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Phosphoinositide 3-kinase δ (PI3Kδ) in respiratory disease.

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Abstract

Defining features of chronic airway diseases include abnormal and persistent inflammatory processes, impaired airway integrity and function, and increased susceptibility to recurrent respiratory infections. Phosphoinositide 3-kinases (PI3K) are lipid kinases, which contribute to multiple physiological and pathological processes within the airway, with abnormal PI3K signalling contributing to the pathogenesis of several respiratory diseases. Consequently, the potential benefit of targeting PI3K isoforms has received considerable attention, being viewed as a viable therapeutic option in inflammatory and infectious lung disorders. The class I PI3K isoform, PI3Kδ is of particular interest given its multiple roles in modulating innate and adaptive immune cell functions, airway inflammation and corticosteroid sensitivity. In this mini-review, we explore the role of PI3Kδ in airway inflammation and infection, focusing on oxidative stress, ER stress, histone deacetylase 2 (HDAC2) and neutrophil function. We also describe the importance of PI3Kδ in adaptive immune cell function, as highlighted by the recently described Activated PI3K Delta Syndrome (APDS), and draw attention to some of the potential clinical applications and benefits of targeting this molecule.

Abbreviations

Chronic obstructive pulmonary disease (COPD)

Bronchial epithelial cell (BEC)

Cystic fibrosis transmembrane conductance regulator (CFTR)

Alveolar macrophage (AM)

Phosphoinositide 3-kinase (PI3K)

Activated PI3K Delta Syndrome (APDS)

Phosphatidylinositol-3,4,5-trisphosphate ($PI(3,4,5)P_3$)

Phosphatidylinositol-3-phosphate (PI3P)

Histone deacetylase 2 (HDAC2)

Reactive oxidative species (ROS)

Cigarette smoke (CS)

Nuclear erythroid-2 related factor (Nrf2)

Protein kinas B (AKT)

Ovalbumin (OVA)

Lipopolysaccharide (LPS)

Interleukin-6/8/17 (IL-6/IL-8/IL-17)

Vascular endothelial growth factor (VEGF)

Airway hyper-responsiveness (AHR)

Endoplasmic Reticulum (ER)

Immunoglobulin E/M/A/G (IgE/IgM/IgA/IgG)

Tumor necrosis factor α (TNFα)

Neutrophil elastase (NE)

Metalloproteinase-9 (MMP-9)

Activation-induced cytidine deaminase (AID)

Cytomegalovirus (CMV)

Epstein-Barr virus (EBV)

Monocyte-derived macrophages (MDMs)

Bacillus Calmette Guerin (BCG)

Introduction

Inspired oxygen is distributed throughout the lungs via the branching airways , diffusing across the alveolar membrane into the circulating red blood cells. Environmental toxins and pathogens also enter the lungs, potentially inciting inflammatory reactions and/or establishing intra-pulmonary infections. Airway diseases such as chronic obstructive pulmonary disease (COPD) and bronchiectasis are characterized by persistent and damaging airway inflammation, both compounded by and perpetuating respiratory infection. COPD is the most prevalent chronic respiratory disease globally, and is triggered by inhaled insults including smoke (from cigarettes and biomass fuels) and pollution. It is characterized by progressive, non-reversible airflow limitation, associated with persistent airway inflammation. Bronchiectasis (which may co-exist with COPD) is associated with airway damage due to severe or recurrent infection (often in the context of impaired adaptive immunity) or aberrant inflammation, and is characterized by airway damage and dilatation with resulting impairment of lung defense.

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Bronchial epithelial cells (BECs) sit at the interface between external and internal environments and are thus the initial target of inhaled insults, which initiate processes such as TLR signalling, oxidative stress and endoplasmic reticulum (ER) stress (Nyunoya, van t'Wout,). Consequences include enhanced secretion of chemokines and cytokines (Mio, Yanigasawa), initiating/perpetuating aberrant inflammatory cell accumulation (Hoenderdos Condliffe); airway cell apoptosis (Henson); and mucus hyper-secretion and CFTR dysfunction, which contribute to impaired ciliary function and small airway luminal obstruction (Gao). Ciliary dysfunction (Yasghi and Dolovich) and diminished anti-microbial peptide release from damaged epithelial cells is compounded by decreased alveolar macrophage (AM) phagocytic capacity (for both invading pathogens and apoptotic cells) (Donnelly and Barnes), together contributing to both the recurrent and damaging disease exacerbations that punctuate the disease course, and to microbiome disturbance (Sze, Wang). A vicious cycle is established, with infection further perpetuating airway inflammation. BEC-, AM- and pathogen-derived mediators all recruit neutrophils (Hoendereos Condliife), which secrete a wide range of mediators

(such as proteases, most classically neutrophil elastase (NE), and reactive oxygen species (ROS)) that contribute to COPD pathogenesis (Hoenderdos Condliffe). Finally, perturbed adaptive immunity (particularly B cell dysfunction) is associated development of bronchiectasis, and there is increasing evidence (eg abundant lymphoid follicles and T cell airway infiltration) that B and T cell dysfunction is also associated with COPD (reviewed in Caramori), although the significance of these findings is not yet fully established.

Symptomatic treatments for airway disease such as bronchodilators have limited efficacy and little impact on disease progression. There is evidence that anti-inflammatory effects of oral glucocorticoids are of benefit in COPD exacerbations (Niewoehner, Woods), the use of longterm inhaled corticosteroids is currently recommended only for certain COPD endotypes such frequent exacerbators (Hurst, Magnussen) or those with eosinophilia (Bafadel). Antibiotics with anti-inflammatory function such as macrolides have been shown to be beneficial in both COPD (Taylor) and bronchiectasis (Hill), but longterm outcomes are unknown, and this strategy confers the risk of promoting anti-microbial resistance (Taylor, Hill). Therapies directed at neutrophil-derived products such as NE and myeloperoxidase have limited efficacy (Nordenmark, Stockley) except in highly specific circumstances such as individual with α1-antitrypsin deficiency, who are more susceptible ton NE-mediated damage and who may derive limited benefit from regular treatment with α1-antitrypsin (Parr) There is thus an ongoing need for novel treatments which can modulate the multiple cellular targets contributing to airway disease.

Airway defences may be further compromised by maladaptive innate and adaptive immune responses. The regulation of these events is complex, with various signalling pathway networks mediating downstream events initiated by ligation of cell surface receptors. The phosphoinositide 3-kinase (PI3K) pathway regulates responses across multiple cell types and mediates pleiotropic functions in both normal physiology and disease pathophysiology. PI3K signalling is important in regulating airway epithelial function, myeloid cell recruitment and activation, and B and T lymphocyte development and effector function. As such, aberrant PI3K signalling can thus contribute to a range of

respiratory diseases (Figure 1) depending on the inciting injury, target cell types, and the precise PI3K isoform affected. This mini-review will focus on the impact of disturbances of PI3Kδ function, in particular in the setting of COPD and a recently described immune deficiency, the Activated PI3K Delta Syndrome (APDS).

Brief overview of Class I PI3Ks

Class I PI3Ks, the most extensively studied group of lipid kinases, exist as heterodimeric complexes comprising p110α, β, δ or γ catalytic subunits, with each isoform named according to the catalytic subunit present; their activity is controlled by several regulatory subunits (p85, p55 and p50 regulate p110α, β and δ, whilst p110γ is separately regulated by p101 or p84). They share the ability to phosphorylate the 3rd hydroxyl group of membrane-localised phosphoinositides, generating a network of signalling secondary messengers. The best characterised, phosphatidylinositol-3,4,5-trisphosphate ($PI(3,4,5)P_3$) and phosphatidylinositol-3-phosphate (PI3P), facilitate the recruitment and activation of several downstream effector proteins, (e.g Protein Kinase B/Akt) that coordinate numerous signalling, and regulated intracellular vesicular trafficking processes, thereby controlling functions such as cell growth, migration and survival (reviewed in detail in (1)). The four Class I PI3K isoforms play distinct roles within the airway and elsewhere, and their tissue distribution varies accordingly. PI3Kα and PI3Kβ are widely distributed, whereas PI3Kγ and PI3Kδ are predominantly but not exclusively expressed within leukocytes, playing important roles in both innate and adaptive immunity.

PI3Kδ and airway inflammation

Pharmacological studies plus genetic evidence, including the recently described APDS, have implicated dysfunctional PI3Kδ signalling in airway inflammation, and studies exploring the potential therapeutic benefit of targeting PI3Kδ have yielded encouraging results. For example, either aerosolised or systemically administered dual selective PI3Kδ/γ inhibitors reduced inflammatory cell infiltrates in murine models of inflammatory lung disease, including airway neutrophilia induced by inhaled cigarette smoke (CS) or

lipopolysaccharide (LPS) and ovalbumin (OVA)-induced asthma, demonstrating the potential effectiveness of both delivery routes in these settings (2, 3). Furthermore, selectively targeting PI3Kδ using the isoform specific inhibitor, IC87114, diminished allergen-induced airway inflammation and airway hyper-responsiveness (AHR) (4), with PI3Kδ kinase-dead mice yielding similar results in comparable models (5, 6). More recently, a clinical study exploring the efficacy of a new inhaled PI3Kδ inhibitor (GSK2269557) within a COPD patient cohort demonstrated reduced sputum IL-8 and IL-6 levels (7), further highlighting the anti-inflammatory potential of targeting this molecule in chronic lung disease. Depending on the balance of the cell types and functional responses affected by aberrant PI3Kδ signalling, airway inflammation or respiratory infection (or both) may result (Figure 1).

PI3Kδ, oxidative stress and histone deacetylase 2

Enhanced oxidative stress is characteristic of chronic lung diseases, with reactive oxygen species (ROS) production influenced by external environmental factors such as CS, and by the interplay of genetic abnormalities (e.g. cystic fibrosis) with inflammatory insults (8). PI3Ks have been associated with ROS generation and oxidative stress at multiple levels (Figure 2A): augmenting ROS produced by normal cellular metabolism, infection and/or inflammatory cell activation, being activated in response to ROS, and regulating antioxidant expression under certain conditions via nuclear erythroid-2 related factor (Nrf2) (9). Importantly, activation of PI3Kδ has been shown to reduce the activity of histone deacetylase 2 (HDAC2) (Figure 2A), which modifies DNA-binding proteins to suppress inflammatory gene expression in response to CS-induced oxidative stress, hence perpetuating inflammatory processes in this setting (10). COPD patients with neutrophilic airway inflammation typically respond poorly to steroid therapy (11), a phenomenon attributed in part to a reduction in HDAC2 expression and activity (12). Importantly, restoration of HDAC2 activity and consequently corticosteroid sensitivity, has been demonstrated both in in vitro and in vivo models of COPD following direct targeting of PI3Kδ (10, 12, 13). HDAC2 activity in alveolar macrophages was found to be reduced in moderate to severe asthmatics (14), in whom steroid resistance is also a frequent challenge (15), particularly when there is persistent

lymphocyte activation or a prominent neutrophilic component (16). PI3Kδ is highly expressed within these cell types, and recent work demonstrates that T-cell derived cytokine generation can be suppressed by PI3Kδ inhibition, with multiple T cell lineages targeted (17). Similar observations have also been demonstrated specifically in the context of COPD and asthma, with PI3Kδ inhibition broadly reducing lymphocyte-derived cytokines such as IL-17 (Figure 2A) (18, 19). IL-17 is elevated within the airways of COPD patients and severe asthmatics, coordinating neutrophilic inflammation in these diseases (20, 21). Given that IL-17 has been shown to reduce HDAC activity and glucocorticoid sensitivity in bronchial epithelial cell lines (22), that similar effects observed in macrophages are associated with oxidative stress and PI3Kδ activity (23), and that corticosteroids have little anti-inflammatory effect on COPD lung neutrophils (24), it is plausible that targeting PI3Kδ would not only alleviate detrimental inflammation observed within lung disease, but also improve/restore glucocorticoid sensitivity.

PI3Kδ and Endoplasmic Reticulum (ER) stress

Although primarily expressed in leukocytes, PI3Kδ can be detected in non-immune cells albeit at much lower levels (25, 26). Furthermore, PI3Kδ expression is inducible under certain inflammatory conditions, for example in TNFα-stimulated endothelial cells (25). Increased PI3Kδ expression was observed in asthmatic versus healthy volunteer airway epithelial sample in human bronchial biopsies, although the expression was predominantly nuclear rather than cytoplasmic (18); the significance of this nuclear localisation is unclear. Might airway epithelial PI3Kδ play a role in regulating airway inflammation in response to infection? This hypothesis is supported by recent studies demonstrating that LPS exposure promotes PI3Kδ activation (27), and that PI3Kδ-dependent regulation of aspergillus-induced airway inflammation occurs via the induction of ER stress pathways (Figure 2A) (28). Several studies highlight the importance of ER stress in driving inflammation in both asthma and COPD, particularly in the context of oxidative stress (28-30), with prolonged activation contributing to airway remodelling (31). Whilst the interplay between airway inflammation, ER stress and PI3Kδ remains poorly understood, ER

stress and PI3Kδ activity are both associated with steroid-resistance within lung disease via oxidative stress-dependent processes (23, 30), hence targeting PI3Kδ may regulate adverse inflammatory processes through multiple mechanisms.

PI3Kδ and aberrant neutrophil function in COPD

Neutrophils are of key importance in pathogen clearance but are also a prominent feature of airway inflammation in chronic lung diseases, where they are thought to exert detrimental effects (32). PI3K signalling influences several key neutrophil functions including chemotaxis, oxidative burst and survival (33-35). Neutrophils from COPD patients (36) and elderly individuals (37) exhibit less accurate chemotaxis, a defect that is reversed by PI3Kδ or PI3Kγ inhibition (36). Although the precise function of PI3Kδ in this context has not been fully elucidated, its role is likely to be significant given its known role in regulating neutrophil trafficking and directional movement (35, 38). Neutrophil activation and degranulation also play important roles in the pathogenesis of chronic airway diseases, with dysregulated ROS, neutrophil elastase (NE) and matrix metalloproteinase-9 (MMP-9) contributing to lung tissue damage (Figure 2A) and disease severity in COPD (39). In vitro studies reveal that NE and MMP-9 release is PI3K-dependent (40), and although not solely attributed to PI3Kδ, it is likely to involve PI3Kδ in certain contexts given that TNFα-induced NE release can be reduced by PI3Kδ inhibition (41). Furthermore, specific targeting of PI3Kδ suppressed ROS release from neutrophils obtained from both stable and exacerbating COPD patients (42), providing further evidence to support the targeting of PI3Kδ to manage unfavourable neutrophilic activity in this disease. The outcomes of clinical trials of PI3Kδ inhibition in COPD (and other airway diseases) are eagerly awaited.

Lessons from the Activated PI3Kδ Syndrome (APDS)

The recently described Activated PI3KDelta Syndrome (APDS) provides further evidence that aberrant PI3Kδ activity can drive lung disease, in particular recurrent respiratory infections and airway damage (43). The initial reports described mutations (E1021K, E525K, N334K) in the p110δ catalytic subunit

of PI3Kδ (43, 44); further p110δ mutations have been identified, as have splice site mutations which lead to loss of exon 11 of the p85 regulatory subunit (45, 46). All of the mutations described to date affect the interaction of the catalytic and regulatory subunits (47), and all are gain-of-function leading to enhanced PI3Kδ signaling (for example there is both enhanced constitutive and stimulated activation of the AKT/PKB and mTOR pathways), Whilst there are some differences in the clinical manifestations in APDS1 (p110δ mutations) and APDS2 (p85 mutations), respiratory infections are near universal in both settings, and there is an extremely high incidence of bronchiectasis (48, 49). Augmented PI3Kδ activity has been confirmed both in vitro and in patient-derived B and T lymphocytes (43, 44), with clinical and laboratory evidence suggesting aberrant PI3Kδ signalling in myeloid cells also (43, 50).

B Lymphocytes in APDS

Whilst PI3Kδ has been shown to have a subtle influence on B cell development in mouse models (51), APDS patients have greatly increased circulating transitional (immature) B cells (43, 44), an unexpected observation that is currently unexplained but which may serve as a biomarker for aberrant PI3Kδ activation. Enhanced PI3K signalling in mature B cells impairs antibody class switching (from IgM to IgA/IgG) (52), and this may be due at least in part to the role of PI3Kδ in regulating the expression and function of AID (activation-induced cytidine deaminase) (53). The majority (although not all) APDS patients have increased levels of circulating IgM and many also have low circulating IgG/IgA levels (48, 49), consistent with a defect in class switch recombination (Figure 2B); in limited studies, defective class switching in APDS-derived cells was improved by PI3Kδ inhibition (44), supporting a causal link. The clinical manifestations of APDS are dominated by respiratory infections that are closely associated with antibody deficiency (principally encapsulated bacteria Streptococcus pneumoniae and Haemophilus influenzae). These recurrent infections (including otitis media, bronchitis and pneumonia) lead to a high incidence of end-organ damage including hearing loss and bronchiectasis, further impairing host defence and increases infection susceptibility. However, the near-universal respiratory infections and high incidence of bronchiectasis in APDS do not correlate precisely with antibody

deficiency (for example, higher frequency of reduced IgG but lower incidence of bronchiectasis in APDS2 (49) versus APDS1 (48)), suggesting that antibody-independent B cell properties or other host defence cellular dysfunction may play a role (see below); alternatively or additionally, perturbed airway cell function with enhanced oxidative and ER stress as described above may contribute to diminished lung defences.

T Lymphocytes in APDS

Patients with APDS also experience an excess of respiratory infections with viruses such as Adenovirus, Echovirus, Coxsaskievirus and Respiratory Syncytial Virus (48), and also have a marked propensity to develop systemic herpes viral infections (with CMV and EBV in particular: (43, 44)), marking APDS as a combined rather than just a B cell immunodeficiency disorder. APDS is associated with pronounced circulating T cell abnormalities, including hyper-proliferation, differentiation to terminal effector cells associated with dysregulated cytokine production, T cell senescence (44) and increased sensitivity to activation-induced apoptosis (43, 54) (Figure 2B). Excessive viral infections may also reflect that fact that many viral pathogens subvert host cell PI3K signalling to support replication (55), hence constitutively enhanced PI3K activation may tip the balance in favour of the pathogen. Whether enhanced PI3Kδ signalling in airway epithelial cells promotes viral entry and/or replication in APDS is currently unknown, but it is interesting to note that increased airway cell PI3Kα expression is COPD results in increased susceptibility to influenza viral infection (56).

Myeloid cells in APDS

Myeloid dysfunction has been little studied in APDS, with initial (but limited) studies in neutrophils in response to soluble agonists suggesting at least partial preservation of function (43). However, with reference to the data of Sapey et al. (36) implicating PI3Kδ in the impaired chemotactic ability of COPD neutrophils, the directional migration of APDS neutrophils has not been explored, and the incidence of COPD in APDS is unknown (it is a rare disease with many patients dying young). However, monocytes-derived macrophages (MDMs) from a single APDS patient demonstrated impaired ability to kill

Bacillus Calmette Guèrin (BCG) in vitro, with macrophage mycobactericidal activity restored by the isoform-selective PI3Kδ inhibitor IC87114 (50). Of interest, instances of significant local infection following BCG vaccination have been reported following BCG vaccination in APDS patients (48) (Figure 2B). Impaired alveolar macrophage function in APDS could contribute to defects in handling respiratory bacterial pathogens, as has been demonstrated in COPD (57), although inhibition of PI3Kδ did not restore phagocytic ability of COPD macrophages (58). Further studies of myeloid cell signalling and function in APDS would be of considerable interest.

Concluding remarks

PI3K signalling has a fundamental role in various airway responses, coordinating immune cell effector functions and airway epithelial stress responses. Considerable progress has been made in deciphering the multiple roles of PI3Kδ within lung disease [Figure 1], with much insight gained from the recently described APDS. Dysregulated PI3Kδ activity contributes to lung disease pathology through numerous mechanisms: potentiating inflammation, modulating epithelial and inflammatory cell function, and increasing susceptibility to viral and bacterial respiratory infections. PI3Kδ specific inhibitors are already in development for the treatment of COPD (19) and APDS (59), with the prospect to inhibit both systemic targets (Rao: eg to limit neutrophil recruitment) and (with inhaled therapy, Cahn) to deliver maximal inhibition to the airway epithelial cells and recruited inflammatory cells. Furthermore, combining PI3Kδ inhibitors with existing (eg macrolides, which also target a range of inflammatory signals, and corticosteroids, thereby inhibiting both corticosteroid-sensitive and corticosteroid-resistant pro-inflammatory pathways) and novel therapies (eg combined Pi3Kγ/δ inhibitors, to maximize the inhibitory effect on both innate and adaptive immunity) may enhance treatment effectiveness, particularly in the context of corticosteroid resistance, and may provide opportunities to tailor therapies for individual patient needs.

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Declarations of interests

We have no competing interests to disclose.

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Author contribution statement

A.M.C developed the framework for the review. C.A.S and A.M.C contributed equally to the writing of the manuscript and the preparation of the figures.

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Figure 1. Abnormal PI3K signalling within the lung. Aberrant PI3Kδ signalling can contribute to a range of respiratory diseases, depending on the inciting stimulus and the cell types affected. Dysfunction of the same targets es (including airway epithelial cells, myeloid cells, and B and T lymphocytes) may contribute to infection or inflammation, or both may occur simultaneously, determining the disease phenotype.

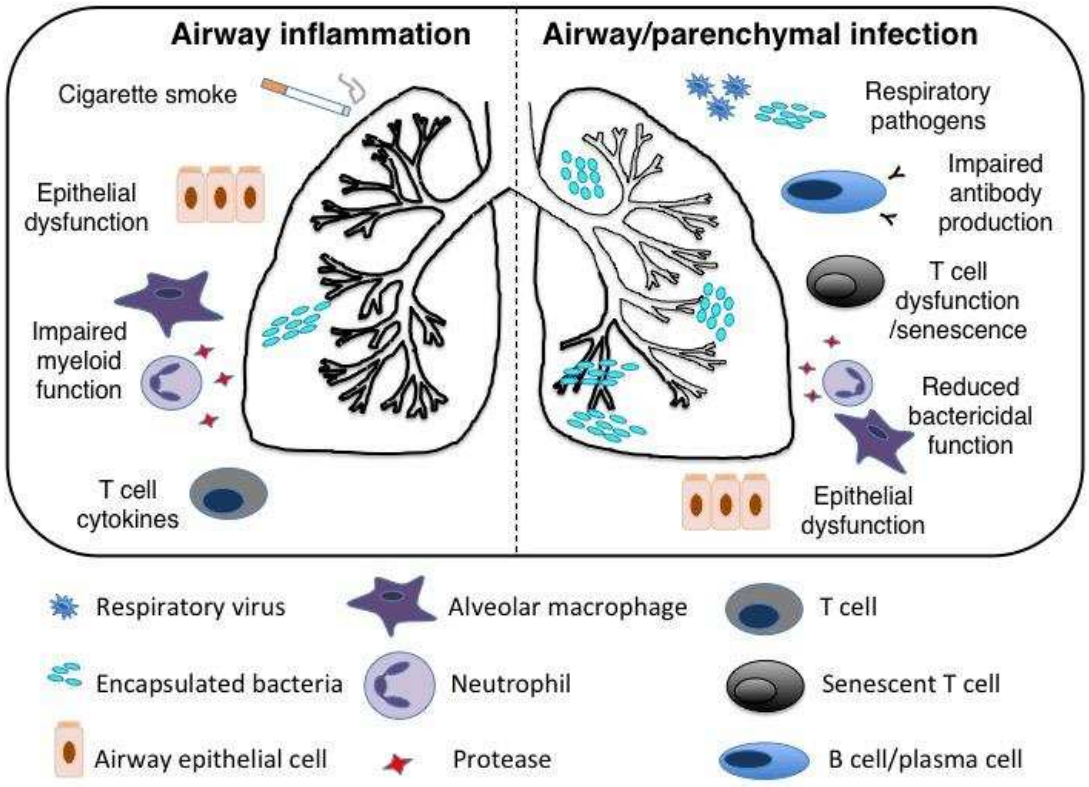

Figure 2. The multiple roles of PI3Kδ in COPD and APDS

A. COPD. PI3Kδ activity is elevated within the COPD airway, being further enhanced by oxidative stress arising through exposure to cigarette smoke and respiratory pathogen infection (I). Enhanced PI3Kδ activity within the airway epithelium, macrophages and T cells reduces HDAC2 activity (II), impairing corticosteroid effectiveness, enhancing proinflammatory cytokine generation and inflammatory cell recruitment. Enhanced PI3Kδ activity and oxidative stress within the epithelium results in the activation of ER stress processes (III), an important pathological driver of COPD. **B. APDS.** Epithelial PI3Kδ activity (I) and T cell dysfunction/senescence (II) promote viral entry, replication and epithelial damage. Failure of antibody class-switching (III) and impaired myeloid function (IV), compounded by viral-induced damage, leads to increased bacterial infection (V) and further airway damage, with pro-inflammatory cytokines produced by multiple cell types propagating dysregulated inflammation.