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Kinase inhibitors in the treatment of obstructive pulmonary diseases

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Chronic pulmonary diseases, including chronic obstructive pulmonary disease (COPD) and asthma, are major causes of death and reduced quality of life. Characteristic of chronic pulmonary disease is excessive lung inflammation that occurs in response to exposure to inhaled irritants, chemicals, and allergens. Chronic inflammation leads to remodeling of the airways that includes excess mucus secretion, proliferation of smooth muscle cells, increased deposition of extracellular matrix proteins and fibrosis. Protein kinases have been implicated in mediating inflammatory signals and airway remodeling associated with reduced lung function in chronic pulmonary disease. This review will highlight the role of protein kinases in the lung during chronic inflammation and examine opportunities to use protein kinase inhibitors for the treatment of chronic pulmonary diseases.

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Introduction

Obstructive pulmonary disease

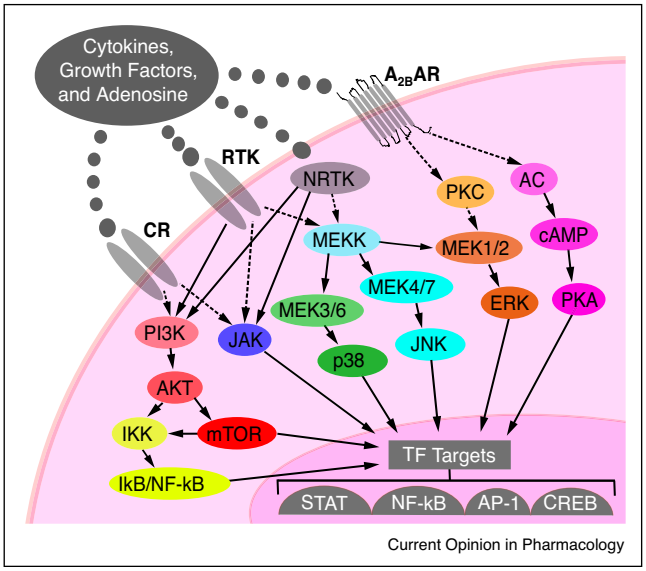
Asthma and chronic obstructive pulmonary disease (COPD) are the two most common chronic pulmonary diseases, affecting approximately 300 million and 250 million individuals worldwide, respectively, and causing 250 000 and 3.1 million deaths annually, respectively [1]. Asthma and COPD share symptoms of cough and dyspnea, the presence of chronic airway inflammation driven by exposure to inhaled immune stimuli, airway wall thickening, and the contribution of cellular senescence of airway epithelium. But the two diseases differ in the segment of the bronchial tree affected, the nature of the inflammation, the inciting immune stimulants, and their long-term course.

In asthma, the entire airway is involved while in COPD, pathologic changes are most pronounced in the small airways. Inflammation in asthma is typically allergen-driven and IgE-driven, and involves TH2 lymphocytes, mast cells and eosinophils [2]. In COPD, inflammation is driven by inhaled toxins and irritants, including those in tobacco smoke, non-tobacco biomass smoke, air pollution, and inhaled endotoxin, and is characterized by TH1 and TH17 lymphocytes, CD8+ lymphocyte predominance, neutrophil infiltration, and macrophage activation [3••]. Inhaled therapy with short-acting and long-acting beta agonists and corticosteroids are effective in both diseases. However, airway obstruction in asthma is usually more reversible with beta agonist therapy and more responsive to corticosteroid therapy than in COPD [4•]. Corticosteroids have been shown to reduce the rate of exacerbations, airway inflammation, and the rate of quality of life deterioration in COPD patients; however, an increased risk of pneumonia along with local and systemic adverse effects has also been observed [5]. Inhaled long-acting muscarinic agonists are more effective in COPD than asthma [6•]. More recently a growing number of injectable biologics targeting specific inflammatory pathways have become available for treating subclasses of asthma, but do not appear to be effective in most patients with COPD. It should be noted that asthma and COPD are both heterogenous diseases with a substantial overlap between the two, including a defined asthma-COPD overlap syndrome [7].

Inflammatory signals and protein kinases

The chronic release of inflammatory cytokines and growth factors from epithelial and immune cells enhances protein kinase signalling pathways and underlies the pathology of asthma and COPD. Several cytokines and growth factors are implicated in chronic pulmonary disease and include the interleukins (IL) IL-1β IL-4, IL-5, IL-6, IL-13, IL-17A, IL-27, IL-33, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) [8•,9–13]. Many protein kinases have been implicated in the signal transduction pathways linking inflammatory mediators and the hyper-contractility of airways, mucus hypersecretion, immune cell infiltration, and airway remodelling that leads to debilitating lung function observed in chronic pulmonary disease [14,15•]. Figure 1 summarizes protein

Figure 1



Kinase signalling pathways involved in obstructive pulmonary disease. Receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (NRTK; Abl, c-Src, Syk, Lyn) regulate mitogen-activated protein (MAP) kinases including the extracellular signal-regulated kinases (ERK), p38 MAP kinases, and c-Jun N-terminal Kinases (JNK). MAP kinases are activated by the MAP/ERK kinases (MEK1/2/3/4/6/7) which are regulated by the MEK kinases (MEKK). Cytokine receptors (CR) activate Janus kinases (JAK) and the phosphatidylinositide 3-kinases (PI3K), which regulate protein kinase B (AKT), mechanistic target of rapamycin (mTOR), and IκB kinase (IKK). Increased adenosine in the lungs of asthma and COPD patients activates the A2B adenosine receptor (A_{2B}AR), which regulates ERK through protein kinase C (PKC) and protein kinase A (PKA) through adenylate cyclase (AC) production of cyclic 3′5′-adenosine monophosphate (cAMP). Transcription factor (TF) targets include signal transducer and activator of transcription proteins (STAT), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1 (AP-1), and cAMP response element-binding protein (CREB).

kinases that are involved in the pathology of asthma and COPD.

Protein kinases involved in obstructive lung disease

Inflammatory signals mediate the pathology of obstructive lung disease through the activation of protein kinase activity [16]. Cytokine receptors (CR) and receptor tyrosine kinases (RTK) at the plasma membrane communicate cytokine and growth factor signals through several mitogen-activated protein (MAP) kinases, phosphatidylinositide 3-kinases (PI3K), and Janus kinases (JAK). Inflammation causes increased adenosine generation, which via activation of G-protein coupled adenosine receptors (A_{2B}AR) and downstream kinase signalling cascades, contributes to the pathologic changes in asthma and COPD [17]. Gene expression associated with inflammation and tissue remodelling is regulated predominantly by a subset of transcription factors that include nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1 (AP-1), cAMP response element-binding protein (CREB), and signal transducer and activator of transcription (STAT) proteins [18].

MAP kinases that respond to cellular stress, such as the c-Jun N-terminal kinases (JNK) and p38 MAP kinases, have long been implicated in mediating inflammatory signals relevant to lung disease [16,19]. However, to date, none of the JNK or p38 MAP kinase inhibitors have shown efficacy in clinical trials and are dose limiting due to unwanted toxicity and side effects. Targeted inhibition of pro-inflammatory p38 MAP kinase substrates such as mitogen-activated protein kinase activated protein kinase-2 (MAPKAPK-2 or MK2) may overcome toxicity issues associated with p38 inhibitors and treating chronic pulmonary disease [20•]. MK2 is a mediator of inflammatory signals such as TNF-α, IL-6, and IL-1β so MK2 mediators might further reduce the inflammatory response [21]. Eynott *et al.* provided evidence that targeted inhibition of JNK could mitigate allergen-induced inflammation and proliferation of airway epithelial and smooth muscle cells [22]. While one phase II clinical trial evaluating the JNK inhibitor Tanzisertib for treating idiopathic pulmonary fibrosis ended due to lack of efficacy, no JNK inhibitors are currently being tested for asthma or COPD.

Mitogen activation of the extracellular signal-regulated kinases (ERK) MAP kinases in airway smooth muscle (ASM) cells stimulates cell proliferation and subsequent airway remodelling associated with asthma [23]. This was supported by studies that showed that serum from atopic asthma patients enhanced the expression of cyclin D1, which increases proliferation of human ASM cells [24]. Activated ERK signalling enhances cell proliferation by increasing the expression of cyclin D1.

There is evidence that protein kinases associated with deregulated angiogenesis contribute to the progression of chronic lung disease including COPD [25•]. Angiogenic factors such as cytokines and growth factors that are released as a result of obstructive pulmonary disease progression leads to the stimulation of direct and indirect proangiogenic markers that generate and stabilize new blood vessels [26•]. This microvascular dysfunction leads to re-modulation and inflammation of the bronchi. Recent studies suggest that targeted inhibition of inflammation-mediated activation of the receptor tyrosine kinases vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor-2 (FGFR-2) reduces angiogenesis associated with lung remodelling in COPD [26•]. Similarly, a small clinical study suggested that inhibition of PDGF and the related c-Kit receptor tyrosine kinase with Masitinib is effective in severe corticosteroid-dependent asthma [27].

In COPD patients, protein kinases play an important role in the loss of tissue architecture by enhancing degradation of the extracellular matrix by proteinases such as matrix metalloproteinases-9 (MMP-9) [28]. Proinflammatory triggers including allergens, cigarette smoke, bacterial lipopolysaccharides (LPS), interleukins (IL-17 and IL-1β), and other inflammatory signals that induce an oxidative stress response, activate MAP kinases and PI3K signalling, which enhances AP-1-mediated expression of MMP-9 [22,29,30,31•]. Another key regulator of inflammatory signals is the NF-κB transcription factor. Targeted inhibition of the inhibitor of κB kinase (IKK) is a potential approach to prevent NF-κB translocation to the nucleus and inflammatory gene expression. The status of past and current clinical trials evaluating protein kinase inhibitors for treatment of asthma or COPD is listed in Table 1.

Targeted inhibition of kinases in lung and immune cells

Epithelial cells

Inflammation-inducing chemicals and irritants disrupt airway epithelium and stimulate aberrant kinase signaling both within epithelial cells. Increased expression of the receptor tyrosine kinase EGFR, and its ligands have been reported in the epithelium of asthmatic airways [39,40]. Activation of epithelial EGFR can lead to corticosteroid-insensitivity and plays a key role in airway remodeling, mucus secretion, and inflammation. The EGFR-tyrosine kinase inhibitors, Erlotinib and Osimertinib, attenuate EGFR signaling and expression of IL-6 and IL-8 in a dose-dependent manner in human bronchial epithelial cells *in vitro* stimulated with house dust mite (HDM) allergen [41]. However, Osimertinib was more effective than Erlotinib at inhibiting EGFR auto-phosphorylation and downstream PI3K/AKT and STAT3 signaling [41]. In COPD patients, lung fibrosis can be caused by the epithelial-mesenchymal transition (EMT). Giacomelli *et al.* recently determined that activation of the A_{2B} adenosine receptor (A_{2B}AR) decreased the expression of epithelial marker E-cadherin while increasing the mesenchymal markers vimentin and N-cadherin [42•]. Upon further investigation, these studies found that PKA signaling can counteract EMT while ERK signaling can promote EMT. The use of PKA or ERK inhibitors, which enhanced or inhibited the EMT, respectively, suggested that targeted manipulation of kinase signaling could be a mechanism to control EMT related to COPD [42•].

Goblet cells

The mucus secreting goblet cells normally provide protection to the epithelial layer of cells but, inappropriate mucus secretion can contribute to chronic cough and sputum production that reduces quality of life in patients with chronic pulmonary disease. Cytokines released during lung inflammation lead to an increase in the number of goblet cells causing enhanced mucus production, which reduce the airway luminal diameter and increase airway resistance. The goblet cell number increases due to basal cell differentiation shifting from a ciliated epithelial cell fate toward a goblet cell fate. Strategies to prevent goblet cell hyperplasia or persistent goblet cell differentiation (GCD) include pharmacological inhibition of kinase signaling pathways [43]. Several signaling pathways regulate goblet cell differentiation; however, the EGFR family and downstream PI3K and ERK signaling pathways are all viewed as

Table 1

Clinical trials evaluating kinase inhibitors for treatment of asthma or COPD

Target	Compound	Stage	Disease	Route	Current status	Identifier
p38 MAPK	Dilmapimod	Phase 2	COPD	Oral	No results posted	NCT00564746
	Losmapimod	Phase 2	COPD	Oral	Discontinued: not effective [32]	NCT02299375
			COPD	Oral	Discontinued: not effective [33]	NCT01541852
	PH-797804	Phase 2	COPD	Oral	No results posted	NCT00559910
	PF-03715455	Phase 2	Asthma	Inhaled	Terminated	NCT02219048
		Phase 2	COPD	Inhaled	Terminated	NCT02366637
	AZD7624	Phase 2	COPD	Inhaled	Discontinued: not effective [34]	NCT02238483
		Phase 2	Asthma	Inhaled	No results posted	NCT02753764
p38 and Src	RV-568	Phase 2	COPD	Inhaled	No results posted	NCT01475292
PI3K	GSK2269557	Phase 2	COPD	Inhaled	Completed: acceptable safety profile for progression to larger study [35]	NCT02130635
		Phase 2	COPD	Inhaled	Completed: progression to phase IIb study supported [36•]	NCT03189589
	RV-1729	Phase 1	COPD	Inhaled	No results posted	NCT02140346
RTK	BIBW 2948	Phase 2	COPD	Inhaled	Not effective [37]	NCT00423137
	Masitinib	Phase 3	Asthma	Oral	Ongoing	NCT03771040
		Phase 3	Asthma	Oral	Ongoing	NCT01449162
	Imatinib	Phase 2	Asthma	Oral	Completed: decreased airway hyperresponsiveness, mast-cell counts, and tryptase release [38]	NCT01097694
c-Kit/Abl JAK1	Imatinib Itacitinib	Phase 2	Asthma	Oral	Recruiting	NCT04129931

candidates for inhibition in preventing persistent GCD [43]. Unfortunately, an EGFR inhibitor (BIBW 2948) failed to show efficacy in reducing epithelial mucin in COPD clinical trials [37]. While these studies postulated that higher doses may improve efficacy, there is also a strong probability for increased adverse drug events.

The role of Rho kinases in airway hyperresponsiveness and inflammatory events has prompted their examination as potential drug targets to treat asthma [44]. A recent study by Zhang *et al.* found that Rho-kinase inhibitors can attenuate airway mucus hypersecretion and inflammation via the downregulation of IL-13 and AP-1 signaling in a model of HDM-induced asthma [45•]. The studies also provided evidence that inhibition of Rho-kinase was as effective as dexamethasone in mitigating asthma pathology in this model, suggesting it could be another treatment option in cases of corticosteroid resistance. Rho kinase inhibitors are currently being evaluated for the treatment of ocular disorders [46].

Airway smooth muscle cells

Inflammatory signals in asthma and COPD lead to an increase in ASM cell proliferation that contributes to basal narrowing of airway lumens and bronchoconstriction which combine to cause airway obstruction. Increased ASM cell mass is primarily driven by growth factors such as PDGF and EGF in cooperation with cytokines and chemokines [47]. Since ERK signalling through the AP-1 transcription factor is a central regulator of PDGF and EGF expression, AP-1 plays a key role in mediating inflammatory signals associated with tissue remodelling in asthma and COPD [48,49]. In a study by Defnet *et al.*, an ATP-competitive ERK inhibitor that blocks all ERK signalling was compared to a novel function-selective ERK inhibitor for inhibition of ASM cell proliferation through AP-1 [50•]. This study found that both inhibitors effectively inhibited PDGF-mediated ASM cell proliferation, AP-1 promoter activity, collagen production, and IL-6 secretion in ASM cells. Additionally, the function-selective inhibitor allowed some ERK activity, which potentially reduced selective pressure to develop drug resistance, and caused fewer changes in protein expression compared to the ATP-competitive inhibitor suggesting there would be less off-target effects [50•].

Alternatively, studies have taken a polypharmacology approach to inhibit kinases for the treatment of patients that have corticosteroid-resistant airway inflammation COPD. Knobloch *et al.* evaluated a narrow-spectrum protein kinase inhibitor (NSKI) referred to as RV1088 that reduces inflammatory signals by targeting p38 MAPK and the c-Src, Syk, and JAK tyrosine kinases [51]. The authors found that RV1088 was able to suppress corticosteroid-sensitive and –insensitive cytokine production in *in vitro* models of COPD and are more effective than single kinase inhibitors of p38 MAPK, Src, or Syk alone. However, off-target effects of these kinase inhibitors will need further investigation as the promiscuity of some of the current kinase inhibitors has limited their clinical applications. A phase II clinical trial (NCT01867762) evaluating the efficacy and safety of another NSKI (RV568) that targets p38 MAPK and c-Src for treatment of moderate to severe COPD has yet to post results.

Immune cells

Targeted inhibition of kinases in immune cells has potential to mitigate airway remodeling and hyperresponsiveness associated with obstructive pulmonary disease. Mast cells, T-cells, eosinophils, and neutrophils all play key roles in the inflammatory response seen in obstructive pulmonary diseases [2]. Mast cell activation involves the RTK c-Kit, non-receptor tyrosine kinases, such as Lyn and Syk, PKC, and ERK MAP kinase signaling [52]. PI3K isoforms play a prominent role in the differentiation, proliferation, survival, and cytokine production of immune cells [53] and pharmacological inhibition of PI3K suppresses T-helper cell cytokine production and eosinophil infiltration in mice challenged with ovalbumin [54]. Similarly, inhibition of the JAK-STAT signaling pathway suppresses the activity of neutrophils, mast cells, eosinophils, and T-cells [55,56].

The significant role of the JAK-STAT signaling pathway in the expression of cytokines and interferons involved in pulmonary disease makes it an attractive therapeutic target. Previous work utilized an orally administered JAK1/2 inhibitor in a mouse model of asthma that showed promising physiological changes, but due to systemic side effects, it did not move into patients [57,58]. To address this setback, Dengler *et al.* synthesized an inhalable small molecule JAK1 inhibitor called iJak-381 for local JAK1 inhibition in the lung [55]. This inhibitor shows local inhibition of ovalbumin-induced JAK1 activity in rodents with no observed changes in systemic JAK1 activity. Furthermore, iJAK-381 suppressed STAT6 and IL-13, reduced airway hyperresponsiveness in mice, and was more potent than corticosteroids in suppressing neutrophil-driven inflammation caused by clinically relevant allergens [55]. As indicated above, new clinical trials evaluating oral JAK1 inhibitors for asthma therapy began recruiting patients at the end of 2019. Time will tell whether systemic side effects due to oral delivery will limit the efficacy of these compounds.

Conclusions and future directions

Currently, obstructive lung disease treatments focus on counteracting episodes of bronchospasm and reducing allergic inflammation through corticosteroids, which, although such strategies have shown success, they neither cure nor prevent disease progression [59•,60•,61]. Kinase inhibitors could provide a more targeted therapeutic option to meet this unmet need.

The effectiveness of protein kinases inhibitors will likely depend on delivery methods that limit off-target effects. The ubiquitous functions of protein kinases in many cell types have prompted new approaches to deliver inhibitors through an inhaled route and reduce systemic off-target effects when the drugs are taken orally. Promising clinical results with Nemiralisib (GSK2269557), a PI3Kδ isoform-selective inhibitor, support the efficacy of the inhaled route of delivery [36•]. Bach *et al.* have identified potent pan-JAK inhibitors that show good retention in the lung following intra-tracheal administration [62]. Importantly, these compounds reduced LPS-induced lung inflammation in a mouse model and had poor oral bioavailability suggesting reduced unwanted systemic effects [62].

Mitigation of off-target effects of kinase inhibitors requires new approaches to block kinase functions associated with disease but preserve functions that may be desirable. Most protein kinases have dozens of substrates with some involved in promoting a response such as proliferation or inflammation while other substrates are inhibiting that response. To date, nearly all small molecule protein kinase inhibitors approved for clinical use compete with ATP in the catalytic site, which blocks all enzymatic activity. Not only does this approach block desirable kinase functions but given the highly conserved nature of the ATP binding site on kinases, ATP-competitive inhibitors are generally non-specific and affect the activity of other kinases. In addition, cells invariably develop resistance to ATP-competitive kinase inhibitors. One approach to mitigate off-target effects and the development of drug resistance is to identify compounds that are function-selective. Currently, this approach is being used to develop inhibitors of the ERK and p38 MAP kinases [50•,63•,64•]. These approaches use structural information on the interactions between kinases and substrates and apply computational predictions and experimental testing to identify compounds that disrupt specific interactions between the kinase and substrates involved in disease. In the context of obstructive pulmonary disease, the goal would be to identify compounds that block pro-inflammatory signals that cause tissue damage and remodeling while preserving beneficial anti-inflammatory signals.

Alternatively, polypharmacology approaches could mitigate tissue remodelling in chronic obstructive pulmonary disease. Targeted inhibition of signalling pathways that regulate key transcription factors involved in the pathology of asthma and COPD may provide therapeutic benefits. For example, ERK activation of AP-1 promotes increased ASM cell proliferation, while activation of the retinoic acid receptor (RAR) is a negative regulator of AP-1 and ASM cell proliferation [65,66]. Loss of retinoic acid (RA) signaling has been linked to hypertrophy and hypercontractility of ASM cells, suggesting defects in RA may contribute to obstructive pulmonary disease [67]. Thus, combining ERK inhibitors and RAR agonists could effectively control ASM cell proliferation and airway remodeling in asthma.

Obstructive lung diseases pose many therapeutic challenges due to the diversity of inflammatory signals released and cell types affected. Further, chronic inflammation leads to airway remodeling and exacerbation of airflow obstruction. However, protein kinases play a key role in regulating transcription factors that modulate the proliferative and secretive functions of airway cells. As such, appropriately designed and targeted kinase inhibitors may mitigate airway remodeling and pathology of obstructive pulmonary disease. Further research on the basic mechanisms involved in the pathology of obstructive lung disease will help identify the most appropriate kinase targets, the best approach to design selective inhibitors, and the development of efficacious drugs to combat obstructive lung diseases.

Credit author statement

Amy E. Defnet, Jeffery D. Hasday, and Paul Shapiro all contributed to the writing, review, and editing.

Conflicts of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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