Review Article

Unveiling the Role of Kinases as Novel Therapeutic Targets in Asthma and Chronic Obstructive Pulmonary Disease

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory airway disorders that contribute significantly to global morbidity and mortality. Despite advances in conventional therapies such as bronchodilators, corticosteroids, and biologics, a substantial proportion of patients continue to experience poor disease control, frequent exacerbations, and corticosteroid resistance. This highlights the urgent need for novel, mechanism-based therapeutic strategies. Emerging evidence identifies protein kinases as central regulators of inflammatory signaling, immune cell activation, airway smooth muscle contraction, and structural remodeling in both asthma and COPD. Key kinase pathways, including mitogen-activated protein kinase (MAPK), Janus kinase–signal transducer and activator of transcription (JAK–STAT), Rho-kinase, and PI3K–Akt–mTOR signaling, have been implicated in disease pathogenesis and treatment resistance. In addition, emerging targets such as SYK, BTK, and EGFR further expand the therapeutic landscape. This review critically examines the role of kinase-mediated signaling pathways in chronic airway diseases and evaluates their potential as novel therapeutic targets, supporting future precision medicine approaches.

Keywords: Asthma; Chronic obstructive pulmonary disease; Protein kinases; MAPK pathway; JAK–STAT pathway; Rho-kinase; PI3K–Akt–mTOR; Emerging kinase targets; Precision medicine.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are among the most prevalent chronic respiratory disorders worldwide and represent a major public health challenge [1]. Both diseases are characterized by chronic airway inflammation, airflow limitation, and recurrent exacerbations, leading to significant morbidity, mortality, and socioeconomic burden. Asthma is a heterogeneous airway disease marked by variable and usually reversible airflow obstruction, bronchial hyperresponsiveness, and chronic inflammation, while COPD is characterized by persistent, largely irreversible airflow limitation resulting from small airway disease and parenchymal destruction [2]. Together, these diseases account for a substantial proportion of global disability-adjusted life years (DALYs) and health-care utilization.

According to recent global respiratory disease reviews, asthma affects hundreds of millions of people worldwide, with epidemiological modeling estimating around 250–270 million prevalent cases in recent years [3]. These assessments show that despite improvements in management and medication use, the burden remains high, particularly in low- and middle-income countries where access to diagnostic services and controller therapies is limited. Asthma remains a leading cause of chronic disease in children and continues into adulthood for many, contributing to lost productivity, reduced quality of life, and increased health-care costs.[4]

COPD, in contrast, is a leading cause of mortality globally and contributes substantially to chronic disease burden. Global reviews of COPD epidemiology demonstrate that COPD is responsible for a major share of chronic respiratory disease mortality and ranks among the top three causes of death worldwide [5]. Although cigarette smoking remains the primary risk factor in many regions, a significant portion of COPD cases especially in low and middle-income countries are attributable to other exposures such as household air pollution (from biomass fuel combustion), occupational dusts and chemicals, ambient particulate matter, and recurrent respiratory infections. These broader risk profiles underscore the complex and multifactorial nature of COPD beyond smoking alone.[6]

The global distribution of asthma and COPD shows marked geographic and socioeconomic variation. Historically, higher asthma prevalence was reported in high-income regions, reflecting urbanization, environmental exposures, and diagnostic practices. However, recent epidemiological reviews indicate a rising burden of asthma in many low- and middle-income nations, driven by factors such as urban air pollution, changing lifestyles, and increased recognition and recording of the disease. For COPD, prevalence remains high in regions with high smoking prevalence and environmental exposures; nonetheless, non-smoking causes have gained prominence in global COPD analyses, especially in regions with substantial biomass fuel use and outdoor air pollution.[7]

An added dimension of chronic airway disease is asthma-COPD overlap (ACO), a condition that shares clinical features of both disorders and is associated with worse health outcomes and higher mortality. Global prevalence remains uncertain but may affect several percent of chronic airway disease populations, and its epidemiology points to

a greater combined burden than asthma or COPD alone. This overlap challenges diagnostic and management strategies and further emphasizes the need for tailored therapeutic approaches.[8]

In India, chronic respiratory diseases constitute a significant component of the national disease burden. Reviews specifically focused on Indian COPD data indicate that prevalence rates among adults vary across regions but are consistently substantial. Spirometry-based and community studies report COPD prevalence estimates in the range of approximately 5–8% among adults aged 30 years and older, with regional variation and higher rates in populations exposed to biomass smoke, occupational risks, and poor air quality. These findings align with broader reviews that emphasize the high and often under-recognized COPD burden in India.[9]

Asthma epidemiology in India also demonstrates a large affected population. Asthma in India estimate tens of millions of people living with the disease and emphasize that under-recognition, suboptimal inhaler use, and limited access to detailed spirometric diagnosis contribute to continued morbidity and mortality.. Indian reviews highlight that chronic respiratory disease burden in India is not uniform: urban areas face high pollution-related risks, while rural regions confront biomass fuel exposure and health-service access limitations [10]

Acute exacerbations episodes of symptom worsening requiring additional treatment drive much of the morbidity and health-care utilization seen in these diseases. Reviews reveal that exacerbations are commonly triggered by environmental pollution, respiratory infections, and poor disease control, especially in densely populated urban settings. Frequent exacerbations accelerate lung function decline, increase hospital admissions, and heighten health-care costs, placing disproportionate strain on health systems in resource-limited settings.[11]

Despite advances in pharmacotherapy such as bronchodilators, inhaled corticosteroids, and, more recently, targeted biologic agents for specific asthma phenotypes, many patients do not achieve adequate disease control. Corticosteroid insensitivity particularly in COPD and in non-type-2 asthma phenotypes limits the effectiveness of conventional anti-inflammatory therapy. These persistent gaps in effective disease management underscore the pressing need for novel therapeutic strategies that move beyond symptom control to address underlying pathogenic mechanisms [12]

Kinase-mediated signalling pathways have emerged as promising targets in this context. Protein kinases regulate key processes involved in airway inflammation, immune cell activation, bronchoconstriction, mucous hypersecretion, and airway remodelling all central features of asthma and COPD pathobiology. Targeting dysregulated kinase pathways offers the potential to modulate disease pathways more precisely than broad-spectrum anti-inflammatories, thereby addressing unmet therapeutic needs, particularly in severe and refractory disease subsets. Given the persistent global and regional burden of asthma and COPD, translational research that integrates epidemiological insights with targeted molecular interventions is critical for developing future therapies with improved efficacy and safety profiles.[13]

Pathophysiology

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory disorders of the airways that, despite sharing certain clinical features, differ significantly in their underlying pathophysiological mechanisms.[14] Both diseases are characterized by airflow limitation, airway inflammation, and structural changes within the respiratory tract; however, the nature of inflammation, reversibility of airflow obstruction, and molecular drivers differ between asthma and COPD. Understanding these pathophysiological processes is essential for identifying novel therapeutic targets, particularly kinase-mediated signaling pathways that regulate inflammation, immune responses, and airway remodeling.[15]

Asthma is primarily an immune-mediated disease marked by chronic airway inflammation and variable airflow obstruction that is often reversible either spontaneously or with treatment.[16] The inflammatory response in asthma is typically dominated by type 2 (T2) immune pathways, involving T-helper 2 (Th2) lymphocytes, group 2 innate lymphoid cells (ILC2s), eosinophils, mast cells, and basophils. These cells release key cytokines such as interleukin (IL)-4, IL-5, and IL-13, which promote IgE production, eosinophil survival, mucus hypersecretion, and airway hyperresponsiveness. The interaction between allergens and IgE-coated mast cells leads to the release of histamine, leukotrienes, and prostaglandins, resulting in acute bronchoconstriction and airway edema.[17]

In addition to immune cell activation, structural cells of the airway—including epithelial cells, fibroblasts, and airway smooth muscle cells play a crucial role in asthma pathophysiology. Airway epithelial damage caused by allergens, pollutants, or viral infections leads to the release of alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which further amplify type 2 inflammation.[18] Chronic inflammation results in airway remodeling characterized by subepithelial fibrosis, increased smooth muscle mass, angiogenesis, and goblet cell hyperplasia. These structural changes contribute to persistent airflow limitation and reduced responsiveness to conventional therapies in severe asthma.

COPD, in contrast, is characterized by persistent and largely irreversible airflow limitation resulting from a combination of small airway disease and parenchymal destruction (emphysema). The inflammatory profile in COPD is predominantly driven by innate immune responses and is associated with neutrophils, macrophages, and $CD8^+$ cytotoxic T lymphocytes.[19] Long-term exposure to noxious particles, particularly cigarette smoke and biomass fuel smoke, triggers chronic inflammation through oxidative

stress and activation of inflammatory signaling pathways. Activated macrophages release proteases such as matrix metalloproteinases and neutrophil elastase, leading to destruction of alveolar walls and loss of elastic recoil.[20]

Although asthma and COPD have traditionally been viewed as distinct entities, there is increasing recognition of overlapping pathophysiological features, particularly in patients with asthma–COPD overlap (ACO).[21] These individuals may exhibit mixed inflammatory patterns, including eosinophilic and neutrophilic inflammation, airway remodeling, and partial reversibility of airflow limitation. The heterogeneity of inflammatory mechanisms across asthma, COPD, and ACO highlights the limitations of a "one-size-fits-all" therapeutic approach and underscores the need for targeted interventions based on underlying molecular pathways.[22]

At the molecular level, both asthma and COPD are regulated by complex intracellular signaling cascades that control immune cell activation, cytokine production, smooth muscle contraction, and tissue remodeling. Protein kinases play a central role in these processes by mediating signal transduction from cell surface receptors to the nucleus. Dysregulation of kinase-driven pathways contributes to chronic inflammation, exaggerated immune responses, airway hyperresponsiveness, and structural changes in the lungs.[23] Key kinase pathways implicated in airway disease pathophysiology include mitogen-activated protein kinases (MAPKs), Janus kinase–signal transducer and activator of transcription (JAK–STAT), phosphoinositide 3-kinase (PI3K), and Rho-kinase signaling pathways.[24]

Activation of these kinase pathways leads to transcription of pro-inflammatory genes, increased survival of inflammatory cells, enhanced smooth muscle contractility, and mucus overproduction. In asthma, kinase signaling amplifies type 2 cytokine responses and airway hyperresponsiveness, while in COPD it promotes neutrophilic inflammation, oxidative stress, and steroid resistance.[25] Importantly, these pathways operate at multiple levels of disease pathogenesis, influencing both inflammatory and structural components of airway disease.

In summary, the pathophysiology of asthma and COPD involves a complex interplay between immune cells, structural airway cells, environmental exposures, and intracellular signaling mechanisms.[26] Chronic inflammation, airway remodeling, and airflow limitation are central features of both diseases, although driven by distinct yet overlapping molecular processes. Protein kinases represent critical regulators of these pathogenic mechanisms, making them attractive targets for novel therapeutic interventions.[27] A deeper understanding of disease-specific and shared kinase-driven pathways provides a strong biological rationale for the development of kinase-targeted therapies aimed at improving disease control, overcoming treatment resistance, and advancing precision medicine in asthma and COPD.

Causes and Etiological Factors

Asthma is primarily driven by chronic airway inflammation associated with immune dysregulation, particularly involving type 2 (T2) immune responses.[28] Genetic susceptibility plays a significant role, with multiple genes implicated in immune regulation, epithelial barrier function, and airway responsiveness. Environmental exposures such as allergens (house dust mites, pollen, animal dander), respiratory viral infections during early life, and air pollutants act as triggering factors that initiate or exacerbate airway inflammation.[29] In many individuals, asthma develops early in life, although adult-onset asthma is increasingly recognized, often associated with occupational exposures or hormonal and metabolic factors.

COPD, in contrast, is largely caused by prolonged exposure to noxious particles and gases that induce chronic inflammation and structural damage in the airways and lung parenchyma.[30] Cigarette smoking remains the most prominent etiological factor globally; however, non-smoking causes are increasingly acknowledged. Long-term exposure to biomass fuel smoke, occupational dusts and chemicals, outdoor air pollution, and recurrent lower respiratory tract infections contribute substantially to COPD development, particularly in low- and middle-income countries. These exposures lead to persistent inflammatory responses, airway remodeling, and destruction of alveolar structures, resulting in irreversible airflow limitation.

Risk Factors

Risk factors for asthma include genetic predisposition, family history of atopy, exposure to indoor and outdoor allergens, air pollution, tobacco smoke (including passive smoking), obesity, and early-life respiratory infections.[31] Occupational asthma represents an important subset, where repeated exposure to sensitizing agents such as isocyanates, flour dust, or chemicals leads to airway inflammation and hyperresponsiveness. Socioeconomic factors, urbanization, and lifestyle changes also influence asthma prevalence and severity.[32]

COPD risk factors extend beyond smoking and include age, cumulative exposure to environmental pollutants, poor socioeconomic conditions, and impaired lung growth during childhood. Childhood respiratory infections and poor nutrition may predispose individuals to reduced lung function later in life, increasing vulnerability to COPD.[33] In many regions, women exposed to biomass fuel smoke for cooking are at high risk despite never smoking. Genetic factors, such as alpha-1 antitrypsin deficiency, although rare, significantly increase susceptibility to early-onset COPD.[34]

Clinical Symptoms

Asthma is characterized by episodic respiratory symptoms that vary in intensity and frequency. Common symptoms include wheezing, shortness of breath, chest tightness, and cough, often worse at night or in the early morning.[35] Symptoms are typically triggered by allergens, exercise,

cold air, or respiratory infections and are usually reversible either spontaneously or with bronchodilator therapy. Disease severity ranges from mild intermittent symptoms to severe, persistent asthma with frequent exacerbations and significant impairment of daily activities.[36]

COPD presents with chronic and progressive respiratory symptoms. The hallmark features include persistent dyspnea, chronic cough, and sputum production.[37] Unlike asthma, symptoms in COPD are usually continuous and worsen gradually over time. Exacerbated acute episodes of symptom worsening are common and are often triggered by infections or air pollution. Advanced COPD may be associated with systemic manifestations such as weight loss, muscle wasting, fatigue, and cardiovascular comorbidities, reflecting the systemic inflammatory nature of the disease.

An important clinical entity is asthma–COPD overlap (ACO), where patients exhibit features of both diseases, including variable airflow limitation alongside persistent symptoms.[38] These individuals often experience more frequent exacerbations, poorer quality of life, and higher health-care utilization.

Diagnosis

Accurate diagnosis of asthma and COPD relies on a combination of clinical history, physical examination, and objective lung function testing.[39]Spirometry is the cornerstone of diagnosis for both conditions. In asthma, spirometry typically demonstrates variable airflow obstruction that is reversible following bronchodilator administration. Peak expiratory flow variability and bronchial provocation tests may support the diagnosis in uncertain cases.[40]

In COPD, spirometry reveals persistent airflow limitation defined by a reduced post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC).[41] Unlike asthma, airflow obstruction in COPD shows limited reversibility. Disease severity is further assessed using spirometric grading, symptom assessment tools, and exacerbation history.[42]

Additional diagnostic tools include chest imaging, which may help exclude alternative diagnoses or identify emphysematous changes in COPD. Biomarkers such as blood eosinophil counts, exhaled nitric oxide, and serum IgE levels are increasingly used to characterize asthma phenotypes and guide targeted therapy. In COPD, assessment of comorbidities, oxygen saturation, and exercise capacity contributes to comprehensive disease evaluation.[43]

Conventional Treatment of Asthma

The primary goals of asthma management are to achieve good symptom control, maintain normal lung function, and reduce the risk of exacerbations. Inhaled corticosteroids (ICS) are the mainstay of long-term asthma therapy and act by suppressing airway inflammation through inhibition of pro-inflammatory cytokine production and immune cell activation.[44] They are often combined with long-acting β_2-agonists (LABAs), which provide bronchodilation by relaxing airway smooth muscle via stimulation of β_2-adrenergic receptors. Short-acting β_2-agonists (SABAs) are commonly used as rescue medications for rapid relief of acute bronchoconstriction.[45]

Additional therapies include leukotriene receptor antagonists (LTRAs), which inhibit leukotriene-mediated bronchoconstriction and inflammation, and anticholinergic agents such as tiotropium, which reduce airway smooth muscle contraction.[46] In patients with severe allergic or eosinophilic asthma, biologic therapies targeting immunological mediators such as anti-IgE, anti-IL-5, anti-IL-4/IL-13 monoclonal antibodies have significantly improved outcomes by reducing exacerbation rates and steroid dependence.[47.]

Conventional Treatment of COPD

COPD management primarily focuses on symptom relief, reduction of exacerbation frequency, and slowing disease progression. Bronchodilators form the cornerstone of therapy and include long-acting muscarinic antagonists (LAMAs) and LABAs, which improve airflow limitation and reduce dyspnea. Inhaled corticosteroids are prescribed in selected COPD patients, particularly those with frequent exacerbations and eosinophilic inflammation, often in combination with LABAs.[48]

Other pharmacological options include phosphodiesterase-4 (PDE-4) inhibitors such as roflumilast, which reduce inflammation by increasing intracellular cyclic AMP levels, and mucolytic agents that improve sputum clearance.[49] Non-pharmacological interventions, including smoking cessation, pulmonary rehabilitation, vaccination, and oxygen therapy, are also integral components of COPD management.

Limitations of Conventional Therapies

Despite the availability of multiple therapeutic options, conventional treatments for asthma and COPD exhibit several significant limitations. One of the major challenges is disease heterogeneity. Both asthma and COPD encompass multiple phenotypes and endotypes driven by distinct molecular pathways.[50] Standard therapies, particularly corticosteroids, are effective mainly in type-2 inflammatory asthma but show limited efficacy in non-type-2 asthma and in many COPD patients.

Corticosteroid resistance represents a critical limitation, especially in COPD and severe asthma. Oxidative stress, chronic inflammation, and impaired histone deacetylase-2 (HDAC2) activity contribute to reduced steroid responsiveness, resulting in persistent inflammation despite high-dose corticosteroid therapy.[51] Long-term corticosteroid use is also associated with systemic adverse effects, including osteoporosis, adrenal suppression, metabolic disturbances, and increased risk of infections.

Bronchodilators, while effective in relieving airflow obstruction, do not adequately address underlying airway

inflammation or structural remodeling. Consequently, they do not prevent disease progression or reverse airway damage. Biologic therapies, although highly effective in selected asthma phenotypes, are expensive, require parenteral administration, and benefit only a limited subset of patients. Their role in COPD remains restricted and under investigation.[52]

Another major limitation is the lack of disease-modifying treatments for COPD. Current therapies primarily alleviate symptoms but do not halt the progressive decline in lung function or repair structural lung damage. Additionally, poor inhaler technique, medication non-adherence, and limited access to advanced therapies further compromise treatment effectiveness, particularly in low- and middle-income countries.[53]

Need for Novel Therapeutic Approaches

The limitations of conventional therapies underscore the need for innovative treatment strategies that target fundamental molecular mechanisms involved in airway disease pathogenesis. Increasing evidence suggests that kinase-mediated signaling pathways play a pivotal role in regulating inflammation, immune cell activation, airway smooth muscle contraction, and tissue remodeling in asthma and COPD.[54] Unlike conventional therapies that act downstream, targeting kinases offers the potential to modulate multiple disease-driving pathways simultaneously.

Kinase inhibitors represent a promising class of therapeutics capable of addressing corticosteroid resistance, reducing chronic inflammation, and improving disease control in severe and refractory cases. Understanding the shortcomings of existing treatments provides a strong rationale for exploring kinase-targeted therapies as novel and potentially disease-modifying approaches in the management of asthma and COPD.[55]

Introduction to Kinases

Protein kinases are a large and diverse family of enzymes that play a fundamental role in regulating cellular signaling processes.[56] They function by catalyzing the transfer of a phosphate group, usually from adenosine triphosphate (ATP), to specific amino acid residues on target proteins. This process, known as phosphorylation, is a reversible post-translational modification that alters protein structure, activity, localization, or interactions with other molecules. Through phosphorylation, kinases act as molecular switches that control nearly all aspects of cellular physiology, including cell growth, differentiation, metabolism, immune responses, and apoptosis.[57]

The human genome encodes more than 500 protein kinases, collectively referred to as the “kinome.” Based on their substrate specificity, protein kinases are broadly classified into two major categories: tyrosine kinases and serine/threonine kinases.[58] Tyrosine kinases phosphorylate tyrosine residues and are further divided into receptor tyrosine kinases (RTKs), which are embedded in the cell membrane, and non-receptor tyrosine kinases, which function within the cytoplasm or nucleus. Serine/threonine kinases, on the other hand, phosphorylate serine or threonine residues and include important signaling families such as mitogen-activated protein kinases (MAPKs), Janus kinases (JAKs), and protein kinase B (Akt).[59] Together, these kinases form complex signaling networks that allow cells to respond precisely to external and internal stimuli.

Kinase signaling pathways are tightly regulated under physiological conditions to ensure balanced cellular responses. Activation of kinases typically occurs through ligand–receptor interactions, conformational changes, phosphorylation by upstream kinases, or interaction with adaptor proteins. [60] Conversely, kinase activity is negatively regulated by phosphatases, inhibitory proteins, and feedback mechanisms that prevent excessive or prolonged signaling. Disruption of this tightly controlled balance can lead to abnormal kinase activation, which is increasingly recognized as a central mechanism underlying many chronic inflammatory, autoimmune, and proliferative diseases.[61]

Inflammatory and immune-mediated disorders, kinases play a crucial role in transmitting signals from cell surface receptors to the nucleus, resulting in the activation of transcription factors and the production of inflammatory mediators.[62] Immune cells such as T lymphocytes, B lymphocytes, macrophages, mast cells, and neutrophils rely heavily on kinase-dependent pathways for their activation, migration, survival, and cytokine release.[63] Consequently, dysregulated kinase signaling can lead to exaggerated or persistent inflammation, a hallmark feature of chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).[64]

Asthma and COPD are characterized by complex inflammatory processes involving both innate and adaptive immune responses. Kinases regulate many of the cellular events that drive airway inflammation, including cytokine and chemokine production, immune cell recruitment, airway smooth muscle contraction, and structural remodeling of the airway wall.[65] For example, activation of specific kinase pathways enhances the release of pro-inflammatory mediators such as interleukins, tumor necrosis factor-α, and growth factors that contribute to airway hyperresponsiveness and mucus hypersecretion. At the same time, kinases influence airway epithelial cell responses to environmental triggers such as allergens, pollutants, and respiratory infections.

One of the major reasons kinases have gained attention as therapeutic targets is their central position within signaling cascades. Unlike conventional therapies that often act downstream to relieve symptoms, kinase-targeted approaches aim to intervene earlier in the signaling process, thereby modulating multiple pathogenic pathways simultaneously. This upstream regulation offers the potential for more effective control of inflammation and disease progression, particularly in patients who respond poorly to standard treatments such as corticosteroids.

Moreover, the development of selective kinase inhibitors allows for targeted intervention with reduced off-target effects compared to broad immunosuppressive therapies.[66]

Advances in molecular biology and medicinal chemistry have significantly improved the understanding of kinase structure, function, and regulation. Structural studies have revealed conserved catalytic domains within kinases, providing opportunities for rational drug design.[67] As a result, several kinase inhibitors have already been successfully developed and approved for use in oncology and inflammatory diseases, demonstrating the clinical feasibility of targeting kinase pathways. These successes have encouraged exploration of kinase inhibition as a strategy for managing chronic respiratory diseases.[68]

MAPK pathway

Mitogen-Activated Protein Kinase (MAPK) signaling pathways play a central role in regulating cellular responses to extracellular stimuli, including inflammatory mediators, oxidative stress, allergens, and infectious agents.[69] In chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), dysregulation of MAPK signaling has been extensively implicated in the development and persistence of airway inflammation, bronchial hyperresponsiveness, mucus hypersecretion, and structural airway remodeling. The MAPK family consists of three major signaling cascades: extracellular Owing to their critical involvement in disease pathophysiology, MAPK pathways have emerged as attractive therapeutic targets for novel anti-inflammatory interventions in asthma and COPD.[70]

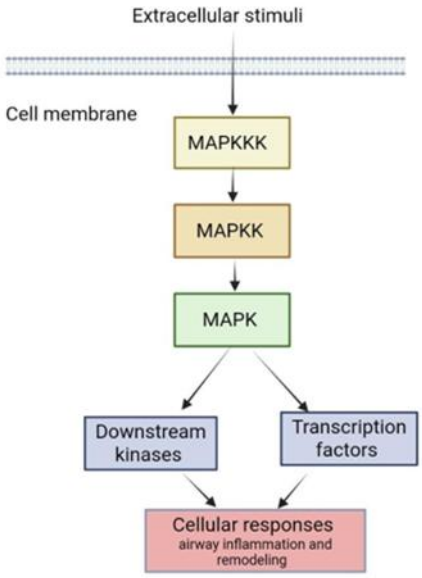

Figure 1: Extracellular inflammatory stimuli trigger a kinase cascade, activating the p38 MAPK signalling module.

The p38 MAPK signalling module is activated by an upstream kinase cascade that is itself initiated by inflammatory stimuli from outside the cell.

Signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK), and p38 MAPKs.[71] These kinases function through a highly conserved phosphorylation cascade involving MAPK kinase kinases (MAP3Ks), MAPK kinases (MAP2Ks), and MAPKs, ultimately leading to the activation of transcription factors that regulate gene expression. Each MAPK pathway responds to distinct stimuli and mediates specific cellular functions, yet significant cross-talk exists among them, contributing to the complexity of inflammatory signaling in airway diseases.[72]

In asthma, MAPK pathways are activated in multiple cell types, including airway epithelial cells, smooth muscle cells, mast cells, eosinophils, and T lymphocytes.[73] ERK signaling is particularly associated with airway smooth muscle proliferation, contributing to airway wall thickening and remodeling. Enhanced ERK activation promotes the expression of growth factors, cytokines, and extracellular matrix proteins, thereby sustaining chronic inflammation and structural changes in the asthmatic airway. JNK signaling is involved in stress-induced inflammatory responses and regulates the production of pro-inflammatory cytokines through activation of transcription factors such as activator protein-1 (AP-1). These processes collectively amplify allergic inflammation and airway hyperresponsiveness.[74]

Among the MAPK family members, the p38 MAPK pathway has received the greatest attention in both asthma and COPD research.[75] p38 MAPK is strongly activated by inflammatory cytokines, oxidative stress, and environmental pollutants factors that are highly relevant to chronic airway diseases. In asthma, p38 MAPK contributes to the production of type-2 cytokines, chemokines, and adhesion molecules, facilitating immune cell recruitment and activation. Inhibition of p38 MAPK has been shown in experimental models to reduce eosinophilic inflammation, mucus production, and airway hyperresponsiveness, highlighting its therapeutic potential.[76]

The role of MAPK signaling is even more pronounced in COPD, where chronic exposure to cigarette smoke and air pollutants induces persistent activation of stress-responsive kinases, particularly p38 MAPK and JNK.[77] These pathways drive the release of pro-inflammatory mediators such as tumor necrosis factor-α, interleukin-8, and matrix metalloproteinases, which contribute to neutrophilic inflammation, tissue destruction, and emphysema development. Moreover, p38 MAPK signaling has been implicated in corticosteroid resistance in COPD, as it interferes with histone deacetylase-2 activity, thereby reducing the anti-inflammatory efficacy of glucocorticoids. This mechanism partly explains the limited responsiveness of COPD patients to conventional steroid therapy.[78]

Given their central role in airway inflammation and steroid resistance, MAPK pathways particularly p38 MAPK have been explored as therapeutic targets. Several p38 MAPK inhibitors have progressed into clinical trials for asthma and COPD.[79] While early studies demonstrated reductions in inflammatory biomarkers, the overall clinical benefits were modest, and concerns regarding systemic adverse effects limited their long-term use. These outcomes underscore

the challenges associated with targeting ubiquitously expressed kinases involved in multiple physiological processes. Nonetheless, ongoing research is focused on developing more selective inhibitors, inhaled formulations, and combination therapies to improve efficacy while minimizing systemic toxicity.[80]

In addition to direct kinase inhibition, modulation of upstream activators and downstream transcription factors of MAPK pathways is being investigated as an alternative therapeutic strategy.[81] Such approaches aim to fine-tune inflammatory signaling rather than completely suppress it, thereby preserving essential cellular functions. Advances in understanding MAPK pathway regulation, cell-specific signaling, and disease endotypes may enable more precise targeting of MAPK signaling in selected patient populations.[82]

JAK–STAT Pathway

The Janus kinase signal transducer and activator of transcription (JAK–STAT) pathway is one of the most important intracellular signaling mechanisms involved in immune regulation and inflammatory responses.[83] This pathway plays a critical role in the pathogenesis of several immune-mediated and inflammatory diseases, including asthma and chronic obstructive pulmonary disease (COPD). Increasing evidence from experimental and clinical studies suggests that dysregulation of JAK–STAT signaling contributes significantly to chronic airway inflammation, immune cell activation, and disease persistence, making it an attractive therapeutic target in chronic respiratory disorders.[84]

The JAK–STAT pathway is initiated when extracellular cytokines, growth factors, or interferons bind to their specific cell surface receptors. These receptors are associated with Janus kinases (JAKs), a family of intracellular tyrosine kinases that includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[85] Ligand binding induces receptor dimerization, leading to activation of JAKs through trans-phosphorylation. Activated JAKs then phosphorylate specific tyrosine residues on the receptor, creating docking sites for STAT proteins. Once recruited, STATs are phosphorylated, dimerize, and translocate to the nucleus, where they regulate the transcription of genes involved in inflammation, immune responses, cell survival, and differentiation.[86]

In asthma, the JAK–STAT pathway is closely linked to type-2 immune inflammation, which is characterized by elevated levels of cytokines such as interleukin-4 (IL-4), IL-5, IL-9, and IL-13.[87] These cytokines signal predominantly through JAK1, JAK3, and STAT6, leading to eosinophilic inflammation, immunoglobulin E (IgE) production, mucus hypersecretion, and airway hyperresponsiveness. Activation of STAT6 is particularly important in driving Th2 cell differentiation and promoting allergic airway inflammation. Additionally, IL-5 signaling through the JAK–STAT pathway enhances eosinophil survival and activation, contributing to persistent airway inflammation and frequent exacerbations in allergic asthma.[88]

Beyond type-2 asthma, JAK–STAT signaling is also involved in non-type-2 and severe asthma phenotypes. Cytokines such as IL-6, interferon-γ (IFN-γ), and IL-17 activate STAT3 and STAT1 pathways, which are associated with neutrophilic inflammation, corticosteroid resistance, and poor clinical outcomes.[89] Enhanced STAT3 activation has been linked to airway remodeling, increased smooth muscle proliferation, and persistent inflammation, highlighting the broad involvement of JAK–STAT signaling across different asthma endotypes.[90]

In COPD, the JAK–STAT pathway contributes to chronic inflammation, immune dysregulation, and tissue damage. Pro-inflammatory cytokines such as IL-6, tumor necrosis factor-α (TNF-α), and interferons activate JAK–STAT signaling in airway epithelial cells, macrophages, and neutrophils.[91] Persistent STAT3 activation has been associated with neutrophil recruitment, oxidative stress, and impaired resolution of inflammation in COPD. Furthermore, JAK–STAT signaling plays a role in the development of corticosteroid resistance, a major therapeutic challenge in COPD management. Oxidative stress and chronic inflammation can alter JAK–STAT-dependent gene regulation, reducing the anti-inflammatory effectiveness of corticosteroids.[92]

The involvement of the JAK–STAT pathway in both asthma and COPD has stimulated interest in JAK inhibitors as potential therapeutic agents.[93] Unlike biologic therapies that target individual cytokines, JAK inhibitors can block multiple cytokine signaling pathways simultaneously, offering broader anti-inflammatory effects. Several small-molecule JAK inhibitors have already been approved for inflammatory and autoimmune diseases, and their potential application in respiratory diseases is actively being explored.[94] In asthma, JAK inhibition has shown promise in reducing airway inflammation, eosinophilia, and cytokine production in preclinical models. Inhaled JAK inhibitors are particularly attractive as they may provide targeted airway effects while minimizing systemic adverse effects.

In COPD, JAK inhibitors may help suppress chronic neutrophilic inflammation and overcome corticosteroid resistance. By modulating STAT3- and STAT1-mediated inflammatory pathways, JAK inhibition could reduce exacerbation frequency and improve lung function.[95] However, the broad immunosuppressive effects of systemic JAK inhibition raise safety concerns, including increased risk of infections. Therefore, careful patient selection, dose optimization, and development of inhaled formulations are essential for successful clinical translation.[96]

Rho-kinase pathway

The Rho-kinase (ROCK) signaling pathway has emerged as an important molecular regulator in the pathophysiology of chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).[97] Rho-kinases are serine/threonine kinases that function as key downstream

effectors of the small GTPase RhoA. Two major isoforms, ROCK1 and ROCK2, are expressed in various cell types relevant to airway disease, including airway smooth muscle cells, epithelial cells, endothelial cells, fibroblasts, and inflammatory cells. [98]Increasing experimental and clinical evidence suggests that dysregulation of the RhoA/ROCK pathway contributes significantly to airway hyperresponsiveness, inflammation, remodeling, and disease progression in both asthma and COPD.[99]

One of the most prominent roles of the Rho-kinase pathway in airway disease is the regulation of airway smooth muscle contraction. Activation of RhoA leads to stimulation of ROCK, which in turn inhibits myosin light chain phosphatase.[100] This inhibition results in sustained phosphorylation of myosin light chains, thereby enhancing smooth muscle contraction independently of intracellular calcium levels, a process referred to as calcium sensitization. In asthma, exaggerated activation of this pathway contributes to airway hyperresponsiveness, a hallmark feature characterized by excessive bronchoconstriction in response to stimuli. Similarly, in COPD, increased Rho-kinase activity has been associated with persistent airflow limitation due to enhanced smooth muscle tone and structural changes in the airway wall.[101]

Beyond its effects on smooth muscle contraction, the Rho-kinase pathway plays a crucial role in airway inflammation. ROCK signaling influences the migration, adhesion, and activation of inflammatory cells such as eosinophils, neutrophils, macrophages, and lymphocytes.[102]In asthma, Rho-kinase activation promotes eosinophilic inflammation by facilitating leukocyte recruitment and enhancing the production of pro-inflammatory cytokines. In COPD, where neutrophilic inflammation predominates, the Rho-kinase pathway contributes to neutrophil chemotaxis, oxidative stress, and the release of proteolytic enzymes that damage lung tissue. These inflammatory processes amplify airway injury and accelerate disease progression.[103]

Airway remodeling is another critical pathological feature of asthma and COPD in which the Rho-kinase pathway plays a substantial role. Chronic activation of ROCK promotes fibroblast proliferation, myofibroblast differentiation, and excessive deposition of extracellular matrix proteins such as collagen and fibronectin.[104] These changes lead to thickening of the airway wall, subepithelial fibrosis, and loss of airway elasticity. In asthma, remodeling contributes to irreversible airflow limitation in severe disease, while in COPD, it exacerbates small airway narrowing and emphysematous destruction. Rho-kinase signaling also regulates epithelial–mesenchymal transition, a process implicated in structural alterations of the airway epithelium in chronic lung diseases.[105]

The Rho-kinase pathway further interacts with other signaling networks involved in asthma and COPD, including MAPK, PI3K, and inflammatory transcription factors. This cross-talk enhances inflammatory gene expression, cytokine release, and cellular survival pathways.[106] Rho-kinase activation has been linked to corticosteroid resistance, particularly in COPD. By modulating inflammatory signaling and oxidative stress pathways, ROCK activity may reduce the responsiveness of airway cells to glucocorticoids, thereby limiting the effectiveness of conventional anti-inflammatory therapy. [107] This finding has significant clinical implications, as steroid resistance remains a major challenge in the management of severe asthma and COPD.

Given its multifaceted involvement in airway hyperresponsiveness, inflammation, and remodeling, the Rho-kinase pathway has gained attention as a promising therapeutic target. Pharmacological inhibition of ROCK using small-molecule inhibitors has shown encouraging results in preclinical models of asthma and COPD. These inhibitors have been demonstrated to reduce airway smooth muscle contraction, suppress inflammatory cell infiltration, and attenuate airway remodeling. In experimental studies, Rho-kinase inhibitors improved lung function, decreased bronchial hyperresponsiveness, and reduced cytokine production, supporting their potential as disease-modifying agents.[108]

Several challenges remain in translating Rho-kinase inhibition into clinical practice. Systemic inhibition of ROCK may lead to adverse effects such as hypotension and vascular complications due to its role in vascular smooth muscle regulation.[109] Therefore, strategies such as inhaled delivery and the development of isoform-selective inhibitors are being explored to enhance airway specificity and minimize systemic toxicity. Further clinical trials are required to establish long-term safety, optimal dosing, and therapeutic efficacy in diverse patient populations.[110]

The Rho-kinase pathway plays a pivotal role in the pathogenesis of asthma and COPD by regulating airway smooth muscle contraction, inflammation, remodeling, and treatment responsiveness. Targeting this pathway represents a novel and promising approach to address unmet therapeutic needs, particularly in severe and steroid-resistant forms of chronic airway disease. Continued research into Rho-kinase signaling and inhibitor development may contribute significantly to the advancement of precision medicine in asthma and COPD management.[111]

PI3K–Akt–mTOR pathway

The phosphoinositide 3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) signaling pathway is a central intracellular cascade that regulates key cellular processes including metabolism, proliferation, survival, autophagy, and immune responses.[112] In recent years, growing evidence has highlighted the critical involvement of this pathway in the pathophysiology of chronic inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Dysregulation of PI3K–Akt–mTOR signaling contributes to persistent airway inflammation, oxidative stress, immune cell dysfunction, airway remodeling, and corticosteroid resistance, making it an attractive therapeutic target.[113]

PI3Ks are a family of lipid kinases that phosphorylate phosphatidylinositol lipids, leading to the activation of downstream signaling molecules. Among the different PI3K isoforms, class I PI3Ks particularly PI3K-δ and PI3K-γ are highly expressed in inflammatory and immune cells such as neutrophils, macrophages, eosinophils, and lymphocytes.[114] Activation of PI3K leads to phosphorylation of Akt (protein kinase B), which in turn regulates multiple downstream targets, including mTOR, a serine/threonine kinase that acts as a master regulator of cellular growth and immune responses. Aberrant activation of this pathway has been observed in airway epithelial cells, immune cells, and structural cells of the lung in both asthma and COPD.[115]

In asthma, the PI3K–Akt–mTOR pathway plays a significant role in regulating allergic inflammation and airway hyperresponsiveness. Activation of PI3K-δ promotes the survival and activation of eosinophils, mast cells, and T helper 2 (Th2) lymphocytes, leading to increased production of type-2 cytokines such as interleukin-4, interleukin-5, and interleukin-13.[116] These cytokines contribute to mucus hypersecretion, airway edema, and bronchial hyperresponsiveness. In addition, mTOR signaling influences T-cell differentiation, favoring Th2 and Th17 responses that are implicated in severe and steroid-resistant asthma. Enhanced PI3K–Akt–mTOR activity has also been linked to airway smooth muscle cell proliferation and subepithelial fibrosis, key features of airway remodeling in chronic asthma.[117]

In COPD, the PI3K–Akt–mTOR pathway is strongly associated with neutrophilic inflammation, oxidative stress, and accelerated lung aging. Chronic exposure to cigarette smoke and environmental pollutants leads to sustained activation of PI3K signaling in airway epithelial cells and macrophages.[118] One of the most clinically important consequences of PI3K activation in COPD is corticosteroid resistance. Increased PI3K activity, particularly PI3K-δ, results in oxidative stress–mediated inhibition of histone deacetylase-2 (HDAC2), an enzyme required for the anti-inflammatory effects of corticosteroids.[119] Reduced HDAC2 activity diminishes corticosteroid responsiveness, explaining why many COPD patients exhibit poor response to conventional anti-inflammatory therapy.[120]

Activation of mTOR signaling in COPD contributes to impaired autophagy, cellular senescence, and abnormal immune responses.[121] Dysregulated autophagy in airway epithelial cells and macrophages leads to defective clearance of damaged proteins and organelles, exacerbating inflammation and tissue injury. The PI3K–Akt–mTOR pathway also influences macrophage polarization and neutrophil survival, thereby sustaining chronic inflammation and increasing susceptibility to infections, which are major triggers of COPD exacerbations.[122]

Given its central role in disease mechanisms, the PI3K–Akt–mTOR pathway has emerged as a promising therapeutic target. Selective PI3K-δ inhibitors have demonstrated anti-inflammatory effects in preclinical models of asthma and COPD by reducing cytokine production, inflammatory cell recruitment, and airway hyperresponsiveness.[123] Similarly, dual PI3K-δ/γ inhibitors have shown potential in suppressing both adaptive and innate immune responses. Inhibition of mTOR using rapamycin and related agents has also been explored, particularly for its effects on immune regulation and airway remodeling; however, systemic toxicity has limited its clinical application.[124]

To overcome safety concerns, inhaled PI3K inhibitors are being actively investigated as a strategy to deliver high drug concentrations directly to the airways while minimizing systemic exposure.[125] Early clinical studies suggest that inhaled PI3K-δ inhibitors may improve inflammatory profiles and restore corticosteroid sensitivity in selected patient populations. Nevertheless, challenges remain, including achieving sufficient selectivity, avoiding immunosuppression, and identifying patient subgroups most likely to benefit from PI3K-targeted therapy.[126]

The PI3K–Akt–mTOR signaling pathway plays a pivotal role in the pathogenesis of both asthma and COPD by regulating inflammation, immune cell function, airway remodeling, and corticosteroid responsiveness.[127] Its involvement in severe and treatment-resistant disease phenotypes highlights its importance as a novel therapeutic target. Continued research into isoform-selective inhibitors, inhaled drug delivery systems, and biomarker-based patient stratification may enable effective and safe targeting of this pathway, thereby addressing major unmet needs in the management of chronic airway diseases.

Emerging Kinase Targets

Despite advances in conventional and biologic therapies, asthma and chronic obstructive pulmonary disease (COPD) remain inadequately controlled in a substantial proportion of patients. The heterogeneity of disease mechanisms, persistent inflammation, airway remodeling, and corticosteroid resistance highlight the need for novel molecular targets beyond well-established pathways.[128] In this context, emerging kinase targets such as spleen tyrosine kinase (SYK), Bruton's tyrosine kinase (BTK), and epidermal growth factor receptor (EGFR) have gained increasing attention due to their central roles in immune signaling, airway inflammation, and structural changes in the respiratory tract.[129] Targeting these kinases offers promising opportunities to modulate disease processes more selectively and effectively.

SYK is a non-receptor tyrosine kinase that plays a crucial role in immune cell activation, particularly in cells expressing immunoreceptor tyrosine-based activation motifs (ITAMs), such as mast cells, B cells, macrophages, and neutrophils.[130]

In asthma, SYK signaling is a key mediator of IgE-dependent mast cell activation, leading to the release of histamine, leukotrienes, cytokines, and other inflammatory mediators that contribute to bronchoconstriction and airway inflammation. [131] Activation of SYK downstream of FcERI engagement amplifies allergic responses and sustains chronic inflammation. In COPD, SYK has been implicated in

innate immune responses, macrophage activation, and neutrophilic inflammation, which are central features of disease pathogenesis.[132] Preclinical studies have demonstrated that inhibition of SYK reduces inflammatory cell infiltration, cytokine production, and airway hyperresponsiveness, suggesting therapeutic potential in both allergic asthma and neutrophilic COPD phenotypes. The selective targeting of SYK may therefore provide a means to suppress immune-driven inflammation without broadly impairing host defense.[133]

Bruton's tyrosine kinase (BTK), another member of the Tec family of non-receptor tyrosine kinases, is best known for its role in B-cell receptor signaling and B-cell development. However, BTK is also expressed in various innate immune cells, including macrophages, neutrophils, and dendritic cells, where it regulates inflammatory signaling pathways.[134] In asthma, BTK contributes to allergic inflammation through modulation of B-cell activation, antibody production, and cytokine release. Emerging evidence suggests that BTK signaling may influence type-2 and non-type-2 inflammatory responses, making it relevant across different asthma endotypes. In COPD, BTK has been associated with innate immune dysregulation, chronic inflammation, and exaggerated responses to environmental insults such as cigarette smoke and air pollutants. Experimental models indicate that BTK inhibition can attenuate inflammatory mediator release and reduce immune cell recruitment to the airways. Given the clinical success of BTK inhibitors in hematological malignancies, repurposing or adapting these agents for chronic airway diseases represents a promising area of translational research, provided safety and long-term tolerability can be ensured.[135]

EGFR is a transmembrane receptor tyrosine kinase that plays a pivotal role in epithelial cell proliferation, differentiation, and survival.[136]] In the respiratory tract, EGFR signaling is critically involved in airway epithelial repair, mucus production, and structural remodeling. Dysregulated EGFR activation has been strongly linked to mucus hypersecretion, goblet cell hyperplasia, and subepithelial fibrosis hallmark features of both asthma and COPD, particularly in chronic bronchitis phenotypes.[137] Environmental factors such as cigarette smoke, pollutants, and respiratory infections can activate EGFR signaling, leading to persistent epithelial dysfunction and excessive mucus production. In asthma, EGFR contributes to airway remodeling and exacerbation severity, while in COPD it is associated with chronic cough, sputum production, and airflow limitation. Inhibition of EGFR signaling in experimental models has been shown to reduce mucus hypersecretion and attenuate airway remodeling, highlighting its potential as a therapeutic target. However, given the physiological importance of EGFR in tissue repair, careful modulation rather than complete inhibition may be necessary to avoid adverse effects.[138]

SYK, BTK, and EGFR represent a group of emerging kinase targets that address key pathogenic mechanisms not fully controlled by current therapies.[139] Unlike conventional anti-inflammatory treatments, which broadly suppress inflammation, kinase-targeted approaches offer the possibility of selectively interrupting disease-specific signaling pathways. This precision may be particularly valuable in patients with severe, refractory, or steroid-resistant asthma and COPD. Moreover, these kinases operate at the intersection of immune responses and structural airway changes, making them attractive candidates for disease-modifying interventions.[140]

Several challenges remain in translating these emerging kinase targets into clinical practice. Potential issues include off-target effects, systemic immunosuppression, and long-term safety concerns, especially in chronic diseases requiring prolonged treatment. Strategies such as inhaled delivery, improved kinase selectivity, and patient stratification based on molecular endotypes may help overcome these limitations. Continued preclinical and clinical research is essential to determine the optimal therapeutic window and to identify patient populations most likely to benefit.[141]

Emerging kinase targets such as SYK, BTK, and EGFR expand the therapeutic landscape of asthma and COPD by addressing immune dysregulation, airway inflammation, and remodeling at a molecular level. Their exploration reflects a shift toward precision medicine and offers promising avenues for improving outcomes in patients who remain inadequately controlled with existing treatment options.[142]

Challenges and future directions

The identification of kinase signaling pathways as key regulators in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD) has opened new avenues for therapeutic intervention.[143] Despite strong mechanistic rationale and promising preclinical evidence, the clinical translation of kinase-targeted therapies in chronic airway diseases has faced several challenges. Understanding these limitations is essential for guiding future research and optimizing the development of effective and safe kinase-based treatments.[144]

One of the major challenges in targeting kinases for asthma and COPD is the complexity and redundancy of intracellular signaling networks.[145] Kinase pathways such as MAPK, JAK–STAT, PI3K–Akt–mTOR, and Rho-kinase are highly interconnected, with significant cross-talk and compensatory mechanisms. Inhibition of a single kinase may lead to the activation of alternative signaling routes, thereby reducing therapeutic efficacy.[146] This redundancy partly explains the modest clinical benefits observed with some kinase inhibitors despite strong anti-inflammatory effects in preclinical models. Moreover, chronic airway diseases are heterogeneous, comprising multiple phenotypes and endotypes, each driven by distinct molecular mechanisms. As a result, a "one-size-fits-all" approach to kinase inhibition is unlikely to be successful.[147]

Another critical limitation is the issue of safety and tolerability. Protein kinases regulate fundamental cellular processes not only in diseased airways but also in normal tissues. Systemic inhibition of kinases may therefore result in off-target effects, immunosuppression, increased susceptibility to infections, cardiovascular complications, and metabolic disturbances. These concerns are particularly relevant in asthma and COPD, which often require long-term or lifelong treatment.[148] Past clinical trials of oral kinase inhibitors have reported dose-limiting toxicities that restrict their widespread use. This highlights the need for strategies that enhance airway selectivity while minimizing systemic exposure.

Drug delivery also represents a significant challenge in kinase-targeted therapy. Achieving sufficient drug concentration in the lungs without systemic toxicity is difficult, especially for small-molecule inhibitors designed for oral administration. [149] Inhaled delivery of kinase inhibitors has emerged as a promising solution, offering direct targeting of airway tissues and reduced systemic absorption. However, formulation challenges, drug stability, uniform lung deposition, and long-term safety of inhaled kinase inhibitors remain areas that require further investigation. Advances in aerosol technology and nanocarrier-based drug delivery systems may help overcome these barriers in the future.[150]

Another important obstacle is corticosteroid resistance, particularly in COPD and in non-type-2 asthma. While kinase inhibitors have been proposed as potential agents to restore steroid sensitivity, clinical evidence supporting this concept is still limited.[151] Identifying the specific kinase pathways responsible for steroid resistance and validating them as therapeutic targets remains an active area of research. Additionally, reliable biomarkers that can predict response to kinase-targeted therapy are currently lacking, making patient selection for clinical trials challenging.[152]

Despite these limitations, the future of kinase-based therapy in asthma and COPD remains promising. One key direction is the integration of precision medicine approaches. Advances in genomics, transcriptomics, and proteomics have enabled better characterization of disease endotypes and molecular signatures.[153] This knowledge can be leveraged to identify patient subgroups most likely to benefit from specific kinase inhibitors. Biomarker-guided therapy has the potential to improve treatment outcomes while reducing unnecessary exposure to ineffective drugs.

Combination therapy represents another important future strategy. Rather than targeting a single pathway, combining kinase inhibitors with existing therapies such as inhaled corticosteroids, bronchodilators, or biologics may provide synergistic benefits. Rational combination approaches may help overcome pathway redundancy, enhance anti-inflammatory effects, and reduce the required dose of individual agents, thereby improving safety profiles.[154]

The development of next-generation kinase inhibitors with improved selectivity and safety is also a critical research priority. Structure-based drug design, allosteric inhibitors, and targeted protein degradation technologies such as proteolysis-targeting chimeras (PROTACs) offer innovative approaches to modulate kinase activity with greater precision.[155] These emerging technologies may enable selective targeting of disease-relevant kinases while sparing normal physiological functions.

In conclusion, while kinase-targeted therapies hold substantial promise as novel treatments for asthma and COPD, multiple scientific, clinical, and translational challenges remain. Addressing issues related to pathway complexity, safety, drug delivery, patient heterogeneity, and biomarker development will be crucial for successful clinical implementation. Continued interdisciplinary research integrating molecular biology, pharmacology, and clinical science is essential to realize the full potential of kinase-based therapies. With ongoing advances in precision medicine and drug development technologies, kinase inhibitors are likely to play an increasingly important role in the future management of chronic airway diseases.[156]

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