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REVIEW

Targeting IL-13 and IL-4 in Asthma: Therapeutic Implications on Airway Remodeling in Severe Asthma

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Abstract

Asthma is a chronic respiratory disorder affecting individuals across all age groups. It is characterized by airway inflammation and remodeling and leads to progressive airflow restriction. While corticosteroids remain a mainstay therapy, their efficacy is limited in severe asthma due to genetic and epigenetic alterations, as well as elevated pro-inflammatory cytokines interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-5 (IL-5), which drive structural airway changes including subepithelial fibrosis, smooth muscle hypertrophy, and goblet cell hyperplasia. This underscores the critical need for biologically targeted therapies. This review systematically examines the roles of IL-4 and IL-13, key drivers of type-2 inflammation, in airway remodeling and their potential as therapeutic targets. IL-4 orchestrates eosinophil recruitment, immunoglobulin class switching, and Th2 differentiation, whereas IL-13 directly modulates structural cells, including fibroblasts and epithelial cells, to promote mucus hypersecretion and extracellular matrix (ECM) deposition. Despite shared signaling pathways, IL-13 emerges as the dominant cytokine in remodeling processes including mucus hypersecretion, fibrosis and smooth muscle hypertrophy. While IL-4 primarily amplifies inflammatory cascades by driving IgE switching, promoting Th2 cell polarization

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Key messages

- Airway remodeling contributes to asthma severity by reducing the reversibility of structural changes leading to persistent airway obstruction.
- IL-4 and IL-13 play a central role in airway remodeling and inflammation, making them promising therapeutic targets.
- The impact of IL-4 and IL-13 targeted therapies on airway remodeling in asthma requires further investigation to establish their therapeutic benefits.

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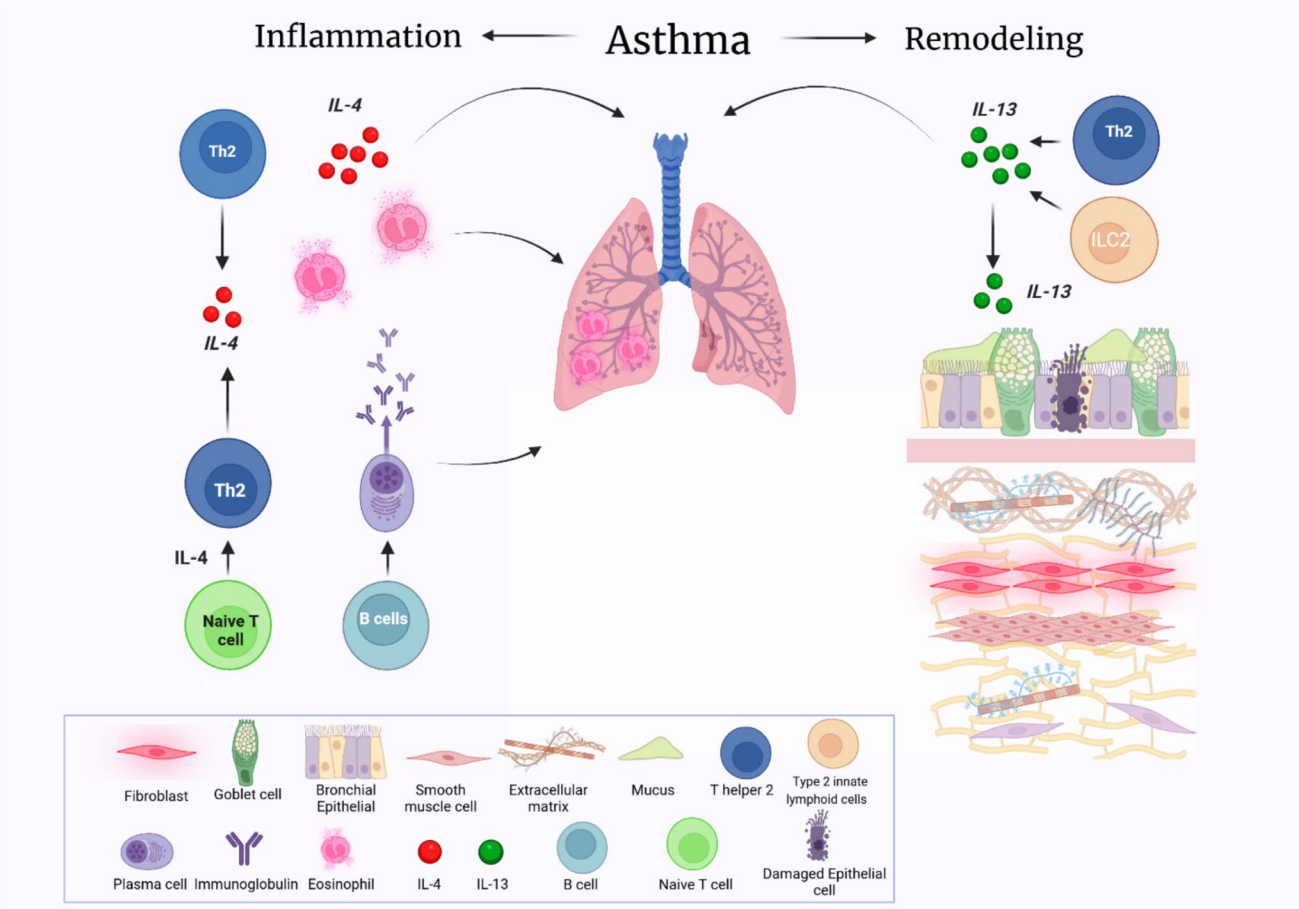
that sustain cytokine release, and inducing chemokines to recruit eosinophils. In steroid-resistant severe asthma, biologics targeting IL-4/IL-13 show promise in reducing exacerbations and eosinophilic inflammation. However, their capacity to reverse established remodeling remains inconsistent, as clinical trials prioritize inflammatory biomarkers over long-term structural outcomes. This synthesis highlights critical gaps in understanding the durability of IL-4/IL-13 inhibition on airway structure and advocates for therapies combining biologics with remodeling-specific strategies. Through the integration of mechanistic insights and clinical evidence, this review emphasizes the need for long-term studies utilizing advanced imaging, histopathological techniques, and patient-reported outcomes to evaluate how IL-4/IL-13-targeted therapies alter airway remodeling and symptom burden, thereby informing more effective treatment approaches for severe, steroid-resistant asthma.

Graphical Abstract

Schematic representation of the roles of IL-4 and IL-13 in driving inflammation and airway remodeling in asthma. IL-4 primarily contributes to inflammation by (1) promoting Type 2 helper T (Th2) cell differentiation from naïve T cells, (2) stimulating IgE production by B cells, and (3) enhancing eosinophil recruitment. Conversely, IL-13 is predominantly involved in airway remodeling through (1) inducing goblet cell hyperplasia and excessive mucus production, (2) promoting fibrosis, (3) driving smooth muscle hypertrophy and hyperresponsiveness, and (4) activating or damaging airway epithelial cells (AEC).



Keywords Asthma, airway remodeling · Interlukin-4 (IL-4) · Interlukin-13 (IL-13) · Anti-IL-4 · Anti-IL-13

Introduction

Asthma is a chronic inflammatory disorder and one of the most common lung diseases, affecting individuals of all ages [1]. It is characterized by persistent airway inflammation and recurrent respiratory symptoms such as wheezing, coughing, and breathing difficulty, often leading to bronchoconstriction [2]. Globally, asthma impacts over 300 million people and was responsible for approximately 500,000 cases of death in 2019, according to the World Health Organization (WHO) [3].

The complexity of asthma arises from the interplay of genetic and environmental factors, resulting in diverse clinical, biochemical, and pathophysiological phenotypes. These subtypes are defined by differences in lung function,

atopy, age, sex, symptom duration, treatment responses, and inflammatory patterns [4–6]. Advances in diagnostic tools have refined the classification of asthma subtypes, revealing distinct molecular pathways and genetic influences that underscore its heterogeneity [7].

Corticosteroids remain the cornerstone of asthma management, with dosage adjusted according to disease severity. While it is effective in reducing exacerbations and improving symptom control, long-term use is limited by steroid resistance and adverse side effects such as osteoporosis, diabetes, and adrenal suppression [8, 9]. This has spurred the development of targeted therapies that block specific inflammatory pathways, including those mediated by Type 2 (T2) cytokines, including IL-4, IL-5, and IL-13. These biologics offer improved symptom control with fewer systemic side effects, making them the preferable choice for corticosteroid resistance patients [10, 11]. Notably, these cytokines are central to the pathogenesis of T2 asthma, a subtype characterised by eosinophilic airway infiltration and driven by innate and adaptive immune responses involving type 2 innate lymphoid cells (ILC2s) and T helper 2 (Th2) lymphocytes [12].

T2 cytokines modulate inflammation in T2 asthma from different aspects: IL-5 directly governs eosinophil activation and recruitment, amplifying airway inflammation, while IL-4 and IL-13 promote eosinophil accumulation by IL-5 induction and chemokine secretion [13, 14]. Additionally, IL-4 and IL-5 support mast cell survival, potentially triggering acute respiratory symptoms such as airway constriction [15–17]. Whereas IL-4 and IL-13 drive Th2 cell differentiation and immunoglobulin E (IgE) production [18]. Beyond inflammation, these cytokines influence airway structural cells, including fibroblasts, epithelial cells, and airway smooth muscle (ASM), contributing to remodeling features such as fibrosis, epithelial detachment, and ASM thickening [19, 20]. These changes result in narrow, stiffer airways, leading to airflow limitation, persistent symptoms, and reduced responsiveness to standard therapies. Although IL-5 receptors are expressed on structural cells, their functional role remains poorly understood [21, 22].

Given the central the role these cytokines play in both inflammatory and structural aspects of asthma, research has increasingly focused on their contributions to disease progression [23]. In this review, we explore the recent advances in understanding the roles of IL-4 and IL-13 in asthma pathophysiology, particularly in airway remodeling. We also discuss their potential as therapeutic targets and their implications for asthma treatment.

Classification of Asthma

Asthma is a heterogeneous disease that manifests in several phenotypes, distinguished by features such as age of onset, disease intensity, inflammatory patterns, and the presence of atopic conditions [7]. Initially, the classification of asthma focused on assessing a patient's atopic status, which refers to their sensitivity to allergens and the likelihood of developing asthma symptoms [24]. While atopic and non-atopic asthma phenotypes are often considered as separate forms of asthma, they have significant overlap in their clinical presentation and the underlying inflammatory processes [25].

An alternative approach categorizes asthma pathophysiology based on cellular inflammation patterns, particularly eosinophil and neutrophil infiltration in the airways. Sputum analysis has identified four inflammatory subtypes, including eosinophilic, mixed eosinophilic and neutrophilic, neutrophilic, and paucigranulocytic (neutrophils and eosinophils both within normal range) [26]. Non-eosinophilic asthma is characterized by the presence of neutrophils and the absence of eosinophils. It can also include a paucigranulocytic subtype, where there is no increase in inflammatory cells, such as neutrophils or eosinophils, in the airways [27]. In contrast, eosinophilic asthma is driven by T2 inflammation, mediated by Th2 cells and ILC2s, leading to eosinophil accumulation [20].

Mosmann et al. introduced additional classification of asthma characterized by two distinct T helper cell types in mice [28]. Subsequent gene expression studies stratified asthma into two molecular phenotypes based on Th2 inflammation levels: Th2 "high" and Th2 "low" [29, 30]. Th2 "high" asthma, a well-recognized subtype, is marked by severe symptoms, including impaired lung function and frequent exacerbations [31]. It is characterized by elevated activity in T2 immune pathways, eosinophilic airway inflammation, and increased level of cytokines like IL-4, IL-5, and IL-13, often requiring more intensive and targeted treatments. On the other hand, Th2 "low" asthma generally has a different inflammatory profile and can be harder to manage due to its unpredictable response to standard asthma treatment [32].

Severe Asthma: The Underlying Pathophysiological Features

Severe asthma is a chronic respiratory disorder characterized by persistent and intense airway inflammation [33]. Approximately 10% of adult asthma patients exhibit poor or partial responsiveness to current steroid therapies, classifying them as severe asthmatics [33]. According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) definition, severe asthma was defined as "asthma which requires treatment with high-dose inhaled/systemic corticosteroids (ICS) plus a second controller to prevent it from becoming 'uncontrolled,' or which remains 'uncontrolled' despite this therapy" [33]. Although severe asthma affects a small group of patients, it accounts for most healthcare costs.

Recent studies highlighted distinct phenotypic severe asthma subgroups, including gender-based disparities, as severe asthma is more prevalent in females than males [34]. These disparities in asthma severity between genders are primarily attributed to hormonal fluctuations, particularly the effects of estrogen and progesterone, along with genetic differences that contribute to gender-specific asthma phenotypes, influencing immune system responses, airway inflammation, and sensitivity to environmental triggers. When combined with hormonal changes, these genetic factors can further exacerbate asthma severity in women, particularly during puberty, pregnancy, and menopause [35].

Impaired steroid responsiveness is another hallmark of severe asthma, influenced by genetic variability and molecular mechanisms such as glucocorticoid receptor (GR) isoforms [36]. Glucocorticoid receptor alpha (GR-α) is an active form of the receptor found in all lung cells, while glucocorticoid receptor beta (GR-β) is an inactive form that is associated with steroid resistance [37]. Additional mechanisms include reduced anti-inflammatory gene expression and elevated pro-inflammatory cytokines (e.g., IL-2, IL-4, IL-13), which suppress T-cell responses by diminishing ligand-receptor binding affinity [37–40]. Thus, severe asthma is determined by cytokine-mediated pathways detectable in peripheral blood or airways.

Individuals with Th2 "high" asthma tend to have several features of increased asthma severity; this type is orchestrated by T2 cytokines IL-4, IL-5, and IL-13 functioning as a second-order cytokine released from activated Th2 cells and ILC2 [31]. Previous research indicated that mutations in IL-4, IL-13, and/or their respective receptors correlate with asthma severity; for instance, mutations in interleukin-4 receptor Alpha (IL-4Rα) were linked to severe asthma exacerbations, impaired lung function, and heightened mast cell-related tissue inflammation [41]. Furthermore, another study indicated that mutations in IL-4 allele are a risk factor for life-threatening asthma, while mutations in the IL-4Rα allele are associated with reduced lung function in asthmatic individuals [42]. Similarly, IL-13 polymorphisms may alter asthma-related signaling pathways [43]. These findings raise questions about whether T2 cytokine mutations directly contribute to steroid hypo-responsiveness.

Beyond the established role in inflammation, IL-4 and IL-13 also play a significant role in airway remodeling, a process marked by structural changes such as fibrosis and epithelial thickening. [44].

Airway Remodeling in Asthma

Airway remodeling refers to the permanent or semi-permanent structural changes in the large and small airways following airway tissue injury [45]. These changes include alterations to cellular and ECM components, epithelial cell apoptosis and detachment, mucus hypersecretion, ASM proliferation, and fibroblast activation (Fig. 1, Table 1) [45]. Deposition of ECM components, including collagen, fibronectin, and tenascin, from various airway structural cells is one of the key elements associated with airway remodeling [46, 47].

Asthmatic airway remodeling and pathogenesis are further driven by an imbalance in the matrix metalloproteinase (MMP) to tissue inhibitor of metalloproteinase (TIMP) ratio. MMP, a family of enzymes that degrade ECM proteins, are regulated by TIMP (endogenous MMP inhibitors). Dysregulation of this balance disrupts ECM homeostasis, contributing to pathological tissue changes [48, 49]. However, the exact mechanism of IL-4 and IL-13 involvement in airway remodeling in severe asthma and their role in ECM, structural cells, and MMP:TIMP ratio distribution warrants further research.

Pathophysiological Role of IL-4 and IL-13 in Asthma

The pathogenesis of asthma has been associated with Th2 cytokine-producing cells [50, 51]. Investigation of the role of the classic Th2 cytokines, IL-4 and IL-13, has garnered significant interest in the effort to comprehend the processes by which Th2 cell-derived cytokines impact the development of asthma. Initially, it was thought that IL-4 and IL-13 would have overlapping functions in the development of allergic asthma [50]. The overlap in function between IL-4 and IL-13, inferred from their shared genetic proximity, regulatory elements (e.g., GATA-3), and receptor components (IL-4Rα/IL-13Rα1), is reinforced by their co-production from overlapping cellular sources, primarily Th2 lymphocytes, which drive type 2 inflammation in allergic asthma. [52]. However, their distinct roles in disease pathogenesis may arise from differences in secondary cellular origins including Th2, and ILC2, with a lower secretion level from other cells, including Natural Killer (NK) Cells, Th1 cells, B lymphocytes, mast cells, macrophages, basophils, and eosinophils, in addition to basophils and CD8 + T lymphocytes [53–55]. Although the functional roles of IL-4 and IL-13 are similar, it is probable that these two closely related cytokines have distinct pathobiological effects in asthma and their contribution to airway remodeling.

This figure illustrates key structural changes in severe asthma, including goblet cell hyperplasia and mucus plugging, epithelial damage, and basement membrane thickening from subepithelial fibrosis. Smooth muscle hypertrophy and hyperplasia heighten bronchoconstriction and reactivity, Increased vascularization supplies inflammatory cells, reinforcing inflammation.

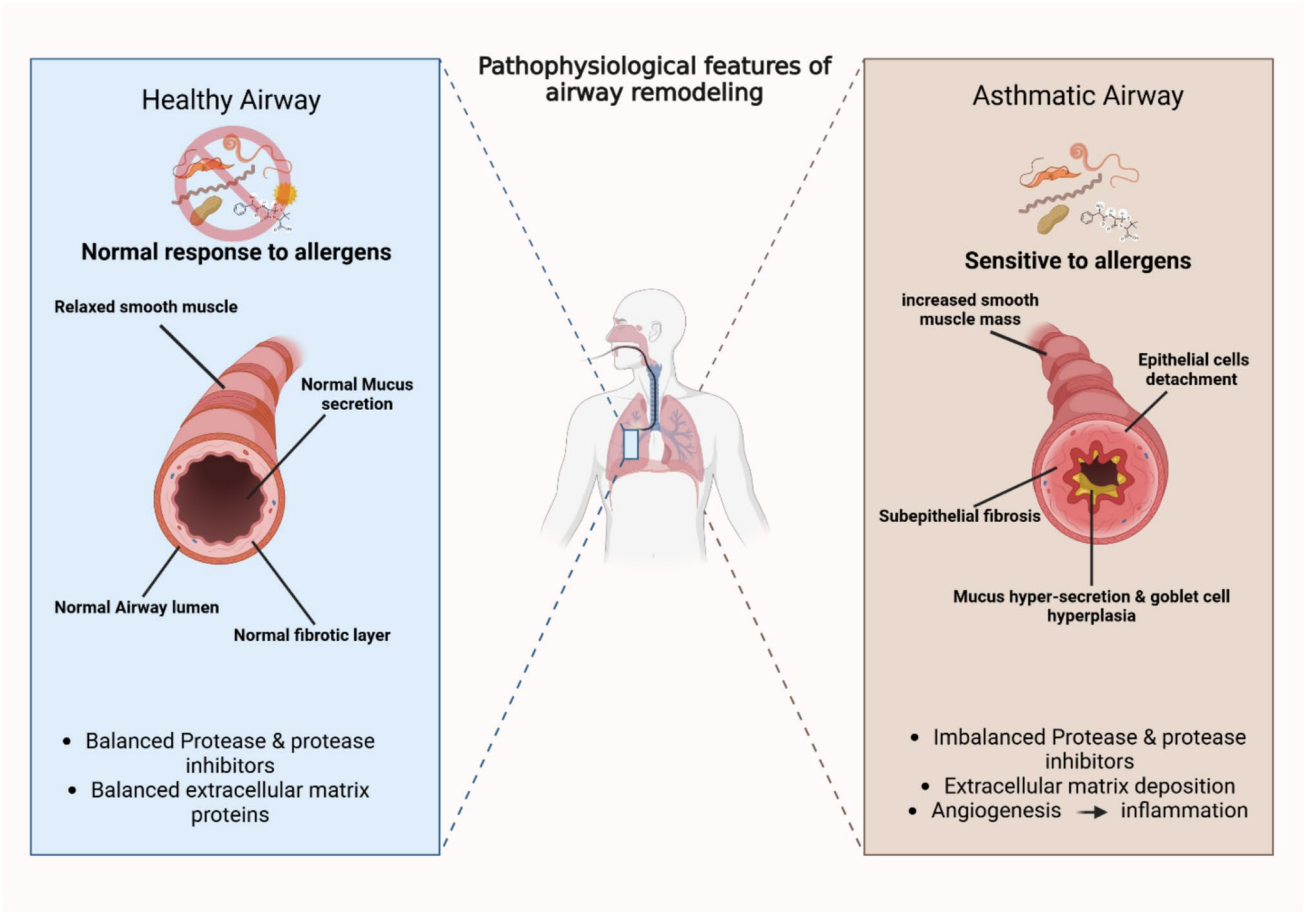


Fig. 1 Pathophysiological features of airway remodeling in severe asthma

Table 1 Summary of key findings on airway remodeling processes and the corresponding study models

Airway Remodeling process	Key findings	Study model	Ref
Epithelial cell changes	Goblet cell hyperplasia, mucus hypersecretion and epithelial cell detachment	Animal model	[56]
Subepithelial Fibrosis	ECM deposition and increase basement membrane thickening	Human in vivo model	[57]
Smooth Muscle Hypertrophy	ASM cell proliferation and increased contractility	Human in vivo model	[58]
Angiogenesis	Increased microvascular density and vascular endothelial growth factor (VEGF) expression	Human in vivo model	[59]
Inflammatory Cell Infiltration	Elevated eosinophils, mast cells, and neutrophils in airway walls	Human in vivo model, Animal model	[60, 61]
Altered ECM Composition	Imbalance of MMP and TIMP	Human in vivo model	[48]

Role of IL-4 and IL-13 in Airway Remodeling in Asthma

Epithelial Cell Detachment and Mucus Hyper-Secretion

The bronchial epithelium is essential for preserving the internal environment of the lung and serves as a barrier to the external environment. It plays a role in the epithelial-mesenchymal trophic unit by regulating the local microenvironment and supporting tissue homeostasis through maintaining the airway microenvironment during key processes including lung growth, tissue healing, and controlling the inflammatory response [62]. However, in case of asthma, the continuous disruption of these regulatory systems results in changes to the physical composition of the air passages [62]. Most of the Airway epithelial cells (AEC) disruption has been induced simply upon IL-13 stimulation with limited functional and structural abnormalities in severe asthma in response to IL-4.

IL-13 and IL-4 play overlapping yet distinct roles in mucus hypersecretion and airway obstruction in asthma. IL-13 directly drives goblet cell hyperplasia and MUC5AC overexpression during epithelial differentiation, significantly increasing mucus-producing cells while suppressing ciliated cell formation [63, 64]. A recent study revealed that one of the hallmarks of asthma is the reversal of the normal MUC5B:MUC5AC ratio, with MUC5AC dominating in asthmatic sputum [65, 66]. IL-13 also has the ability to disrupt mucociliary clearance through binding mucus gels to the epithelium by MUC5AC, impairing ciliary transport without altering ciliary beat frequency [67].

In parallel, IL-4 contributes to mucus hypersecretion by upregulating mucin genes *MUC5* and *MUC4*. Where *MUC4* is mediated through Janus kinase 3 (JAK-3) signaling [68–70]. *MUC4* acts as a ligand to activate Human Epidermal Growth Factor Receptor 2 (HER2/ErbB2), a receptor tyrosine kinase that regulates epithelial cell proliferation in response to airway damage in asthma [71]. While both cytokines promote mucus overproduction, IL-4 indirect effects such as Th2 polarization and amplification of IL-13 release highlight its complementary role in sustaining inflammation and structural changes.

Another mechanism by which IL-4 and IL-13 contribute to epithelial disruption and loss of function in asthma is by impairing tight junction integrity. IL-13 reduces bronchial epithelial barrier function through histone deacetylase (HDAC)-mediated epigenetic regulation, increasing permeability in asthmatic patients [72]. Additionally, it alters tight junction protein expression in allergic rhinosinusitis through decreasing occludin (cldn) and junctional adhesion molecule A (JAM-A) while elevating claudin-2 (cldn 2), which enhances paracellular permeability in AEC [73]. IL-13 also downregulates claudin-18 (cldn18), increasing susceptibility to aeroallergens and airway hyperreactivity in Th2 asthma. [74]. Furthermore, IL-13 induces proteasomal aggregation of tight junction proteins claudin-8 (cldn8), claudin-9 (cldn9), and claudin-16 (cldn16) and E2 ubiquitin conjugating enzyme (UBE2Z), destabilizing epithelial structure [75]. Destabilization and damage to the AEC stimulate the production of fibrogenic cytokines, including IL-4 and IL-13 that in turn reduce further the expression of proteins that maintain the integrity of cell junctions in an autocrine manner [76].

IL-4 similarly disrupts barrier function but through distinct pathways. It increases epithelial permeability by JAK-dependent mechanisms, as shown by IL-4-induced macromolecule leakage of 3 kDa dextran, as this effect was reversed with JAK inhibitors [77]. IL-4 also causes a noticeable decrease in the function of the epithelial barrier and a decrease in the expression of two tight junction components, occludin and Zonula Occludens-1 (ZO-1), displacing these proteins by EGFR-dependent Mitogen-activated protein kinase/ Extracellular signal-regulated kinase (MAPK/ERK1/2) signaling [78].

Additionally, IL-13 drives airway epithelial disruption by dysregulating ECM dynamics. Differentiated fibroblasts known as myofibroblasts are the primary collagen producers in airways [79] and interact with epithelial cells to amplify asthma progression [80]. Prolonged IL-13 exposure induces a persistent epithelial phenotype that secretes elevated Transforming Growth Factor Beta 2 (TGF-β2), stimulating collagen deposition and fibroblast-mediated ECM remodeling [81]. Co-culture studies of asthmatic epithelial cells with lung fibroblasts reveal increased expression of ECM components, collagen Type I Alpha 1 (COL1A1), collagen Type III Alpha 1 (COL3A1), and hyaluronan synthase 2 (HAS2) compared to healthy counterparts, underscoring disease-specific ECM dysregulation [80]. However, addressing the gap of IL-4 and IL-13 contribution in this process is needed to understand their role further in remodeling.

Complementing IL-13 ECM effects, IL-13 also upregulates MMP enzymes critical for ECM degradation [82, 83]. For example, MMP-9 was reported to be released by epithelial cells and cleaves collagen IV and entactin, facilitating structural breakdown [82]. In severe asthma, IL-13 elevates MMP-7 in basal epithelial cells, triggering membrane FasL cleavage and soluble FasL release, which exacerbates epithelial inflammation and damage [83].

While IL-13 primarily disrupts ECM integrity, IL-4 contributes to remodeling through epithelial-mesenchymal transition, a process where epithelial cells undergo a gradual transformation into mesenchymal-like cells, lose adhesion/polarity and gain migratory/invasive properties, leading to airway thickening [84, 85]. IL-4 exhibited a synergistic effect with TGF-β1 in inducing epithelial-mesenchymal transition and epithelial cell cycle activation [86]. This mechanism is further supported by studies showing that inhibiting IL-4 with bioactive alkaloids suppresses epithelial-mesenchymal transition, reduces TGF-β1/Smad3 signaling, and mitigates remodeling [87].

Beyond that, IL-4 stimulates bronchial epithelial cells to produce tenascin C, an ECM protein implicated in structural changes, though the signaling pathways regulating its expression remain unclear [88]. IL-4 also induces eotaxin-3 release by AEC, amplifying inflammation and immune cell recruitment, which would enhance structural alterations and AEC damage [89].

Despite advances in understanding IL-4 and IL-13's role in asthma, critical gaps persist in understanding their exact role in asthma pathogenesis. Both cytokines perpetuate inflammation and barrier dysfunction through fibrogenic feedback loops [76], but their direct versus indirect contributions to mucus hypersecretion, epithelial changes, and

airway remodeling remain unclear. IL-4's effect on profibrotic mediators and IL-13's direct regulation of epithelial ECM production are poorly defined. Resolving these mechanistic uncertainties is vital to disrupting disease progression and advancing targeted therapies.

Subepithelial Fibrosis

Subepithelial fibrosis is another form of airway remodeling that has been known to develop in patients with persistent asthma attacks and causes a gradual reduction in lung function [90]. Subepithelial fibrosis is defined as a thickening in the subepithelial layer, which takes place in the lamina reticularis just below the basement membrane and could extend beyond in severe asthma [91]. Thickening of the basement membrane involves the accumulation and dispositioning of ECM proteins within the lamina reticularis, including collagen types I, III, and V, fibronectin, lumican, tenascin, periostin, and various proteoglycans [92, 93]. Additionally, fibroblasts, which are the main cellular component in the subepithelial layer, in an inflammatory environment such as asthmatic airways get activated or differentiated into myofibroblasts, which leads to further ECM protein disposition and pro-inflammatory mediator secretion [94].

Both IL-13 and IL-4 drive fibrotic processes in asthma by influencing lung fibroblasts and ECM dynamics, though their mechanisms and targets differ. IL-13 directly induces morphological changes in lung fibroblasts, promoting their differentiation into Alpha Smooth Muscle Actin (α-SMA)-positive myofibroblasts and selectively upregulating *COL1A2* in bronchial fibroblasts of moderate asthma patients, whereas this impact does not extend to the expression of *COL1A1* or *COL3A1* genes [95, 96]..

Beyond its direct effect, IL-13 amplifies fibrosis by activating TGF-β1 and MMP, key mediators of tissue remodeling. Studies show IL-13 stimulates MMP-9 and TGF-β1 production in asthmatic fibroblasts, with TGF-β1 activation occurring via MMP-9-dependent processes [96–98]. This interdependence is evident in MMP-9-deficient mice, where IL-13-induced fibrosis is attenuated, and in IL-13 transgenic mice, where TGF-β neutralization reduces lung collagen accumulation [97, 99]. IL-13 further promotes airway fibroblast invasion through TGF-β1/MMP pathways, a mechanism observed in asthmatic patients and reversed by inhibiting TGF-β1/MMP activity [100]. Additionally, IL-13 was shown to suppress elastin expression in airway fibroblasts, contributing to airway remodeling in asthma through increasing the activity of MMP, particularly MMP-1 and MMP-2, which degrade elastin fibers [101]. This reduction increases collagen and alters ECM balance, causing airway elasticity loss and pathological stiffness. Yet IL-4 role on elastin production in airway fibroblasts is less well-documented. Since IL-4 and IL-13 share similar receptor components and signaling pathways, further research is needed to clarify IL-4's impact on elastin production. Moreover, IL-13 was shown to stimulate fibroblast proliferation in asthma, though the underlying mechanisms remain unclear [95, 102–104]. Together, these findings underscore IL-13's dual role by directly driving myofibroblast differentiation and collagen deposition while indirectly amplifying fibrosis via TGF-β1/MMP-9 signaling.

In contrast, IL-4 exhibits broader, context-dependent effects: it induces mRNA expression of procollagen I/III, fibronectin, and tenascin and promotes myofibroblast differentiation in synovial/dermal fibroblasts [105–108] and, in murine lung fibroblasts, promotes collagen synthesis and proliferation [106]. Besides the role of IL-4 in ECM deposition, several findings suggest that IL-4 does not directly induce ECM synthesis. Instead, it largely functions as an indirect signal, potentially by controlling the expression of other stronger fibro-genic factors like TGF-β [103, 109–111]. TGF-β itself amplifies fibrosis by driving connective tissue growth factor (CTGF), α-SMA, collagens, MMP, and TIMP [109, 112, 113], and by converting fibroblasts into ECM-producing myofibroblasts [79, 114–118]. Contrary, to the indirect role, it is reported that IL-4 can directly drive myofibroblast transition in lung fibroblasts by suppressing cyclooxygenase (COX) expression and prostaglandin E2 production [95]. This process is linked to the activation of the c-Jun NH2-terminal kinase (JNK) pathway in asthma fibroblasts, a mechanism shared with IL-13 [119]. However, fibrosis involves the smooth muscle as well as epithelium and fibroblast. Understanding the role of smooth muscle in asthma is important.

Increased Smooth Muscle Mass

The involvement of ASM in asthma is essential, and there has been much focus on understanding its pathophysiological contribution to inflammation and remodeling. ASM is believed to play a significant role in the increased constriction of airways in asthma. Additionally, ASM is involved in poor relaxation of the airways and the promotion of structural alterations [120].

Both IL-13 and IL-4 contribute to airway hyperresponsiveness in asthma by modulating ASM contractility and receptor signaling, though their mechanisms differ. IL-13 directly enhances ASM contraction through multiple pathways; it upregulates histamine (H1) and cysteinyl leukotriene (CysLT1) receptors, amplifies intracellular Ca^{2+} mobilization in response to agonists like histamine and acetylcholine, and impairs β-adrenergic relaxation [121–128]. Additionally, IL-13 promotes ASM proliferation via store-operated Ca^{2+} entry (SOCE) and synergizes with TGF-β to enhance Leukotriene D_4 (LTD_4)-driven proliferation through MAP kinase/ERK and Phosphoinositide 3-kinases

(PI3K) pathways [129–131]. In contrast, the role of IL-4 in ASM mass and contractility is less defined. While initially thought to act indirectly by ECM (MMP-1) production [132], recent evidence shows IL-4 directly increases histamine sensitivity by upregulating HRH1 and CYSLTR1 receptors and boosting Ca^{2+} mobilization in human ASM cells (HASMCs), effects reversible upon IL-4 receptor blockade [128]. Unlike IL-13, IL-4's influence on ASM proliferation remains underexplored, and its downstream mechanisms require further study. Both cytokines converge on receptor-mediated Ca^{2+} signaling to heighten contractility, but IL-13 exhibits broader involvement in proliferative pathways, underscoring its central role in ASM remodeling.

Moreover, IL-13 and IL-4 differentially regulate ASM migration and ECM remodeling in asthma. IL-13 drives ASM migration through multiple pathways; it synergizes with Tumor Necrosis Factor-alpha (TNF-α) to amplify eotaxin release from HASM cells, recruiting eosinophils and exacerbating inflammation [133], while also promoting chemotaxis via Prostaglandin D_2 (PGD_2) and Platelet-derived growth factor (PDGF)-dependent Src-kinase activation. This migration involves IL-4R subunit signaling, upregulation of PDGF receptors, and enhanced cysteinyl leukotriene receptor (CysLTR) expression [134]. However, IL-4 did not induce the same chemoattractant effect although the IL-13-primed migration was inhibited by blocking both the IL-13 and IL-4 receptors. Having said that, cellular migration has been previously observed in various diseases upon IL-4 stimulation [135, 136]. These findings would suggest whether IL-4 induces ASM migration indirectly through other receptors or upon activation of other IL-4 dependent stimulants. Nonetheless, IL-4 is suggested to have a bifunctional role in airway remodeling, one is characterized by suppression of the ASM hyperplasia and the other by the increase in VEGF release from the ASM cells [137].

ECM deposition is another mechanism by which IL-13 induces ASM thickening, as the enrichment of the airway wall with collagen and fibronectin in asthma is potentially important for the regulation of ASM synthetic function. A previous study has indicated that both type I collagen and fibronectin augment the proliferation of healthy ASM cells activated by thrombin or platelet-derived growth factor-BB [138]. In asthmatic subjects, findings indicate that IL-13 increased eotaxin secretion, and an autocrine fibronectin secretion by ASM was suggested to underlie this effect [138]. Another study reported that IL-13 plays an essential role in activating a set of "pro-asthmatic" genes in ASM, including Tenascin C [139], which is known to promote the accumulation of collagen and other ECM components.

However, IL-4 impact on ECM production remains unclear, with limited evidence of direct contributions to collagen or fibronectin deposition. Further studies are needed to elucidate the roles of IL-4 and IL-13 in ASM migration, growth, and ECM production, which would enhance our understanding of their effects on ASM thickening. Additionally, the mechanisms by which IL-13 promotes cellular migration, including the potential role of IL-13-induced chemokines in driving ASM migration, require deeper investigation. In fact, besides IL-4 and IL-13 essential functions in asthma pathogenesis, both cytokines work synergistically to modulate downstream pathways linked to asthma.

IL-4 /IL-13 Receptor Complex: Signaling Pathway

Both IL-4 and IL-13 mediate their response in inflammation, remodeling, and airway hyperresponsiveness upon binding to their corresponding receptor. There are two types of receptors that IL-4 uses to transmit signals. One is the type I receptor, which includes IL-4R alpha and the common gamma chain (γC). The other is the type II receptor, which includes IL-4Rα and IL-13Rα1 [140]. IL-4Rα is observed in low levels in several cell types. In non-hematopoietic cells, γC expression is either inadequate or absent, but IL-13Rα1 expression is strong. Lymphocytes exhibit low amounts of IL-13Rα1 and elevated levels of γC. Myeloid cells express both IL-13Rα1 and γC, positioning them between non-hematopoietic cells and lymphocytes [141]. The γC or IL-13Rα1 are recruited when IL-4 binds IL-4Rα with an extremely high affinity [142]. The interaction between IL-4 and the type I receptor complex leads to the activation of Janus family kinases, namely JAK1, JAK2, and JAK3. This process results in the phosphorylation of signal transducer and activator transcription 6 (STAT6) through establishing specific locations for STAT6 and/or Insulin Receptor Substrate 2 (IRS-2) to attach, and this promotes the formation of phospho-STAT6 homodimers, translocate them into the nucleus, and facilitates gene transcription [50, 143]. Other signaling pathways were reported to be activated upon IRS-2 phosphorylation, including PI3K, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Protein Kinase B (AKT) [144–146]. In addition to IRS, previous study findings reported that IL-4 has a function in protecting cells against apoptosis through a mechanism reliant on the transcription factor NF-κB. Although IL-4 is implicated in the NF-κB pathway, studies suggest that IL-4 alone is not enough to activate this pathway. Yet, IL-4 can enhance NF-κB transcription factor family activation from other stimuli like TNF-α or T-cell receptor (TCR) engagement [147].

However, IL-13 binds to the type II receptor through IL-13R alpha 1 [141], whereby IL-13Rα1 serves either as a particular binding domain for IL-13 or as a dimerizing partner that joins with the ternary complex of the type II receptor. Both IL-4 and IL-13 activate Janus kinase 1 (JAK1) and

a tyrosine kinase 2 (TYK2), which are responsible for the phosphorylation of a STAT-6 and the subsequent translocation of this protein to the nucleus [141, 148]. The activation of receptor type II results in the activation of other tyrosine kinase proteins, such as JAK2, STAT1, and STAT3 [140]. Since JAKs play a crucial role in IL-4 and IL-13 signaling pathways, they are considered a beneficial targeted therapeutic marker to reduce inflammation and remodeling. Several preclinical and clinical studies showed promising findings by improving lung function and limiting the inflammatory response, which in turn can prevent or reduce the structural changes associated with airway remodeling [77, 149]. However, NF-kB was also found to be activated by IL-13 through IL-13Rα1. One recent study demonstrated that IL-13 stimulates β1 integrins in ASM cells, leading to an increase in cell adhesion to the ECM [150]. The enhanced adhesion led to augmented force transmission inside the ASM, a significant feature observed in chronic airway conditions, including asthma. The NF-κB pathway has been defined as a signaling cascade that activates β1 integrin upon IL-13 stimulation; NF-κB increases RhoA and its effector Rho kinase, resulting in the subsequent activation of Phosphatidylinositol-4-phosphate 5-kinase type 1 gamma (PIP5K1γ), which promotes phosphatidylinositol 4,5-bisphosphate (PIP2) synthesis and β1 integrin activation [150]. In addition, IL-13 and IL-4 have been reported to provide a novel mechanism of increasing susceptibility to infections in asthmatic patients, promoting T2 inflammation and exacerbating asthma pathology upon inhibiting activation of NF-κB by suppressing Toll-Like Receptor (TLR) expression on progenitor cells. IL-4 and IL-13 limit the innate immune activation potential of differentiated eosinophils and basophils [151], whereas IL-13 further dampens innate immunity in AEC, reducing their ability to respond to microbial threats [152].

A comparison was made between the signaling potency and kinetics of IL-13 and IL-4, and the results showed that IL-4 is more effective than IL-13 in activating the tyrosine phosphorylation of STAT6 [153], and this was explained in a manner of IL-13 signaling pathway follows a sequence of steps in which IL-13 first attaches to IL-13Rα1 before recruiting IL-4Rα to form a signaling complex with strong affinity [50, 154]. Whereas IL-4 first establishes a robust interaction with IL-4Rα and subsequently recruits IL-13Rα1 to form the signaling complex. This explains why IL-4 has a greater potency than IL-13 at low concentrations, as IL-4 is able to signal more efficiently. Conversely, IL-13Rα1 exhibits a greater concentration in the cellular membrane in comparison to IL-4Rα. At high concentrations, IL-13 has a stronger signaling effect compared to IL-4, particularly through the type II IL-4R receptor [50].

In addition to IL-13Rα1, IL-13 can interact with another type of IL-13R known as IL-13 receptor α2-chain (IL-13Rα2) with greater affinity than IL-13R alpha1. It has been demonstrated that IL-13 does not activate any signaling pathways after binding [155]. As a result, it has been referred to as a decoy receptor and it is founded in both membrane-bound and soluble forms [156, 157]. On the other hand, a recent study provided evidence that IL-13Rα2 is responsible for mediating *MUC5AC* expression through the mitogen-activated protein ERK1/2 pathway as well as the downstream *C-JUN* Activator Protein-1 (*AP-1)*-related gene in human nasal epithelial cells (Fig. 2) [158]. In another study, it was demonstrated that IL-13 is responsible for initiating TGF-β1 production and fibrosis by means of activating IL-13Rα2 signaling, which in turn activates *AP-1* related genes such as *C-Jun* and members of the Fos family (*Fra-2*). This phenomenon was reversed by blocking IL-13Rα2 signaling, which resulted in a significant reduction in TGF-β1 production and collagen deposition [159]. This was additionally supported by Brunner et al. The induction of allograft fibrosis in a mouse model was triggered by TGF-β through IL-13 signaling via IL-13Rα2 [160]. On the other hand, IL-13R alpha 2 was suggested to be a neutralizer/inhibitor of IL-13 signaling, which facilitates the prevention of inflammation and remodeling in asthma [161]. Additionally, subsequent findings provided evidence that the upregulation of IL-13Rα2 expression is the cause of decreased airway hyperresponsiveness, mucus production, and fibrosis in a mouse model [162]. It can be mentioned that asthma is regulated by complex network of multiple pathways, this complexity makes it difficult to identify cures for asthma thus currently can only be managed.

Schematic illustration of the signaling pathways activated by IL-4 and IL-13 through IL-4Rα, a constituent of both type I (IL-4Rα and γc), type II receptors (IL-4Rα and IL-13Rα1), and IL-13Rα2, culminating in the transcription of IL-4/IL-13 responsive genes, fibroblast proliferation, ASM contraction, collagen synthesis, ECM deposition, and TGF-β production.

Asthma Management

Despite advances in asthma medications, 5% to 20% of adult asthma patients still experience uncontrolled or partially controlled symptoms. This has driven the development of monoclonal antibodies (mAbs) (Fig. 3), which have become essential for maintenance therapy. Although targeted therapy reduces the need for oral corticosteroids (OCS), many patients still require low-dose inhaled corticosteroids (ICS) as part of their long-term asthma management [163]. Recent progress in targeting specific therapeutic pathways with mAbs has enabled more personalized treatment options.

This figure illustrates asthma management, focusing on pharmacological strategies to relieve symptoms, enhance lung function, and prevent exacerbations. Treatments

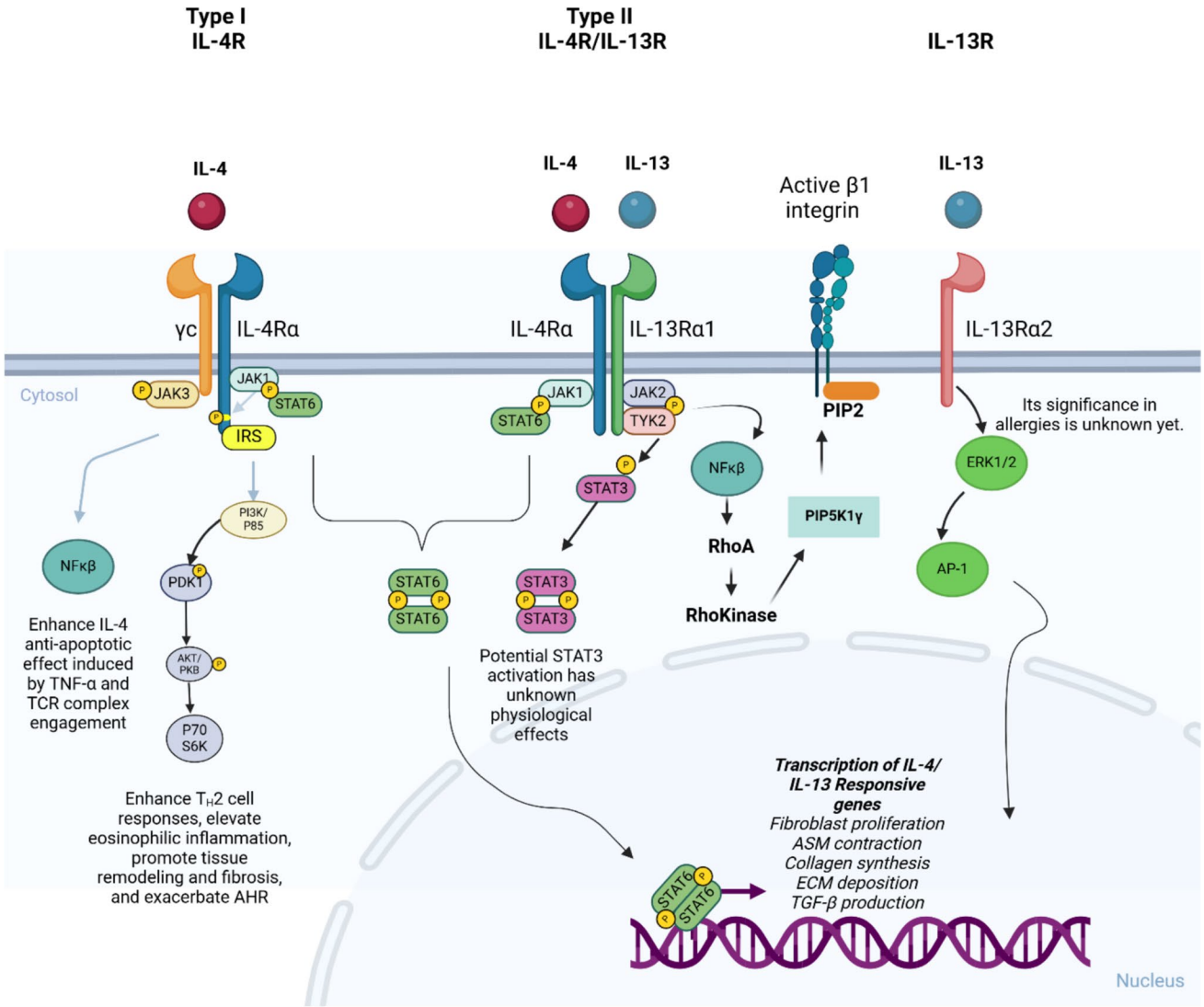


Fig. 2 IL-4 and IL-13 activate intracellular signaling pathways through their specific membrane receptors

include quick-relief Short-Acting Beta-Agonists (SABAs) and controller options such as ICS, Long-Acting Beta-Agonists (LABAs), leukotriene modifiers, and biologics targeting IL-4/IL-13 pathways.

Targeted IL-4 and IL-13 Therapies: Impact on Remodeling

Due to all previous findings and along with the association mechanism of IL-4 and IL-13 signaling in asthma both IL-13 and IL-4 along with their corresponding receptor became a potential target for add/on biological therapy as summarized in Table 2.

Targeted Anti-IL-4 Therapy

As previously stated, IL-4 plays a role in inflammation and remodeling in asthma. Numerous studies have demonstrated that the elimination or inhibition of IL-4 significantly prevents the allergic inflammatory response and other characteristics of asthma [164]. Pascolizumab, a humanized monoclonal antibody, was developed and evaluated in vitro against human cells that target IL-4, preventing IL-4-related inflammation events in asthma, such as eosinophilia, T cells differentiation, and B cell isotype switching where limiting these events may prevents further airway inflammatory cell infiltration and remodeling [165]. In addition to assessing the safety and toxicity profile of Pascolizumab, affinity tests and the kinetics of antibody binding to IL-4 were examined,

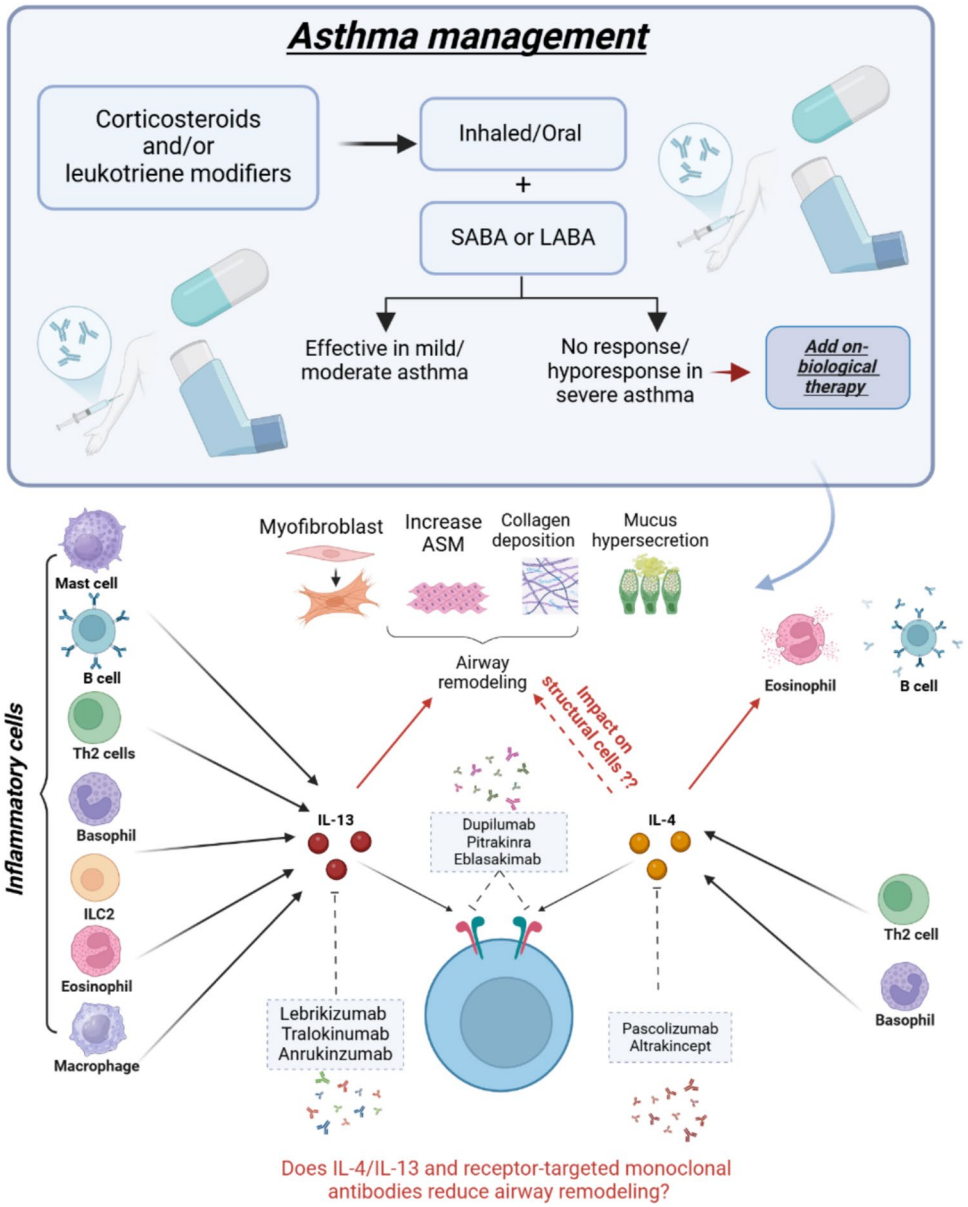


Fig. 3 Asthma management strategies

exhibited fast attachment to IL-4 and a gradual separation phase with a k-on value of $3{\cdot}4\times106\ M-1s-1$ and k-off values of $2\times10-4s-1$. Furthermore, it effectively hindered the binding of IL-4 to its receptor IL-4R alpha, with an IC50 of around 10 nm [165]. The trials showed that Pascolizumab effectively inhibited IL-4-dependent T-cell proliferation, IgE production, and upregulation of the FcεRII (CD23) receptor as an in vivo result showed a positive pharmacokinetics and safety of Pascolizumab in cynomolgus monkeys; these results were highly promising, although the only complication observed was the development of an anti-idiotypic response, which led to the rapid clearance of Pascolizumab [165]. However, insignifcant results were obtained at phase II human clinical trials, yet no treatment safety related issues were raised however further development was terminated [166]. Pascolizumab's failure underscores the complexity of asthma pathophysiology and the need for targeted therapies in biomarker-defined subgroups. Additionally, since IL-4 and IL-13 share signaling components (e.g., IL-4Rα), blocking IL-4 alone may not sufficiently inhibit inflammation, as IL-13 can compensate via these shared receptors. Newer agents that block multiple cytokines or target downstream pathways have since demonstrated greater success.

Another anti-IL-4 targeted therapy known as Altrakincept, an inhaled humanized recombinant IL-4R that is used to neutralize and antagonize endogenously occurring IL-4 in asthmatic patients [167]. The safety and dose finding of altrakincept were initially evaluated by double-blind, placebo-controlled trials, which constituted the first phase of the study [168]. The findings indicated that administering

Table 2 Currently used therapeutic monoclonal antibodies for asthma

Target	Drug	Type of antibody	Clinical outcomes	Impact on remodeling	Stage of development	ClinicalTrials.gov ID	Reference
IL-4	Pascolizumab	IgG1	• Unsatisfactory results in phase II trials in suppressing IL-4 downstream targets including IgE switching, CD23 upregulation, and T cell proliferation	No data available	Discontinued	NCT00024544	[140]
	Altrakincept	Extracellular domain of IL-4R	• No efficacy in improving lung function and FeNO levels in moderate asthma in phase III clinical trial	No data available	Discontinued	NCT00001909	[143, 145]
IL-4Rα	Pitrakinra	Mutated IL-4	• Significant improvement in FEV1 of 17.1 in group 1 and FEV1 of 4.4 in group 2 compared to placebo • Significant reduction in exacerbation rate in moderate-to-severe asthma	No data available	No phase III clinical trial yet	NCT00801853, NCT00535028	[167, 168]
	Dupilumab	IgG4	• Reduced severe asthma exacerbations, increased lung function (FEV1), asthma control, and quality of life, and decreased Th2-associated biomarkers (FeNO, serum IgE, eotaxin-3, and TARC)	Reduced mucus secretion and bronchoconstriction related genes Reverse ASM contraction	FDA approved	NCT01312961, NCT01854047	[169, 170, 178, 83]

Table 2 (continued)

Target	Drug	Type of antibody	Clinical outcomes	Impact on remodeling	Stage of development	ClinicalTrials.gov ID	Reference
IL-13	Anrukinzumab	IgG1	• Reduced immediate and late asthmatic responses at 14 days only in mild allergic asthma • No efficacy in uncontrolled persistent asthma	No data available	Discontinued	NCT 00410280, NCT 00725582, NCT00425061	[149, 150]
	Lebrikizumab	IgG4	• No response in moderate-severe asthma at different doses • Higher response in mild asthma with high eosinophil counts, higher IgE levels, or high periostin levels • Reduced asthma exacerbation rate and increase FEV1 in periostin-high asthmatics	Reduce subepithelial fibrosis	FDA approved	NCT00971035, NCT00781443, NCT01545440, NCT01545453	[153, 155, 156]
	Tralokinumab	IgG4	• Reduced airway hyperresponsiveness, airway eosinophilia and esophageal eosinophilia in murine model • Improve lung function and asthma control in periostin-high or dipeptidyl peptidase-4 (DPP-4) high asthmatics • No improvement in ACQ-6, increase FEV1 in moderate-to-severe asthma • Decreased FENO and IgE concentrations in moderate to severe asthmatics	Reduce airway lumen in severe asthmatics Attenuate fibrosis and reduce epithelial cells apoptosis	FDA approved	NCT00873860, NCT01402986, NCT02449473	[158, 160–162]
IL-13R	Eblasakimab	IgG4	• No clinical study in allergic asthma • Clinically tested in moderate-to-severe AD	No data available	Not FDA approved	NCT03721263	[179]

a nebulized dose of 1.5mg of soluble IL-4R resulted in a considerable preservation of Forced Expiratory Volume in 1 Second (FEV1) and forced expiratory flow, particularly during the mid-expiratory phase. Additionally, it led to the stabilization of asthma symptom scores and a reduction to the need of β2-agonist rescue medication [168]. Borish et al. undertook randomized, double-blind, placebo-controlled research to evaluate the safety and efficacy of long-term soluble IL-4R administration in the treatment of mild persistent asthma. The findings demonstrated that administering 3.0 mg of altrakincept effectively preserved lung function by sustaining FEV1 levels following the discontinuation of corticosteroids. In addition, it contributed to the maintenance of asthma symptom scores [169]. However, in phase III clinical trial altrakincept failed to demonstrate any efficacy in patients with milder asthma therefore, this compound has now been discontinued [170] [167]. The reason behind this failure was suggested to be same as Pascolizumab which is due to the biological overlapping between IL-4 and IL-13 [168, 171, 172]. In addition, smaller recombinant proteins often have shorter half-lives compared to monoclonal antibodies. Altrakicept required frequent dosing due to its short half-life, reducing practicality compared to longer-acting biologics [173]. However, the IL-13 receptor complex consists of the IL-13Rα1 and IL-4Rα chains, meaning that IL-4Rα is necessary for IL-13-mediated signaling but cannot bind IL-13 independently. This raises the possibility that soluble IL-4R (sIL-4R, or altrakincept) could block IL-13 from interacting with the IL-13 receptor complex, potentially providing long-term symptom relief. There is currently limited data on the effect of altrakincept on structural cells in asthma.

Targeted Anti-IL-13 Therapy

IL-13, along with IL-4, plays a critical role in Th2 inflammation and airway remodeling, making it an appealing therapeutic target. Blocking IL-13's interaction with its receptor may help regulate these pathological processes such as inflammation, airway remodeling, and reduced lung function thereby mitigating their contribution to asthma severity. Three monoclonal antibodies have been developed for this purpose, including Anrukinzumab, Lebrikizumab, and Tralokinumab. Anrukinzumab a humanized monoclonal antibody that targets IL-3 and inhibits downstream signal activation [174]. It has undergone phase II investigations in asthma and ulcerative colitis patients [174]. Anrukinzumab has been also subjected to clinical trials in patients diagnosed with mild allergic asthma. The test results showed a substantial improvement in both early and late asthmatic FEV1 response 14 days after treatment with no further effect on allergen-induced airway hyperresponsiveness or sputum eosinophils. Nevertheless, this decrease was not detected 35 days following the treatment [175]. In addition, Anrukinzumab showed limited effectiveness in a clinical trial involving patients with uncontrolled asthma, leading to the discontinuation of its development as a treatment for asthma [176].

Lebrikizumab is an Immunoglobulin G4 (IgG4) humanized monoclonal antibody that acts as an anti-IL-13 antagonist. Its mechanism of action involves blocking the IL-4Rα/IL-13Rα1 signaling pathway by binding with a very high affinity to IL-13 and preventing it from attaching to the receptor [177]. An asthmatic adult cohort underwent a phase II randomized, double-blind, placebo-controlled research, the study observed an improvement in the lung function despite receiving inhaled corticosteroids (ICS) and a long-acting β2-andrenergic receptor agonist [178]. Another phase II study results revealed that patients under lebrikizumab medication experienced a decrease in the frequency of treatment failure and a decrease in fractional exhaled nitric oxide (FeNO) levels, indicating a beneficial impact, with no clinical or statistical significant in FEV1 [179]. Additionally, lebrikizumab effect on mild asthmatics who underwent airway allergen challenge was conducted, the late asthmatic reaction (LAR) was 48% lower in the lebrikizumab group at Week 13 than in the placebo group [180]. However, LAR was found to be more significantly reduced in patients with high eosinophil counts, higher IgE levels, or high periostin levels who were treated with lebrikizumab which suggest that this medication seems to work better for people with asthma who also have a Th2 inflammatory profile [181]. The effect was also tested in moderate to severe asthma, where 37.5, 125, and 250 mg of lebrikizumab reduced asthma exacerbation rate by 60% in periostin-high asthmatics and 5% in periostin-low asthmatics, as well as FEV1 increases of 9.1% and 2.6%, respectively [182]. These data are consistent with the previous findings and would suggest that lebrikizumab effect is influenced by the severity of the disease as it relies on periostin as a biomarker, but its expression fluctuates and lacks standardization which gives a variability between patient's response. Additionally, another key limitation of lebrikizumab was its immunogenicity, with anti-drug antibodies (ADAs) developing in 8–12% of patients in clinical trials [178, 182]. These antibodies reduced the drug's efficacy over time, particularly in lung function and exacerbation outcomes. However, up to date Lebrikizumab has been recently approved by Food and Drug Administration (FDA) to be used clinically yet IL-13 is not the only inflammatory mediated cytokine in asthma several additional cytokines and inflammatory pathways, are involved in asthma disease. Additionally, it has been proposed that lebrikizumab may exhibit greater efficacy in cases of steroid resistance asthma compared to mild asthma. This is because the IL-13 pathway may or may not be activated at all in individuals with mild type of asthma

[181]. While lebrikizumab has been found to enhance lung function in patients with moderate-to-severe uncontrolled asthma, its impact on airway inflammation and remodeling remains uncertain. However, only one study demonstrated that lebrikizumab effectively decreased the extent of subepithelial fibrosis, a key characteristic of asthmatic airway remodeling [183].

Tralokinumab is a humanized monoclonal antibody targeting IL-13 that underwent Phase I, II, and III clinical trials to evaluate its efficacy in neutralizing IL-13 in severe uncontrolled asthma [184–186]. Preclinical studies, including an IL-13-induced murine model by Blanchard et al., demonstrated its ability to reduce airway hyperresponsiveness and eosinophilia in both respiratory and esophageal tissues [184]. Phase I trials in mild-to-moderate asthmatics established its pharmacokinetic profile, tolerability, and safety at doses of 1, 5, and 10 mg/kg, with no serious drug-related adverse effects [185]. However, Phase II trials revealed mixed outcomes: Piper et al. reported no improvement in Asthma Control Questionnaire (ACQ-6) scores in moderate-to-severe asthma patients treated with 150–600 mg tralokinumab, though forced expiratory volume (FEV1) improved without significant adverse effects [186]. A subsequent Phase IIb trial in severe asthma patients using 300 mg tralokinumab also failed to reduce exacerbation rates, though post-hoc analysis suggested improved lung function in subgroups with elevated periostin or dipeptidyl peptidase-4 (DPP-4), hinting at potential biomarkers for patient selection [187]. Additional Phase II data showed reductions in fractional exhaled nitric oxide (FeNO) and IgE levels, but no impact on eosinophilic inflammation [188].

Despite promising results in biomarker-enriched subgroups with a 44% exacerbation reduction in high-FeNO patients in STRATOS 1, tralokinumab's limitations became evident in STRATOS 2, where it failed to replicate efficacy, underscoring its inability to address IL-4-driven redundant pathways [189]. Reliance on nonspecific biomarkers like FeNO further exposed its mechanistic insufficiency in heterogeneous asthma populations. These shortcomings emphasized the need for therapies targeting multiple cytokines.

Beyond inflammation, limited studies explored tralokinumab's impact on remodeling. Brightling et al. (2016) used quantitative computed tomography (QCT) to demonstrate improved subsegmental airway lumen parameters and reduced wall area percentage in severe asthma patients receiving tralokinumab [190]. Preclinical models also suggested antifibrotic effects, including reduced epithelial apoptosis by decreased caspase-3 and clara cell secretory protein (CC16_ levels and increased E-cadherin and surfactant protein expression[191]. However, further research is needed to validate its role in airway remodeling or structural cell modulation in asthma, particularly as tralokinumab is now FDA-approved for atopic dermatitis.

Targeting IL-4R Alpha

Evidence suggests that targeting IL-4 or IL-13 individually does not adequately control asthma, highlighting the need for alternative therapeutic strategies. These may involve targeting both cytokines simultaneously or blocking their common receptor and downstream signaling pathways. Pitrakinra, an IL-4 variant with tyrosine-124 and arginine-121 replaced by aspartate, acts as an IL-4Rα antagonist by binding to the receptor and preventing IL-4/IL-13-induced inflammation without signal transduction [192, 41]. While Phase 2a trials demonstrated short-term improvements in FEV1 via subcutaneous or nebulized administration [41], its modest efficacy and short duration of action became apparent in broader studies. As a recombinant protein, pitrakinra's rapid clearance necessitated frequent dosing, limiting practicality compared to long-acting biologics. This shortcoming contributed to its failure in Phase 2b trials, where no significant efficacy was observed in moderate-to-severe asthma patients overall, though a subgroup with specific IL4RA gene variants showed reduced exacerbations [193]. The transient therapeutic effect and inconsistent outcomes underscored its inability to fully suppress redundant IL-4/IL-13 pathways or maintain durable responses, ultimately halting Phase III development. Additionally, its impact on airway remodeling remains unclear, further emphasizing the need for therapies with robust, sustained activity and broader pathway inhibition. Dupilumab, an FDA-approved fully human monoclonal antibody targeting IL-4Rα, inhibits signaling of both type I (IL-4-activated) and type II (IL-4/IL-13-activated) receptors [194]. An initial phase II trial (2013) evaluated its efficacy in moderate-to-severe eosinophilic asthma. Patients received weekly 300 mg subcutaneous dupilumab injections. By week 4, long-acting beta-agonists (LABA) were discontinued, followed by inhaled glucocorticoids from weeks 6–9[194]. Dupilumab reduced asthma exacerbations by 87% versus placebo, improved FEV1 by > 200 mL, and sustained benefits even after glucocorticoid withdrawal [194]. It also lowered Th2 biomarkers FeNO, IgE, eotaxin-3, TARC without altering peripheral eosinophil counts or causing serious adverse events [194].

A latter phase II trial conducted by Wenzel et al. enrolled 769 uncontrolled asthma patients on inhaled corticosteroids/LABA, regardless of eosinophil levels. Dupilumab (200 mg/300 mg every 2–4 weeks) increased FEV1 by week 12 and reduced exacerbation rates, irrespective of eosinophil counts [195]. These results aligned with phase III trials: both 200 mg and 300 mg doses reduced exacerbations and improved FEV1 by 320 mL [196]. The LIBERTY ASTHMA QUEST study further confirmed enhancements in asthma control, symptoms, and quality of life [197]. while the VENTURE trial demonstrated reduced glucocorticoid dependence and severe exacerbations in steroid-dependent asthma

[198]. Positive outcomes were also observed in severe asthma children, with weight-adjusted dupilumab (100–200 mg) lowering inflammatory biomarkers TARC, FENO, and total IgE compared to placebo [199].

Despite these benefits, dupilumab's long-term impact on lung function decline remains uncertain. The ongoing TLAS trial (phase III/IV) aims to determine whether dupilumab slows lung function loss in T2 asthma over three years and identifies predictive biomarkers [200].

In terms of remodeling only two studies have explored dupilumab's effects on mucus hypersecretion and airway remodeling. These showed reduced mucus scores, airway wall thickness, and cough symptoms [201, 202]. Preclinical studies in HDM-exposed mice revealed dupilumab normalized mucus-related (*MUC5AC, TFF1, ITLN-1*) and remodeling-associated genes (*MMP-12, Arg1, MRGPRG*), while preventing eosinophil infiltration into lungs [203]. These data indicate that dupilumab can effectively reduce airway remodeling and gives vital insights into the processes that lead to the long-term decline in lung function of asthmatic patients. However, murine study may not fully incorporate all aspects of asthma pathophysiology, making it difficult to be clinically applied to human disease. Therefore, it was suggested that additional in vivo models should be conducted to better comprehend the various pathways and mechanisms of severe asthma. This can potentially promote further clinical studies aimed at enhancing patient care.

Furthermore, as mentioned earlier to the ability of IL-4 and IL-13 to induce ASM contractility [128], Dupilumab was able to reverses this effect by blocking histamine H1/CysLT1 receptor upregulation and calcium mobilization [128]. Nevertheless, its long-term effects on remodeling features including fibrosis and ASM hypertrophy remain unclear. Further studies are needed to elucidate intracellular mechanisms and confirm clinical relevance.

Targeting IL-13R Alpha-1

The most studied IL-13 targeted antibodies are tralokinumab and lebrikizumab which show a positive control of lung function and asthma exacerbation rate [182, 189]. Despite that, there is no specific IL-13 receptor targeted antibody that has been developed or evaluated in asthma.

Eblasakimab, a novel monoclonal antibody under investigation for atopic dermatitis (AD), specifically targets IL-13Rα1. By inhibiting its heterodimerization with IL-4Rα and blocks downstream signaling activation [204]. In an 8-week Phase 1b trial involving 52 patients with moderate-to-severe AD, eblasakimab demonstrated favorable safety and efficacy [205]. Results showed significant clinical improvement compared to placebo, though long-term safety effects require further evaluation, and larger trials are needed to confirm these findings [205].

Despite its mechanism of blocking IL-13Rα1 a receptor expressed in airway structural cells [53, 54] no studies have assessed eblasakimab's potential impact on asthma. This raises the question of whether eblasakimab could independently control asthma or act synergistically as a dual-blocking antibody in combination with anti-IL-4 or anti-IL-4Rα therapies.

While IL-13 binds to both IL-13Rα1 and IL-13Rα2 receptors, the role of IL-13Rα2 in asthma remains underexplored despite its variable expression in lung fibroblasts and other tissues. Notably, no biologic therapies targeting IL-13Rα2 have been evaluated for asthma, even though it has emerged as a potential therapeutic target in other diseases, such as cancer. For example, strategies like monoclonal antibodies, vaccines, and immunotoxins targeting IL-13Rα2 have shown promise in mitigating inflammation and tissue remodeling in preclinical cancer models [206, 207].

Conclusion and Future Perspectives

Although systemic corticosteroids (SCS) are effective for managing acute asthma exacerbations and providing long-term symptom control in asthma, results from various studies indicate that their therapeutic options, along with muscle relaxants, have limitations in treating steroid-hyporesponsive severe cases. The combined action of T2 cytokines, IL-4 and IL-13 is critical in the development of allergic asthma. IL-4 promotes the growth of Th2 cells and the production of cytokines and IgE, while IL-13 is responsible for clinical characteristics such as excessive mucus production and collagen deposition. Both cytokines have emerged as promising targets for therapy, and recent studies have shown that monoclonal antibodies targeting IL-4 and IL-13 yield encouraging results. However, despite numerous trials aimed at demonstrating the benefits of anti-IL-4 and anti-IL-13 treatments in severe asthma patients, the mechanisms by which dual inhibition of these cytokines might prevent lung function decline and airway remodeling remain unclear. Collectively, further investigations are needed to understand the underlying molecular processes through which IL-4 and IL-13 contribute to airway remodeling in severe asthma.

Abbreviations *IL*: Interleukins; *T2*: Type 2; *Th2*: Type 2 helper T; *ILC2*: Innate lymphoid type-2 cell; *Th*: T helper cell; *Ig*: Immunoglobulin; *ERS*: European Respiratory Society; *ATS*: American Thoracic Society; *ICS*: Inhaled corticosteroids; *OCS*: Oral corticosteroids; *LABA*: Long-Acting Beta Agonists; *SABA*: Short-Acting Beta-Agonists; *GR*: Glucocorticoid receptor; *MMP*: Matrix metalloproteinases; *TIMP*: Tissue inhibitors of metalloproteinases; *NK*: Natural killer cell; *IL-4Rα*: Interleukin 4 receptor alpha; *IL-13Rα1*: Interleukin 13 receptor alpha 1; *ECM*: Extracellular matrix; *MUC*: Mucus; *HDAC*: Histone deacetylases; *Ocldn*: Occludin; *COL1A1*: Collagen type I alpha 1; *COL3A1*: Collagen type III alpha 1; *COL1A2*: Collagen type 1 alpha

2; *UBE2Z*: E2 ubiquitin conjugating enzyme; *JAM*: Junctional adhesion molecule; *HAS2*: Hyaluronan synthase 2; *α-SMA*: Alpha smooth muscle actin; *ASM*: Airway smooth muscle; *LTD4*: Leukotriene D4; *GPCR*: G-protein-coupled receptors; *PLC*: Phospholipase C; *TARC* : Thymus and activation regulated chemokine; *CysLT*: Cysteinyl leukotriene; *CysLTR*: Cysteinyl leukotriene receptor; PGD_2: Prostaglandin D_2; *ERK*: Extracellular signal-regulated kinase; *MAPK*: Mitogen-activated protein kinase; *JAK*: Janus kinase; *EGFR*: Epidermal growth factor receptor; *AEC*: Airway Epithelial cell; *ZO-1*: Zonula occludens; *COX*: Cyclooxygenase; *JNK*: C-Jun NH2-terminal kinase; *HRH*: Histamine receptor H1; *γC*: Common gamma chain; *STAT*: Signal transducer and activator transcription; *TYK*: Tyrosine kinase; *PI3K*: Phosphoinositide 3-kinases; *NF-κB*: Nuclear factor kappa-light-chain-enhancer of activated B cells; *AP-1*: Activator protein 1; *mAbs*: Monoclonal antibodies; *FEV1*: Forced expiratory volume; *LAR*: Late asthmatic reaction; *FDA*: Food and Drug Administration; *ACQ*: Asthma Control Questionnaire; *DPP-4*: Dipeptidyl peptidase-4; *TFF1*: Trefoil factor family 1; *ITLN-1*: Human intelectin-1; *AD*: Atopic dermatitis; *SCS*: Systemic corticosteroids; *WHO*: World health organization; *TGF-β*: Transforming Growth Factor beta; *CTGF*: Connective Tissue Growth Factor; *TNF-α*: Tumor Necrosis Factor alpha; *VEGF*: Vascular endothelial growth factor; *GATA-3*: GATA binding protein 3; *SOCE*: Store-Operated Ca^{2+} Entry; *TCR*: T-cell receptor; *PIP2*: Phosphatidylinositol 4,5-bisphosphate; *PIP5K1γ*: Phosphatidylinositol-4-phosphate 5-kinase type 1 gamma; *TLR*: Toll-Like Receptor; *HER2*: Human Epidermal Growth Factor Receptor 2; *JAM-A*: Junctional Adhesion Molecule A; *PDGF*: Platelet-derived growth factor; *IRS-2*: Insulin Receptor Substrate 2; *FeNO*: Fractional Exhaled Nitric Oxide; *ADA*: Anti-Drug Antibodies; *QCT*: Quantitative Computed Tomography; *MRGPRG*: MAS Related GPR Family Member G

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Author Contribution LS, RH, QH, and KB were responsible for the literature review and writing (review and editing), while LS was responsible for the literature review and writing (original draft). KB and RH were responsible for the review and editing, and KB, RH, and QH handled the supervision. BM contributed towards editing and writing the revised version. The published version of the manuscript has been read and approved by all authors.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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