smooth muscle via an IL-17 receptor A (IL-17RA)-IL-17RC, nuclear factor κB (NF-κB)-RhoA-ROCK2 signaling cascade, unlike other IL-17 family members IL-17F and IL-22 [55].

Evidence on the effects of IL-17A on increasing asthmatic severity has been mixed. Remarkably, IL17RA$^{-/-}$ mice showed nearly identical AHR to WT mice despite significantly reduced inflammation [72]. IL-17A also failed to enhance the potency of key mediators such as histamine, carbachol, and leukotriene D4 as contractile agonists in human airway smooth muscle cells [81]. However, in another study, co-exposure of IL-17A alongside type 2 cytokine IL-13 increased airway hyperresponsiveness, mucus production, airway inflammation, and IL-13-induced gene expression compared to the administration of IL-13 alone [82]. The effect of IL-17A co-exposure on enhancing IL-13-induced gene expression was also observed in fibroblasts, which can respond to both IL-17A and IL-13. These observations may explain the increased asthma severity in patients who produce high levels of both IL-17A and IL-13 and support a role for IL-17A in increasing asthma severity [82]. IL-17A treatment also upregulated proinflammatory gene expression in cultured human ASM cells [83].

Strikingly, not all IL-17A-mediated remodeling and inflammatory changes are corticosteroid resistant, and IL-17A induces function-specific corticosteroid insensitivity in primary human airway epithelial cells (hAECs) [54]. While inflammatory response genes and mucus production stimulated by IL-17A are largely resistant to corticosteroids, corticosteroids can reverse IL-17A-induced epithelial barrier disruption, which is linked to gene expression changes related to cilia function and development. IL-17A also inhibits canonical corticosteroid-responsive genes like HSD11B2 and FKBP5, and its effects on inflammatory markers, goblet cell metaplasia, cytokine secretion, and mucus production are not prevented by dexamethasone [54].

3.3 | Th2-Associated Cytokines in Asthma

Type 2 asthma is marked by elevated levels of IL-4, IL-5, and IL-13, resulting in typical asthma symptoms, including the buildup of type 2-associated cells like eosinophils and mast cells in lung tissue and increased mucus production [84].

3.3.1 | Interleukin-4 and Interleukin-13

Bronchial inflammation, smooth muscle spasm, and mucus production in allergic asthma are triggered by IL-4, IL-5, and IL-13 released by immune cells during type 2 inflammation. IL-13 plays a major role in mucus secretion and airway hyperresponsiveness (AHR) [85, 86]. IL-4 promotes downstream mast cell release of histamine and other mediators, which causes airway constriction [87].

IL-4 and IL-13 signal through IL-4 receptor alpha (IL-4RA), promoting allergic inflammation via signal transducer and activator of transcription 6. Despite the structural similarities and shared receptor (IL4RA) usage of IL-4 and IL-13, the understanding of their distinct roles in allergic inflammation is complicated. Recent discoveries in receptor distribution, utilization, and affinity differences, as well as the unique production of IL-13 by innate lymphoid 2 cells (ILC2), clarify their contributions [87]. IL-4 is capable of inducing Th2 responses. IL-13 is essential for airway hyperresponsiveness and goblet cell hyperplasia in some asthma models, possibly due to unique signaling, lack of inhibitory effects, or greater potency of IL-13 compared to IL-4 [81, 88].

Subsets of IL-4 and IL-13-activated lung fibroblasts may act as effector cells in asthma pathogenesis and the lung remodeling processes [89]. Stimulation with IL-4 or IL-13 induced differential signal transduction in fibroblasts, upregulating expression of beta1 integrin and vascular cell adhesion molecule 1 and enhancing production of IL-6 and monocyte chemoattractant protein, key inflammatory cytokines in allergic inflammation [90]. Additionally, direct IL-4R effects on smooth muscle were demonstrated in murine asthma models using transgenic mice in which smooth muscle is the only cell type that expresses or fails to express IL-4RA, showing that smooth muscle activation by IL-4, IL-13, or allergen is sufficient but not necessary to induce AHR [91, 92]. IL4RA expressed on smooth muscle and airway epithelia is shown to heavily contribute to developing AHR during asthma [93]. IL-4 and IL-13 have been shown to induce the myofibroblast phenotype in a time- and dose-dependent manner [69]. However, another study demonstrated that IL-4 and IL-13 have limited direct effectiveness in promoting myofibroblast transformation, suggesting instead that their effect occurs through IL-4 or IL-13-mediated release of TGF-β2 from epithelial cells [94].

While IL-13 and IL-4 both affect airway epithelial cells similarly, only IL-13 is essential for developing the allergic asthma phenotype in mouse models [86, 95]. IL-13 directly activates fibrogenic machinery, including upregulating interstitial collagens, several MMPs, and tissue inhibitors of metalloproteinase-1, even in the absence of TGF-β [90]. IL-13 significantly increases both total and active forms of TGF-β1 [95]. IL-13 activated endogenous MMP-2 more in asthma patients than in normal controls, but this activation is inhibited by the MMP-2 inhibitor, highlighting IL-13-mediated airway remodeling via a mechanism involving TGF-β1 and MMP-2 [95].

3.3.2 | Interleukin-5

IL-5 contributes to eosinophil activation and migration leading to bronchial inflammation. The expression of IL-5α receptors in fibroblasts from the lower airways of both healthy volunteers and individuals with asthma suggests a potential role for IL-5 in the pathological processes of airway fibrosis and tissue remodeling in asthma [96].

3.4 | Interleukin-6 Family

The IL-6 family of cytokines includes IL-6, IL-11, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), IL-12, IL-11, IL-27, and IL-31. IL-6 family cytokines, unified by their use of the gp130 receptor subunit, typically signal through STAT3 activation, with IL-27 signaling predominantly via STAT1 [21]. In asthma, they exhibit overlapping and distinct biological activities, contributing to functions such as B-cell stimulation, modulation of regulatory and effector T-cell balance, metabolic regulation, and various neural functions [97].

3.4.1 | Interleukin-6

IL-6 mediates asthma pathogenesis by regulating Th2 and Th17 immune responses and influencing T cell differentiation [98]. IL-6 is produced by both immune cells and lung epithelial cells, with constitutive expression in mouse lung epithelium and additional induction upon allergen exposure [98, 99]. While IL-6 levels are low in normal conditions, they can surge dramatically during inflammation, often increasing thousands of times. A study from Gubernatorova et al. found that IL-6 expression from different cell types promotes different pathways of asthma pathogenesis. Specific downregulation of IL-6 in macrophages ameliorated type 2 inflammatory responses, while downregulation of IL-6 in DCs decreased Th17-driven neutrophil infiltration, suggesting a context-dependent role of IL-6 upregulation in asthma [21]. IL-6 was also found to be essential for mucus hypersecretion in an asthma model using *Aspergillus fumigatus* allergen and increased IL-13 production by CD4+ T cells [100].

3.4.2 | Oncostatin M

OSM is an IL-6 family member that is elevated in severe asthma and other allergic diseases and can stimulate responses in lung epithelial and mesenchymal cells [64]. Recent work showed that bacterial lipopolysaccharide (LPS) can induce oncostatin M, driving a distinct inflammatory and mucus-producing transcriptional profile in severe asthma airway biopsies. Lung epithelial cells, primarily targeted by oncostatin M (OSM) and, to a lesser extent, interleukin (IL)-6 and IL-31 from the IL-6 cytokine family, activate the OSM receptor (OSMR) signaling through STAT3 and mitogen-activated protein kinase pathways to induce genes for differentiated cell functions, reduce cell–cell interactions, and suppress proliferation [101].

3.4.3 | Interleukin-31

IL-31 is a cytokine that contributes to allergic diseases like dermatitis and pruritus [102] and has recently also been implicated in asthma. Elevated IL-31 levels in asthma patients, particularly in severe asthma, correlated positively with Th2 cytokines, asthma severity markers, and total serum IgE while showing inverse correlations with asthma control and FEV1, indicating a potential pathogenic role for IL-31 in asthma [103]. IL-31 enhances STAT3, ERK, JNK, and Akt pathways in human alveolar epithelial cells, profoundly altering cell cycle protein expression to inhibit proliferation via specific STAT3 recruitment at Tyr-721 in IL-31RA, suggesting a critical role in receptor-defined signaling during inflammatory and immune responses involving activated T-cells [101].

Differences in the role of IL-31 versus IL-31RA in asthma pathogenesis are unclear. A recent study from our lab showed elevated levels of IL-31RA expression in lungs and airway smooth muscle cells but not IL-31 in two alternative mouse models of allergic asthma and human asthmatic pediatric tissue samples [104]. The decrease in AHR with the loss of IL-31RA was attributed to muscarinic receptor 3 protein levels in airway smooth muscle cells [104]. IL-4 and IL-13 cytokines are shown to induce IL-31RA via STAT 6 s in macrophages and airway smooth muscle cells [49, 105]. Furthermore, in vitro experiments showed that IL-31RA deficiency in macrophages led to heightened ovalbumin-specific CD4(+) T cell proliferation, while purified naive CD4 T cells from IL-31RA$^{-/-}$ mice exhibited increased proliferation and expression of Th2 cytokines, suggesting an intrinsic regulatory role of IL-31R signaling in T cells and macrophages [106]. Importantly, the study found that IL-31RA deficiency did not affect CD4 T cell-mediated Th1 responses, highlighting the specificity of IL-31R signaling in limiting type 2 inflammation [106].

3.5 | Transforming Growth Factor-β

TGF-β is a cytokine mediator that contributes to airway remodeling in asthma and has context-dependent effects on airway epithelia [107]. TGF-β has been demonstrated to induce mesenchymal cell gene expression in primary airway epithelial cells obtained from asthma patients [107]. Myofibroblasts are commonly regarded as cells that exhibit intermediate morphological characteristics between fibroblasts and smooth muscle cells. TGF-β induces α-smooth muscle actin (αSMA) and smooth muscle protein 22-alpha (SM22α) in fibroblasts through interactions with specific elements in the αSMA promoter, while the maintenance of a stable myofibroblast phenotype requires both TGF-β and adhesion-dependent signals, with the inhibition of TGF-β1-induced focal adhesion kinase phosphorylation on tyrosine 397 suppressing αSMA expression [108, 109]. TGF-β1 promotes human airway smooth muscle (HASM) cell shortening and hyperresponsiveness by increasing cytoskeletal stiffness and enhancing contraction through Rho kinase-dependent pathways, independent of RhoA and calcium [110, 111].

Another in vitro study reveals the role of basic fibroblast growth factor (FGF-2) in the pathophysiology of asthma,

focusing on its effects on TGFβ-stimulated differentiation of ASM cells [112]. FGF-2 inhibits TGFβ-induced increases in contractile protein expression, actin-cytoskeleton reorganization, cell stiffness enhancement, and collagen remodeling in human ASM cells via extracellular signal-regulated kinase 1/2 (ERK1/2) signaling. Despite its effects on ASM cell function, FGF-2 does not affect TGFβ-stimulated IL-6 production, indicating selective regulation of ASM contractile protein expression and function [112].

4 | Conclusions

For decades, the intricate biology of cytokines in asthma has been a focal point of research, yet the precise mechanisms linking airway remodeling to the contraction of ASM cells have remained elusive. Future research should focus on mapping the intricate networks of cytokines involved in AHR and other pathological features of asthma. This includes understanding how different cytokines interact with each other and with various immune cells to influence ASM cell contraction, inflammation, mucus production, and fibrosis in airways [6]. Technologies like single-cell RNA sequencing and proteomics can provide detailed insights into cytokine profiles and interactions at the cellular level. Asthma is a heterogeneous disease with various phenotypes, such as allergic, non-allergic, and severe asthma. Understanding how cytokine regulation differs among these phenotypes can lead to more personalized approaches to treatment. Future studies should investigate cytokine profiles specific to each phenotype and how they correlate with clinical features of asthma and outcomes.

There is a growing interest in targeting cytokines for asthma treatment. Biologic therapies, such as monoclonal antibodies against specific cytokines (e.g., IL-5, IL-4, and IL-13), have shown promise in managing severe asthma [113]. Future research should focus on optimizing these therapies, exploring combination treatments, and identifying converging intermediates downstream of these cytokines to mitigate the pathological features of asthma and identify biomarkers to predict patient response. In our recent study, we have elucidated a critical mechanism in which both Th1 and Th2 cytokines converge on a common molecular target, IL-31RA [49, 105]. This receptor is significantly upregulated in both human and murine models of allergic asthma, serving as a pivotal mediator of smooth muscle cell contraction in asthma (Figure 2). Remarkably, IL-31RA-driven calcium signaling and ASM contraction are not dependent on IL-31 or other agonists, prompting further questions: Does the IL-31RA-driven ASM contraction and AHR is limited to CHRM3 or can it be extended to other Gq ligands involved in SMC contraction? How does an agonist-independent IL-31RA alter CHRM3 or other GPCR levels to promote ASM contraction? What roles do other cytokines such as IL-6 and OSM play in IL-31RA expression and ASM contractility? Does the blocking of IL-31RA and CHRM3 interactions result in effective inhibition of AHR downstream of multiple cytokines? Future studies should address these unknowns and identify the role of IL-31RA in the pathophysiology of asthma.

In summary, numerous cytokines are important in the pathophysiology of asthma. Epithelial cell-derived IL-25, IL-33, and TSLP are responsible for driving the differentiation of T lymphocytes [114]. IL-12, IL-18, and IFNγ promote Th1 and inhibit Th2 differentiation, whereas IL-6, TGFβ, IL-1β, and IL-23 promote the Th17 phenotype [115]. Once in the airways, these cytokines contribute to dysregulated responses in both stromal cells and immune cells in asthma. Therefore, understanding cytokine regulation in asthma holds the potential to transform our understanding and management of airway remodeling in this complex disease. By uncovering new mechanisms, identifying therapeutic targets, and personalizing treatment approaches, researchers can improve outcomes for asthma patients and enhance their quality of life. Collaborative efforts across disciplines, leveraging advanced technologies and methodologies, will be essential in advancing this field.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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