

# The Mechanisms and Therapeutic Implications of PI3K Signaling in Airway Inflammation and Remodeling in Asthma

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**Abstract:** Bronchial asthma is a complex and heterogeneous disease with ongoing airway inflammation and increased airway responsiveness. Key characteristics of the disease include persistent airway inflammation, airway hyperresponsiveness, and airway remodeling. Asthma's chronic and recurrent characteristics contribute to airway remodeling and inflammation, which can exacerbate lung damage. Presently, inflammation is predominantly managed with corticosteroids, yet there is a notable absence of treatments specifically addressing airway remodeling. The phosphoinositide 3-kinase (PI3K) signaling pathway is integral to the processes of inflammation, airway remodeling, and immune responses. Pharmacological agents targeting this pathway are currently undergoing clinical evaluation. This review elucidates the role of PI3K in the immune responses, airway inflammation, and remodeling associated with asthma, examining its underlying mechanisms. Furthermore, we synthesize the existing literature on the therapeutic potential of PI3K inhibitors for asthma management, emphasizing immune modulation, airway inflammation, and remodeling, including drug development and ongoing clinical trials. Lastly, we explore how various PI3K-targeted therapies may enhance efficacy and improve tolerance.

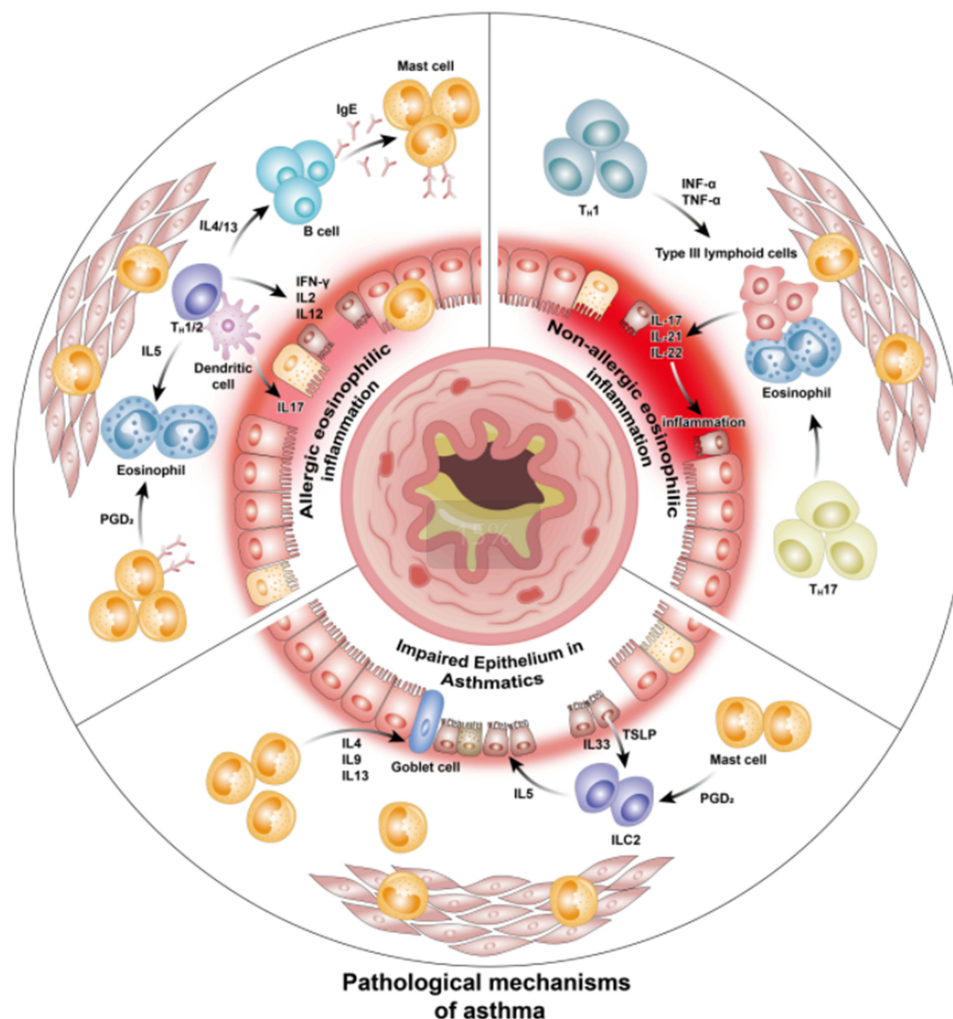
**Keywords:** asthma, PI3K, inflammation, airway remodeling, inhibitor, immune responses

## Introduction

Bronchial asthma is a complex and heterogeneous disease with ongoing airway inflammation and increased airway responsiveness. Key characteristics of the disease include persistent airway inflammation, airway hyperresponsiveness, and airway remodeling.<sup>1,2</sup> During both acute and chronic airway inflammation, there is a notable infiltration of inflammatory cells into the airway epithelium, accompanied by mucosal edema, increased microvascular permeability, bronchial smooth muscle spasm, and enhanced mucus secretion.<sup>3</sup> Prolonged and recurrent inflammation results in airway remodeling.<sup>4</sup> The etiology of asthma is primarily attributed to airway immune-inflammatory mechanisms, neuroregulatory mechanisms, and their interactions.<sup>5,6</sup> Presently, asthma impacts the pulmonary health of over 300 million individuals globally.<sup>7</sup>

The PI3K signaling pathway plays a pivotal role in the cellular regulatory processes associated with asthma,<sup>8</sup> where critical events in the inflammatory response to injury and infection are modulated by the activation status of PI3K.<sup>9</sup> The PI3K signaling pathway is currently classified into three classes: Class I PI3Ks are crucial in the inflammatory process, with Class IA PI3Ks further subdivided into three distinct isoforms—PI3K $\alpha$ , PI3K $\beta$ , and PI3K $\delta$ ; Class Ib PI3K (PI3K $\gamma$  isoform) is activated by G-protein-coupled receptors (GPCRs).<sup>10</sup> Class II PI3Ks consist of three widely expressed isoforms (C2a, C2b, and C2g),<sup>11</sup> while Class III PI3K includes a single member, vacuolar protein sorting mutant 34 (Vps34), which regulates endocytosis, Toll-like receptor (TLR) signaling, and vesicular trafficking.<sup>12</sup> Due to the absence of highly selective pharmacological inhibitors, Class II and III PI3Ks have not been extensively investigated. Currently,

## Graphical Abstract



Class I PI3Ks are the most comprehensively studied within the PI3K family, with AKT phosphorylation frequently utilized as a surrogate marker for Class I PI3K activation.<sup>8</sup> Targeting the immune responses associated with PI3K is a central focus in numerous therapeutic strategies aimed at mitigating inflammation and autoimmune diseases.

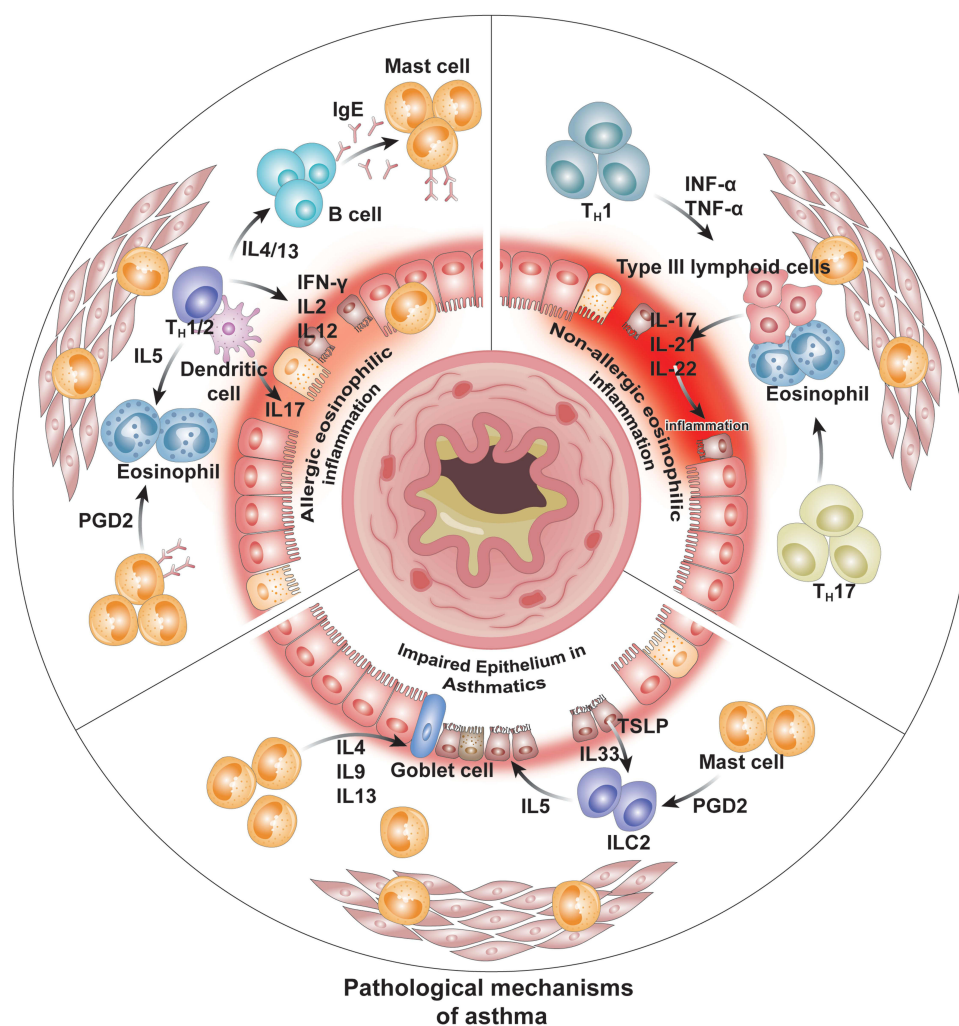
PI3K inhibitors can be categorized into three distinct types: pan-PI3K inhibitors, PI3K isoform-selective inhibitors, and dual inhibitors. These inhibitors are modulated either directly or indirectly by cell surface receptors and are integral to the initial signal transduction processes initiated by receptor activation,<sup>13,14</sup> including key downstream reactions within immune cells and even upstream activation of receptors such as TLRs.<sup>9</sup> In the context of airway inflammation, PI3K is associated with type 2 immune responses and T helper 2 (Th2)-mediated airway inflammation,<sup>15</sup> which further promotes collagen deposition, leading to airway remodeling.<sup>16</sup> Notably, aberrant activation of the PI3K/Akt signaling pathway is considered pro-apoptotic, and its inhibition can reduce cellular proliferation,<sup>17</sup> thereby potentially inhibiting airway remodeling. Consequently, targeting the PI3K pathway presents a unified therapeutic strategy for diminishing inflammation, alleviating airway hyperresponsiveness, and inhibiting airway remodeling, thus offering a promising approach for asthma treatment.

## Pathophysiology of Asthma

The pathogenesis of bronchial asthma is intricate, involving multiple pathways and cell types, thereby rendering it a heterogeneous disease characterized by distinct phenotypes and endotypes. Asthma can be broadly categorized into allergic

(atopic) asthma and non-allergic (non-atopic) asthma. The allergic asthma phenotype, which is the most prevalent, is triggered by sensitization to allergens and is mediated by T-helper type 2 (Th2) cells, type 2 innate lymphoid cells (ILC2s), eosinophils, mast cells, and immunoglobulin E (IgE). Conversely, non-allergic asthma is not induced by allergens but is associated with dysregulated innate immune responses precipitated by factors such as infections, obesity, smoking, and pollution. This variant of asthma involves Th17 cells, type 3 innate lymphoid cells (ILC3s), and neutrophils.<sup>18</sup>

The pathophysiology of asthma is characterized by the activation of immune cells, which subsequently elicit responses from structural cells, including airway smooth muscle (ASM) and airway epithelial cells, ultimately resulting in airway hyperresponsiveness, inflammation, and remodeling.<sup>3</sup> The activation and release of inflammatory mediators, manifested through mast cell degranulation and eosinophil vacuolization, result in chronic inflammation within the lungs (Figure 1).



**Figure 1** The mechanism of PI3K signaling pathway in asthma airway inflammation and airway remodeling.

**Notes:** Allergic Asthma: Allergic asthma is triggered by allergens such as pollen, animal dander, and others, leading to the activation of Th1/Th2 cells, which secrete cytokines like IFN- $\gamma$ , IL-2, and IL-12. This response also involves eosinophils and the production of IgE, which subsequently activates mast cells and promotes eosinophil aggregation. The culmination of these processes results in inflammation and the clinical symptoms of asthma. Non-Allergic Asthma: Non-allergic asthma is typically initiated by environmental factors such as smoking and pollution. This form of asthma is primarily driven by Th1 and Th17-mediated inflammation. Th17 cells activate neutrophils, which play a critical role in the inflammatory response by releasing cytokines such as IL-17, IL-21, IL-22, IFN- $\gamma$ , and TNF- $\alpha$ . These cytokines amplify the inflammatory response by inducing the release of additional inflammatory mediators. Airway Epithelial Damage and Remodeling: Structural and functional damage to the airway epithelium is a key factor in airway remodeling and contributes to the dysregulation of the inflammatory response. Goblet cell metaplasia within the epithelium is driven by the action of IL-4, IL-9, and IL-13, while epidermal growth factor (EGF) contributes to epithelial cell stress and injury.

## Immune Response in Asthma

The immune response in asthma is orchestrated by pivotal cells and cytokines originating from both the innate and adaptive immune systems. Innate immunity is characterized by an immediate inflammatory response, wherein innate immune cells identify pathogen-associated molecular patterns (PAMPs) via Toll-like receptors (TLRs).<sup>19</sup> TLRs play a pivotal role in activating NF- $\kappa$ B and interferon regulatory factors (IRFs), thereby inducing the transcription necessary for immune responses. On the other hand, adaptive immunity involves antigen-specific immune responses and the formation of immunological memory against pathogens and vaccines. PI3Ks are crucial mediators in the responses of airway smooth muscle (ASM) and epithelial cells. In asthma, ASM maintains airway tone, secretes inflammatory mediators, and undergoes hypertrophy and hyperplasia. The PI3K signaling pathway is not merely a simple switch that promotes cellular activation but rather a complex network of interactions that must be properly balanced to ensure appropriate cellular responses and maintain immune homeostasis.<sup>20</sup>

Airway inflammation is a hallmark of the entire asthmatic process. Although the role of Th2 inflammation in eosinophilic inflammation in asthma is not yet fully understood and varies depending on the type of allergen or antigen exposure, PI3K signaling is implicated in various aspects of both allergic and non-allergic eosinophilic airway inflammation.<sup>21</sup> Airway epithelial cells, as the first cellular layer to encounter allergens, are also key regulators of innate and adaptive immune responses in allergic lung inflammatory diseases. TLR4 expressed on airway epithelial cells initiates a cytokine environment that can activate dendritic cells, type 2 innate lymphoid cells (ILC2s), and basophils, facilitating dendritic cell migration to draining lymph nodes and subsequently inducing adaptive immune responses.<sup>19</sup> Additionally, PI3K $\delta$  in airway epithelial cells has been reported as a critical regulator of mitochondrial reactive oxygen species (ROS), which are vital for airway function and the nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome,<sup>22</sup> the latter being closely associated with pulmonary inflammation.

An emerging paradigm posits that airway remodeling constitutes a significant pathological feature of asthma, comparable in importance to inflammation.<sup>23</sup> Consequently, therapeutic strategies targeting inflammation alone may not yield optimal clinical outcomes. Structural and functional damage to the airway epithelium is a key risk factor in asthma, making the host more susceptible to repeated environmental insults, enhancing defective tissue repair and remodeling, and contributing to the dysregulation of inflammatory responses.<sup>24</sup> Goblet cell metaplasia in the epithelium, driven by cytokines such as IL-4, IL-9, and IL-13, and the secretion of growth factors like those from the epidermal growth factor (EGF) family, leads to epithelial cell stress and injury.<sup>25</sup> The PI3K/Akt signaling pathway is involved in regulating various biological functions such as cell proliferation, differentiation, and migration. In PI3K gene-deficient mouse models, reductions in inflammatory cell accumulation, airway hyperresponsiveness, and airway remodeling have been observed.<sup>26</sup>

This evidence suggests that, although asthma is a heterogeneous disease, addressing both inflammation and airway remodeling—especially in cases of recurrent exacerbations or infections leading to complications such as pneumonia and chronic obstructive pulmonary disease (COPD)—is crucial in treatment. These signaling pathways, including PI3K, converge on common mechanisms that trigger these responses.

## PI3K Inhibitors and Allergic Asthma

Allergic asthma is typically characterized by chronic airway inflammation triggered by sensitization to allergens such as house dust mites, animal dander, fungal spores, and pollen from plants or trees.<sup>18,27</sup> Upon allergen sensitization, the body initiates an immune response that usually begins with the activation and differentiation of specific Th2 cells, which produce various cytokines including IL-13.<sup>28</sup> This process is triggered by the allergen and subsequently leads to the production of immunoglobulin E (IgE) specific to the allergen. IgE-dependent activation of mast cells occurs, leading to the aggregation of eosinophils at the site of allergic inflammation, such as the lungs, ultimately resulting in inflammation and asthma-related symptoms.<sup>18</sup> Inhibiting the production of Th2 cytokines and the recruitment of eosinophils to the airway can partially alleviate allergic asthma.<sup>29</sup>

Overexpression of PI3K has been shown to exacerbate inflammation and immune responses in the body, indicating that inhibiting PI3K has a protective effect in animal models of arthritis, asthma, and obstructive airway diseases.<sup>30</sup> This

evidence underscores the potential therapeutic value of PI3K inhibitors in managing allergic asthma by mitigating inflammation and immune dysregulation.

LY294002 is a commonly used PI3K inhibitor that competitively binds to the ATP site, thereby inhibiting PI3K activity. Research has shown that PI3K kinase inhibition can reduce allergen-induced airway responses, suggesting its therapeutic potential as an adjunctive treatment in allergic airway diseases.<sup>31,32</sup> Nobiletin, a polymethoxy flavone (PMF) compound widely found in citrus, may be used to treat allergic asthma. Its mechanism involves inhibiting the PI3K signaling pathway, modulating Th1, Th2, and Th17 cytokine levels, and increasing IFN- $\gamma$  production.<sup>33</sup> PI3K inhibitors and their role in allergic asthma are listed in Table 1.

CZC24832 is the first selective PI3K $\gamma$  inhibitor, shown to be effective in both in vitro and in vivo models of inflammatory diseases in rodents and humans. It regulates Th17 differentiation and promotes PI3K $\gamma$ 's role in controlling innate and adaptive immune mechanisms,<sup>31</sup> suggesting that selective PI3K $\gamma$  inhibitors could be a promising target for treating inflammatory and autoimmune diseases. IC87114 is a selective PI3K $\delta$  inhibitor that significantly reduces airway hyperresponsiveness and allergic airway inflammation in asthma.<sup>36</sup> In animal studies, it has been shown to inhibit OVA-induced eosinophilia in lung tissues, airway mucus production, inflammatory scores, and airway hyperresponsiveness.<sup>34</sup> Additionally, IC87114 treatment markedly attenuates OVA-induced Akt serine phosphorylation.<sup>35</sup> Leniolisib (CDZ173), used to inhibit PI3K $\delta$  hyperactivation, has demonstrated inhibitory effects on B and T cell activation in preclinical models, as well as significant immunomodulatory effects in vivo.<sup>37</sup> However, the dose-limiting toxicity associated with its use remains an unresolved challenge.

AZD8154 and RV-1729 are dual PI3K $\gamma/\delta$  inhibitors that have demonstrated efficacy in animal and clinical trials. Studies in animal models have shown that these inhibitors effectively reduce the proportion of B eosinophils and exhibit prolonged lung retention, making them suitable candidates for inhaled administration.<sup>38-40</sup> TG100-115, another dual PI3K $\delta$ /PI3K $\gamma$  inhibitor, has shown efficacy in allergen-induced asthma models.<sup>41</sup> AKT and mTOR, activated downstream of PI3K, are targets of oral inhibitors such as miltefosine and rapamycin, both of which have shown promising results in experiments. Rapamycin, in particular, has demonstrated potential in inhibiting mTOR activation in chronic obstructive pulmonary disease (COPD),<sup>42</sup> and it suppresses allergic inflammation in allergen-challenged mice while inhibiting eosinophil differentiation.<sup>43,44</sup>

The PI3K signaling pathway plays a crucial role in B cell activation, differentiation, and survival. Allergic asthma is driven by IgE-mediated responses, with B cells being key drivers of allergic inflammation in the lungs. An unexpected role of B cell-derived IL-10 in promoting allergic sensitization has been observed, while Bcl-3 prevents HDM-induced

**Table 1** PI3K Inhibitors and Their Role in Allergic Asthma

Category of Inhibitor	Name	Role in Allergic Asthma	References
Pan-PI3K Inhibitors	LY294002	Reduces the binding of target kinases to the inhibitory matrix, thereby modulating multiple targets in immune assays.	[31, 32]
Pan-PI3K Inhibitors	Nobiletin	Inhibits the PI3K signaling pathway, modulates Th1, Th2, and Th17 cytokine levels, and increases IFN- $\gamma$ levels.	[33]
PI3K Isoform-Selective Inhibitors	CZC24832	Selective PI3K $\gamma$ inhibitor that regulates Th17 differentiation, promoting PI3K $\gamma$ 's involvement in controlling innate and adaptive immune mechanisms.	[31]
PI3K Isoform-Selective Inhibitors	IC87114	Selective PI3K $\delta$ inhibitor that diminishes Akt serine phosphorylation, inhibits eosinophil activity, and reduces airway mucus production.	[34, 35]
PI3K Isoform-Selective Inhibitors	CDZ173	Selective PI3K $\delta$ inhibitor that inhibits various immune cell functions and modulates the immune response.	[36, 37]
Dual Inhibitors	AZD8154	Dual PI3K $\gamma/\delta$ inhibitor that reduces the proportion of eosinophils and B cells.	[38, 39]
Dual Inhibitors	RV-1729	Dual PI3K $\gamma/\delta$ inhibitor that inhibits the accumulation of eosinophils and neutrophils.	[40]
Dual Inhibitors	TG100-115	Combined PI3K $\delta$ /PI3K $\gamma$ inhibitor that significantly reduces pulmonary eosinophilia and associated interleukin-13 and mucin accumulation.	[41]

asthma by inhibiting IL-10 production from B cells. Targeting the Bcl-3/IL-10 axis to inhibit allergic sensitization may offer a promising therapeutic approach for treating allergic asthma.<sup>45</sup>

## PI3K Inhibitors and Non-Allergic Asthma

The primary mechanisms leading to non-Th2 responses in non-allergic asthma are driven by irregular innate immune responses, including endogenous neutrophil abnormalities and the activation of IL-17-mediated pathways.<sup>19</sup> Neutrophilic asthma is often initiated by factors such as obesity, smoking, and pollution. These factors lead to the secretion of IL-13 and IL-23 by airway epithelial cells, which amplify the inflammatory response through the release of pro-inflammatory cytokines. This process promotes the recruitment of neutrophils and stimulates various cells to produce cytokines, acting as intermediaries in T cell regulation of neutrophil involvement in asthma inflammation. Ultimately, this results in airway inflammation, airway hyperresponsiveness, and airway remodeling. Neutrophil-mediated inflammatory events play a crucial role in the development of non-type 2 asthma. IL-17 is a potent inducer of neutrophilic inflammation,<sup>46</sup> and the expression of IL-17A and IL-17F has been shown to correlate with the severity of disease in asthmatic airway tissues.<sup>47</sup> Additionally, tumor necrosis factor (TNF) is also associated with neutrophilic inflammation. An increased presence of IFN- $\gamma$ -positive and IL-17a-positive cells has been observed in the bronchoalveolar lavage fluid of patients with severe asthma.<sup>48</sup> These findings underscore the potential role of IL-17, IFN- $\gamma$ , and TNF- $\alpha$  as underlying factors in the neutrophilic subtype of non-type 2 inflammation.

As a critical molecular mechanism in non-type 2 inflammation, the activation of innate immune signaling pathways in the airways, often triggered by microbial exposure and epithelial damage, frequently occurs within the airway epithelium.<sup>21</sup> The involvement of these pathways highlights the importance of targeting innate immune responses in the treatment of non-allergic asthma, where PI3K inhibitors may offer therapeutic benefits by modulating these key inflammatory processes. PI3K inhibitors and their role in non-allergic asthma are listed in Table 2.

Pan-PI3K inhibitors can target all Class I PI3K isoforms, but their clinical progress has been slow due to significant side effects and toxicity. Examples of these inhibitors include buparlisib, pictilisib, and copanlisib.<sup>56</sup> As a pan-PI3K inhibitor, nintedanib can downregulate inflammatory PI3K/Akt/mTOR pathways and oxidative stress, restore antioxidant systems, and inhibit inflammatory factors and apoptosis.<sup>49</sup> CL27c, designed for localized treatment, is another pan-PI3K inhibitor that reduces insulin-induced Akt phosphorylation in the lungs without affecting other tissues. In a mouse model of acute or steroid-resistant neutrophilic asthma, inhaled CL27c alleviated inflammation and improved lung function.<sup>50</sup> Unlike conventional PI3K inhibitors, CL27c is an inactive, cell-permeable prodrug that is converted into its active form once inside the cytoplasm, effectively controlling airway inflammation.<sup>57</sup> In the lung injury model induced by OVA in asthma, CL27c reduced Akt phosphorylation, leukocyte recruitment, and tissue remodeling. It can specifically target PI3K $\delta$  and PI3K $\gamma$  in the lungs, addressing the accumulation of inflammatory cells in various airway inflammation models.<sup>50</sup> LY294002, another pan-PI3K inhibitor, also exhibits anti-inflammatory effects. Studies have shown that

**Table 2** PI3K Inhibitors and Their Role in Non-Allergic Asthma

Category of Inhibitor	Inhibitor Name	Role in Non-Allergic Asthma	References
Pan-PI3K Inhibitors	Nintedanib	Downregulates inflammatory PI3K pathways and oxidative stress, restores antioxidant systems, inhibits inflammatory factors.	[49]
Pan-PI3K Inhibitors	CL27c	Reduces Akt phosphorylation, leukocyte recruitment, and tissue remodeling.	[50]
Pan-PI3K Inhibitors	LY294002	Significantly inhibits various pro-inflammatory cytokines (TNF $\alpha$ , IL-6, IL-1 $\beta$ , and IFN- $\gamma$ ).	[51]
PI3K Isoform-Selective Inhibitors	CZC24832	Selective PI3K $\gamma$ inhibitor, alters neutrophil recruitment.	[52]
PI3K Isoform-Selective Inhibitors	GSK-2269557	Selective PI3K $\delta$ inhibitor, prevents recruitment of inflammatory cells and release of pro-inflammatory mediators.	[53]
Dual Inhibitors	HM5023507	PI3K $\delta/\gamma$ dual inhibitor, diminishes PI3K $\delta/\gamma$ signaling in human basophils.	[54]
Dual Inhibitors	IPI-145	PI3K $\delta/\gamma$ dual inhibitor affects adaptive immunity by inhibiting B and T cell proliferation, blocking neutrophil migration, and reducing basophil activation.	[55]

LY294002 treatment significantly inhibits the synthesis of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and IFN- $\gamma$ . Additionally, LY294002 markedly inhibits I $\kappa$ B phosphorylation in liver samples from mice with lipopolysaccharide-induced injury.<sup>51</sup>

Selective inhibitors targeting specific PI3K isoforms have fewer side effects, and several of these selective PI3K inhibitors have been approved for clinical use. PI3K $\delta$ , which plays a central role in the inflammatory process, has become a key target for neutrophilic inflammation. While PI3K $\alpha$  and PI3K $\beta$  are expressed in all tissues, PI3K $\delta$  and PI3K $\gamma$  are highly enriched in leukocytes, making them effective targets in various inflammatory diseases. PI3K $\gamma$  inhibitors are compounds that selectively inhibit the Class I PI3K $\gamma$  isoform, playing a critical role in the activation of chemokine-dependent leukocytes and mast cells, particularly in the treatment of inflammatory, respiratory, and immune diseases.<sup>31</sup> Researchers identified CZC24832, a PI3K $\gamma$  inhibitor, through high-throughput chemical proteomics, which has shown promising therapeutic effects in both in vitro and in vivo inflammation models. Further studies indicate that this compound, as an effective PI3K $\gamma$  inhibitor, alters neutrophil recruitment and is involved in sepsis and organ damage (liver and lung).<sup>52</sup> Both inflammation and endothelial injury mechanisms are crucial in the sepsis process, and abnormal interactions between endothelial cells and inflammatory cells, as well as the resulting microvascular damage, may underlie the pathophysiology of sepsis and related organ dysfunction.<sup>58</sup> Notably, PI3K $\delta$  inhibitors have been recognized for their potential use in treating chronic lymphocytic leukemia, respiratory diseases, and inflammatory conditions.<sup>59</sup> Consequently, the therapeutic potential of PI3K $\delta$  inhibitors has garnered increasing interest for these indications, with many of these inhibitors progressing to clinical development stages. For example, GSK-2269557, which targets PI3K $\delta$ , can restore steroid efficacy under oxidative stress conditions in asthma treatment.<sup>60</sup> PI3K $\delta$  inhibition can also prevent the recruitment of inflammatory cells, including T lymphocytes and neutrophils, and the release of pro-inflammatory mediators such as cytokines, chemokines, reactive oxygen species, and proteases. Furthermore, targeting the PI3K $\delta$  pathway can reduce the incidence of pathogen-induced exacerbations by improving macrophage-mediated bacterial clearance.<sup>53</sup>

IPI-145 and HM5023507 are successful examples of PI3K $\delta/\gamma$  dual inhibitors that have demonstrated significant anti-inflammatory properties in respiratory models of Th2 and Th1 inflammation,<sup>54</sup> suggesting that PI3K $\delta/\gamma$  inhibition may be an ideal target for treating respiratory inflammatory diseases by reducing inflammatory responses.<sup>55,61</sup> However, one potential limitation of the clinical efficacy of individual PI3K inhibitors is the activation of compensatory pathways.<sup>62</sup> Efforts are currently underway to evaluate the efficacy of combining PI3K inhibitors with other agents targeting parallel compensatory pathways in the treatment of various diseases.

## PI3K and Airway Remodeling

In both clinical trials and animal studies, inhibition of the PI3K signaling pathway has been shown to improve lung function by modulating airway remodeling.<sup>63</sup> Treatment of patients with airway remodeling using PI3K inhibitors has been found to regulate the remodeling process.<sup>64</sup> Consequently, the PI3K pathway, due to its critical role in cellular proliferation, has garnered increasing attention as a target for improving airway remodeling.<sup>23</sup>

Currently, in addition to the widespread use of pan-PI3K inhibitors in airway remodeling, PI3K isoform-selective inhibitors play a major role in regulating cell proliferation and differentiation. For instance, inhibition of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) can modulate vascular endothelial growth factor (VEGF), thereby alleviating airway hyperresponsiveness, while PI3K $\delta$  signaling is involved in allergen-induced HIF-1 $\alpha$  activation.<sup>65</sup> This review highlights the development of PI3K inhibitors aimed at improving airway remodeling and discusses strategies to reduce adverse effects associated with their use. PI3K inhibitors and their role in airway remodeling are listed in [Table 3](#).

Intratracheal administration of LY294002 in an OVA-induced mouse model of asthma has been shown to significantly inhibit eosinophilia and airway mucus production, suppress AKT phosphorylation, and reduce airway smooth muscle cell (ASMCS) proliferation,<sup>66</sup> thereby alleviating airway remodeling. In vitro studies also suggest that PI3K plays a role in regulating airway smooth muscle cell contraction and migration, as well as in the transition of airway smooth muscle cells to the contractile phenotype observed in asthma.<sup>67</sup> These findings indicate that PI3K is a potential therapeutic target for asthma.

**Table 3** PI3K Inhibitors and Their Role in in Airway Remodeling

Category of Inhibitor	Inhibitor Name	Role in Non-Allergic Asthma	References
Pan-PI3K Inhibitors	LY294002	Inhibits eosinophilia, mucus production, and ASMCS proliferation.	[66, 67]
Pan-PI3K Inhibitors	Rheum Emodin	Inhibits PI3K pathway to alleviate ASMCS proliferation.	[68]
Pan-PI3K Inhibitors	Galectin-1	Inhibits PDGF-BB-induced proliferation, migration, and phenotypic switching of ASMCS.	[69]
PI3K Isoform-Selective Inhibitors	IC87114	Selective PI3K $\delta$ inhibitor, reduces Th2 cytokine, adhesion molecule, and inflammatory factor release, inhibits mucus production and AHR.	[35]
PI3K Isoform-Selective Inhibitors	AZD8154	Selective PI3K $\gamma$ inhibitor, regulates AHR and airway remodeling, reduces eosinophil count.	[38, 70]
PI3K Isoform-Selective Inhibitors	NVP-BEZ235	Selective PI3K inhibitor, reduces PI3K/AKT/mTOR signaling activity.	[71]

Rheum emodin has been shown to alleviate ASMCS proliferation by inhibiting the PI3K/AKT pathway both in vivo and in vitro, providing a potential therapeutic option for airway smooth muscle remodeling in asthma.<sup>68</sup> Galectin-1, by inhibiting the PI3K/AKT signaling pathway, has demonstrated the ability to suppress PDGF-BB-induced proliferation, migration, and phenotypic switching of ASMCS, making it a promising target for asthma treatment.<sup>69</sup>

The development of isoform-specific inhibitors has further enhanced our understanding of the biological roles of specific PI3K isoforms. For instance, inhibition of the PI3K $\delta$  isoform in mast cells leads to defects in stem cell factor-mediated proliferation, adhesion, and migration,<sup>72</sup> as well as impaired allergen IgE-induced degranulation and cytokine release. Targeting PI3K $\delta$  could represent a novel approach for intervening in allergic diseases. In an OVA-induced model, intratracheal injection of the PI3K $\delta$ -specific inhibitor IC87114 has been shown to reduce OVA-induced Th2 cytokine (IL-4, IL-5, and IL-13) production, adhesion molecule (ICAM1 and VCAM1) expression, and inflammatory factor release, while inhibiting OVA-induced airway mucus production and AHR.<sup>35</sup> These studies highlight a novel biological role of the PI3K $\delta$  signaling pathway.

Additionally, PI3K $\gamma$  has been found to play a crucial role in mediating allergen-induced eosinophilic airway inflammation and airway remodeling, potentially by regulating the sensitization/effector phase of allergic airway inflammation, AHR, and remodeling.<sup>70</sup> The inhibitor AZD8154, which targets PI3K $\gamma$ , exhibits prolonged activity in the lungs with minimal systemic exposure and effectively reduces the proportion of eosinophils in bronchoalveolar lavage fluid (BALF), resulting in significant inhibition of airway inflammation and reduced lung function changes, thereby alleviating airway remodeling.<sup>38</sup>

PI3K promotes immune cell survival by regulating anti-apoptotic signaling pathways, with the PI3K/AKT pathway inhibiting pro-apoptotic proteins such as B-cell lymphoma 2 (BCL-2) and related proteins.<sup>61</sup> NVP-BEZ235, a selective PI3K inhibitor, reduces PI3K/AKT/mTOR signaling activity and, compared to LY294002, reverses glucocorticoid resistance by inhibiting transcription factors such as NF- $\kappa$ B, c-FOS, and c-JUN.<sup>71</sup>

Currently, research on PI3K inhibitors in airway remodeling is not as advanced, with therapeutic interventions primarily focused on inflammation. However, since pathological tissue remodeling is also observed in other injury-prone and inflammation-prone tissues and organs, our discussion may have implications beyond asthma and pulmonary diseases.

## PI3K Inhibitors in Clinical Trials for Asthma

Based on the aforementioned studies, PI3K inhibitors have been shown to improve airway inflammation, airway hyperresponsiveness, and airway remodeling to varying degrees in asthma. However, their clinical application still faces several challenges. Class I PI3K pan-inhibitors, such as wortmannin and LY294002, have been excluded from clinical use due to unfavorable pharmacological characteristics.<sup>73</sup> In 2018, Sanjeev Khindri and his team conducted a randomized, double-blind, placebo-controlled, crossover study on nemiralisib (GSK2269557), a PI3K $\delta$  inhibitor, in patients with persistent, uncontrolled asthma. Unfortunately, while nemiralisib could partially inhibit PI3K $\delta$ , it did not

significantly improve patients' clinical symptoms.<sup>74</sup> However, this does not rule out the potential of nemiralisib in asthma treatment, as more detailed clinical and symptom stratification might reveal its benefits. Several preclinical studies are also investigating dual inhibitors such as RV-1729 for asthma, focusing on their safety, tolerability, and pharmacokinetics (NCT02140320, NCT01813084). Additionally, AZD8154, a novel inhaled selective dual PI3K inhibitor targeting airway inflammatory diseases, is undergoing further safety and efficacy evaluations.<sup>39</sup> The Phase II clinical trial of Duvelisib is also assessing its efficacy and safety in mild asthma patients (NCT01653756). Beyond asthma, some PI3K inhibitors have shown promising results in other diseases. For example, Idelalisib, a mature PI3K inhibitor, has demonstrated therapeutic effects in cancer.<sup>75</sup> Similarly, AQX-1125 has proven effective and safe in the treatment of unstable COPD (NCT01954628), suggesting potential for asthma treatment.

Despite the ongoing clinical and preclinical research on various PI3K inhibitors, challenges remain, including issues of specificity, adverse effects, and loss of efficacy. A more detailed differentiation of asthma subtypes and their specific PI3K pathway alterations, along with corresponding inhibitors, could aid in better drug development and clinical application. This review provides a comprehensive view of PI3K activation and the resulting pathological changes in allergic and non-allergic asthma. It also highlights how different types of PI3K inhibitors target specific pathways to improve asthma, offering detailed and reliable theoretical support for clinical treatment.

## Discussion

The aforementioned studies indicate that the inhibition of phosphoinositide 3-kinase (PI3K) in models of allergic airway inflammation confers protective effects in animal models of asthma and COPD.<sup>30</sup> Various cytokines play a pivotal role in orchestrating eosinophilic airway inflammation and airway hyperresponsiveness (AHR). Specifically, interleukin-4 (IL-4) primarily regulates B cell immunoglobulin class switching and mediates allergic responses, while interleukin-13 (IL-13) is instrumental in the production and maintenance of airway mucins associated with AHR.<sup>21</sup> Furthermore, interleukin-5 (IL-5) is closely linked to eosinophilia in both lung tissues and peripheral blood, serving as the most critical cytokine for eosinophil maturation in the bone marrow;<sup>27</sup> the administration of inhibitors can significantly reduce elevated levels of IL-5 protein.<sup>58</sup> PI3K is implicated in the suppression of adaptive Th2 cell-mediated inflammation and associated eosinophilic responses,<sup>76</sup> with inhibitors demonstrating a marked reduction in cytokine production and signaling induced by T cell receptor activation.<sup>77</sup> Nevertheless, there appears to be a degree of functional redundancy among different PI3K isoforms.<sup>78,79</sup> Inhibition of the PI3K signaling pathway has been shown to effectively suppress Th1/Th17 cytokines and tumor necrosis factor-alpha (TNF- $\alpha$ ), thereby mitigating the symptoms of allergic airway diseases.<sup>35</sup>

In non-allergic asthma, PI3K has been shown to affect several critical aspects of neutrophilic inflammation, including chemotaxis, oxidative stress, and neutrophil survival.<sup>52</sup> PI3K $\delta$ , in particular, plays a key role in regulating neutrophil trafficking, chemotaxis, and effector functions,<sup>59</sup> which may be closely related to oxidative stress. Activation of PI3K can lead to the reduction of histone deacetylase 2 (HDAC2),<sup>60</sup> increasing the infiltration of inflammatory cells, including neutrophils, and the subsequent production of pro-inflammatory cytokines and oxidative stress. Taken together, the role of PI3K in adaptive immunity involving T and B cells may be more complex than initially thought.

The role of PI3K $\delta$  in mediating steroid-resistant pulmonary inflammation has recently garnered significant attention in the context of developing treatments for COPD. Despite this focus, the primary anti-inflammatory therapies for asthma have not been entirely successful in enhancing lung function or preventing disease exacerbations, indicating that airway remodeling plays a crucial role in lung function impairment. Alterations such as disruption of epithelial integrity, subepithelial fibrosis, goblet cell hyperplasia/metaplasia, smooth muscle hypertrophy/hyperplasia, and increased vascular supply may contribute to airway hyperresponsiveness, airway obstruction, airflow limitation, and the progressive decline of lung function in asthma patients. Recognizing the importance of airway remodeling, the American Thoracic Society has identified it as a central aspect of asthma and has issued a statement advocating for further research to elucidate the pathology and mechanisms underlying airway remodeling, with the aim of expediting the development of targeted therapies.<sup>80</sup>

The pan-PI3K inhibitor LY294002 is associated with toxic properties and suboptimal pharmacokinetics, which limit its clinical utility.<sup>81</sup> Consequently, research efforts have increasingly focused on isoform-selective PI3K inhibitors. These selective inhibitors, which target specific PI3K isoforms, tend to exhibit reduced side effects, and several

have already received approval for clinical use. PI3K $\delta$  is integral to the inflammatory process and has emerged as a significant target for addressing cellular inflammation. PI3K $\gamma$  inhibitors, which selectively inhibit Class I PI3K isoforms, are pivotal in the activation of chemokine-dependent leukocytes and mast cells, and are employed in the treatment of inflammatory, respiratory, and immune disorders.<sup>59</sup> PI3K $\delta$  and PI3K $\gamma$  inhibitors, as well as dual inhibitors, are promising candidates for drug development. Although PI3K $\gamma$  inhibitors have anti-inflammatory properties, they have not yet been approved for clinical use.<sup>55</sup> Given their anti-inflammatory and bronchodilatory effects, PI3K $\delta$  inhibition may be a promising clinical development strategy, particularly when using inhaled formulations to minimize side effects. The PI3K pathway plays an important role in the response of airway immune cells and structural cells that mediate pathophysiological processes. In vivo experiments have demonstrated the significance of PI3K in asthma, indicating that PI3K inhibitors can prevent allergen-induced AHR and the pathogenesis of inflammation in asthma.<sup>82</sup> Although developing inhaled PI3K inhibitors with adequate efficacy has been challenging, numerous preclinical studies and early clinical trials provide optimism for the potential success of PI3K inhibition in treating airway diseases.

Furthermore, widely utilized animal models for asthma, such as BALB/c mice, have demonstrated that aberrant activation of the PI3K/Akt signaling pathway contributes to the manifestation of asthma-related phenomena. Conversely, the attenuation of PI3K/Akt pathway activation can suppress smooth muscle proliferation and airway remodeling in asthmatic rats.<sup>83</sup> Respiratory viral infections are the most important triggers of acute asthma exacerbations, with respiratory syncytial virus (RSV) and rhinovirus (RV) being the main infectious agents. These infections are strongly associated with respiratory distress in asthma,<sup>27</sup> and RSV-induced delayed neutrophil apoptosis is linked to PI3K.<sup>84</sup> Pan-PI3K inhibitors can profoundly inhibit viral escape from mucosal immunity, which leads to persistent infection.<sup>85</sup> In the context of the post-pandemic era, some patients have experienced tissue damage closely related to cytokine storms, leading to a significantly higher incidence of asthma among COVID-19 patients compared to the general population, with an increased risk of new-onset asthma with age.<sup>86</sup> Additionally, the TGF- $\beta$  signaling pathway, which plays a pivotal role in initiating pulmonary fibroblast proliferation, differentiation, and extracellular matrix production, can be modulated via PI3K inhibition.<sup>50</sup> Autophagy, which is intricately linked to airway inflammation and remodeling, is markedly elevated in asthma patients, with excessive autophagy observed,<sup>83</sup> thereby promoting airway smooth muscle cell (ASMCS) hypertrophy and epithelial-mesenchymal transition (EMT) involved in airway remodeling. Nevertheless, the role of autophagy in the pathogenesis of asthma remains contentious, and strategic modulation of autophagy through this pathway may provide a novel therapeutic avenue for asthma management.

## Conclusion

In summary, PI3K signaling is integral to the pathogenesis of both allergic and non-allergic asthma, impacting critical processes such as airway inflammation, hyperresponsiveness, and remodeling. Inhibition of PI3K has demonstrated considerable therapeutic promise in preclinical models by effectively attenuating inflammatory responses, eosinophilia, and airway smooth muscle cell proliferation, thereby reducing airway remodeling. Although pan-PI3K inhibitors like LY294002 have shown efficacy, their clinical application is constrained by issues of toxicity and suboptimal pharmacokinetics. This has led to a shift towards the development of isoform-selective PI3K inhibitors. These selective inhibitors, particularly those targeting PI3K $\delta$  and PI3K $\gamma$ , offer a more targeted therapeutic strategy with fewer side effects and are currently being explored for clinical use in inflammatory and respiratory diseases. Despite the challenges in developing inhaled PI3K inhibitors with adequate efficacy, ongoing research and early clinical trials provide optimism for their potential role in asthma treatment. Furthermore, the intricate interactions between PI3K signaling, autophagy, and airway remodeling underscore the necessity for continued exploration to fully understand the potential of PI3K inhibitors as a comprehensive therapeutic strategy for asthma and other related pulmonary conditions.

## Data Sharing Statement

No additional data is associated with this paper.

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## Author Contributions

All authors made a significant contribution to the work. Bangguo Song: Writing original draft, Review & editing. Shupeng Chen: Review & editing, Supervision. Jihong Hu: Conception, Study designing, Review & editing, Visualization, Supervision. Yingjian Zeng: Review & editing, Visualization, Funding acquisition. Yang Zhang: Review & editing, Visualization. All authors provided valuable feedback and comments on earlier versions of the manuscript. All authors carefully reviewed and approved the final version of the manuscript.

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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