

Mucus hypersecretion in asthma: intracellular signalling pathways as targets for pharmacotherapy

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Purpose of review

Airway mucus hypersecretion is a pathophysiological feature of asthma and, in many patients, contributes to morbidity and mortality. Although current pharmacotherapy is effective in patients with stable disease, severe asthma is poorly treated, and there is no specific treatment for the hypersecretion. Consequently, identification of potential targets for pharmacotherapy of hypersecretion in asthma is warranted. This review identifies intracellular signalling pathways as rational targets for treatment of excessive airway mucus production.

Recent findings

The inflammatory mediators and the associated intracellular signalling pathways underlying development of goblet cell hyperplasia, an index of mucus hypersecretion, are becoming ever clearer, and include T-helper type 2 (Th2) cytokines, in particular interleukin (IL)-9 and IL-13, as well as IL-1 β , tumour necrosis factor (TNF)- α and cyclooxygenase (COX)-2. IL-9 may act predominantly via calcium-activated chloride channels (CLCAs), IL-13 via STAT-6 and FOXA2, TNF- α via nuclear factor (NF)- κ B, and IL-1 β via COX-2. Epidermal growth factor receptor (EGF-R) and FOXA2 appear to be convergent pathways for a number of mediator signals, with EGF-R up-regulated in the airways of asthmatic patients.

Summary

Although many potential intracellular signalling pathways have been identified as possible targets for pharmacotherapy of airway mucus hypersecretion in asthma, the EGF-R and Th2 cytokine pathways offer the greatest potential for inhibition of excessive mucus production.

Keywords

airway, epidermal growth factor, goblet cell, IL-13, mucin

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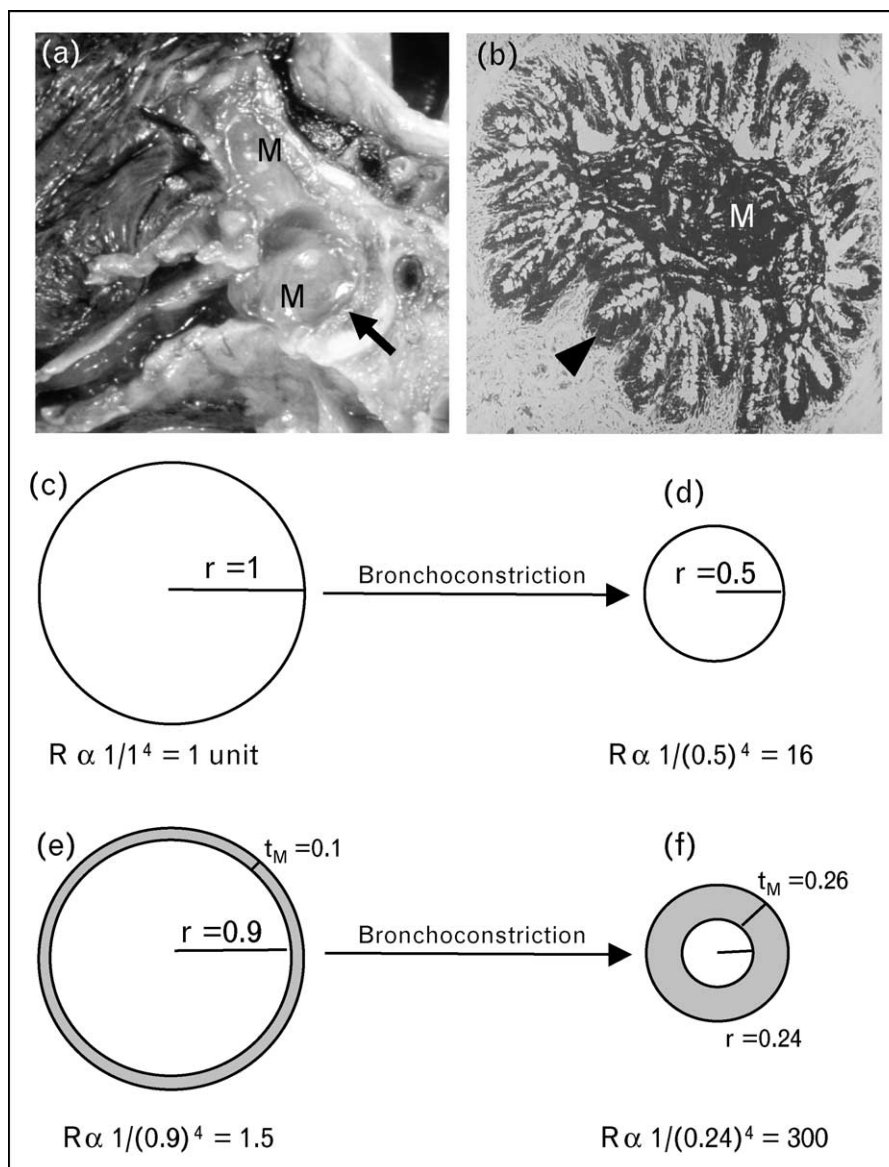
Introduction

Asthma is a respiratory condition that afflicts roughly 300 million people worldwide [1]. Prevalence is highest in developed countries, including the UK (>15%), USA (~11%) and Australia (~15%) [1], where approximately 1–2% of the healthcare budget is spent on asthma annually [2]. There is a positive correlation between healthcare costs and asthma severity [3]. Patients with severe disease and frequent exacerbations represent just 10–20% of sufferers, but account for up to 50% of costs. Mucus hypersecretion contributes strongly to morbidity and mortality during exacerbations (Fig. 1), with current treatments, including ‘mucoactive’ drugs, having minimal efficacy [4,5]. Consequently, there is a need for new pharmacotherapy that addresses this key pathophysiological feature of asthma.

Mucus is a liquid gel that lines the inner surface of the airways and forms the first line of defence against inhaled insult. It protects the underlying airway epithelium from harm by trapping and promoting the removal of foreign debris [6]. However, mucus can become pathological due to chronic hypersecretion during asthma. The associated loss of clearance allows mucus to accumulate and obstruct the airways, causing respiratory distress and sometimes mortality [7]. Release of inflammatory mediators during asthma leads to excessive mucus production via activation of various intracellular signalling pathways [4].

Following an introduction to mucins and the clinical impact of mucus hypersecretion in asthma, the present article focuses on how inflammatory mediators and their signalling pathways lead to chronic mucus hypersecretion

Figure 1 Impact of mucus hypersecretion on airway obstruction in asthma



(a) Mucus plugging in *status asthmaticus*. Necropsy specimen of a lung removed from a patient who died of an acute severe asthma attack showing mucus (M) blocking an airway (arrow), cut in longitudinal section. (b) Interaction between mucus and bronchoconstriction in acute severe asthma. Histology of an intrapulmonary airway (cut in transverse section) showing the epithelium (arrow head) thrown into folds by airway smooth muscle contraction. The remaining portion of lumen is filled with mucus (M). (c-f) Application of Poiseuille's law to the interaction between mucus and bronchoconstriction. Equating the respiratory tract to tubes, the law can be adapted to describe the impact of mucus on airflow in bronchoconstricted airways. Thus, resistance to flow (R) is proportional to the radius of the airway (r) raised to the fourth power, which in (c) equals 1 unit. (d) Reducing the radius by half (as a result of bronchoconstriction) increases airflow resistance to 16 units. (e) The presence of a thin film of mucus, with thickness (t_M) 0.1 units, around the internal perimeter of the airway has little significant impact on resistance (increased by 0.5 units compared with c). (f) Bronchoconstriction of this mucus-containing airway causes an exponential increase in airflow resistance (300 units – compare with d).

in asthma, and how these pathways can be targeted for pharmacotherapy.

Airway mucins

Mucus is a complex dilute aqueous solution of many components and exists as a liquid bi-layer [8]. Particles and microbes are trapped in the viscous, sticky upper gel

layer and are removed from the airways by mucociliary clearance [6]. The mucus, along with trapped debris, can either be swallowed or coughed up as sputum once it reaches the throat. The latter usually occurs during respiratory diseases when mucus production is excessive.

Mucins are glycoproteins that provide mucus with its viscoelasticity, and constitute up to 2% by mass [9]. A

single mucin monomer consists of a peptide backbone with hundreds of O-linked carbohydrate side-chains and can weigh up to 500 kDa [10]. The peptide backbone is encoded by a specific group of mucin (MUC) genes [11] and contains numerous tandemly repeated serine-rich and threonine-rich regions that serve as glycosylation sites [12].

Examples of airway mucins include MUC2, MUC4, MUC5AC and MUC5B [13[•]]. MUC5AC is primarily expressed in airway goblet cells, whereas mucous cells in submucosal glands predominantly express MUC5B [14[•]]. Both MUC5AC and MUC5B can be up-regulated by inflammatory mediators. However, asthma patients tend to produce MUC5AC-rich mucus [15], possibly because the mediators involved activate signal pathways that favour MUC5AC gene expression.

Profile of airway inflammation in asthma

Asthma is a condition characterized by airway hyper-responsiveness to a variety of 'triggers', including environmental allergens, leading to reversible airway obstruction. In asthmatic nonsmokers, inflammatory remodelling is largely limited to the large and small airways, with the lung parenchyma usually unaffected [16].

Classically, inflammation in asthma involves CD4⁺ T-lymphocyte activation. Activated CD4⁺ cells release interleukin (IL)-4, IL-9, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor (TNF)- α , but little IL-2 or interferon (IFN)- γ . This T-helper type 2 (Th2) profile of cytokine release is characteristic of allergic inflammation [17]. Chemokines, including regulated on activation, normal T-cell-expressed and secreted (RANTES), eotaxin and monocyte chemoattractant protein (MCP)-1, are also up-regulated [18]. These agents are involved in further recruitment of immune cells, particularly eosinophils. Neutrophilic inflammation is absent in mild-to-moderate cases but present in very severe asthma [19[•]]. Oedema and inflammatory cell infiltration may thicken the reticular basement membrane by up to 300% [5,20]. Together with mucus hypersecretion, these changes can severely limit airflow through the respiratory tract.

Clinical impact of mucus hypersecretion in asthma

Mucus is produced by submucosal glands and goblet cells scattered along the airway epithelium, and both sources are affected in patients with asthma. Goblet cell hyperplasia (Fig. 2) and submucosal gland hypertrophy are pathophysiological features of asthma, although many patients do not display the latter [6,21,22]. It is possible that the airway epithelium in asthmatics has an inherent

capacity to generate goblet cells. For example, airway epithelial side population cells, akin to stem/progenitor cells, readily generate *in vitro* a multilayered and differentiated epithelial layer, including MUC5AC-producing cells, and these side population cells are markedly elevated in number in asthmatic airways compared with nonasthmatic airways [23[•]]. The goblet cell hyperplasia and gland hypertrophy substantially increase the amount of mucus-producing tissue, and the goblet cell increase may, in particular, contribute to asthma deaths [22].

Airway obstruction by mucus plugs is a feature of asthma and appears to develop as a result of mucus hypersecretion and increased plasma exudation [24]. Airway mucus of asthmatic patients is mixed with inflammatory exudates to form highly viscous plugs that are difficult to remove by cough [24]. These plugs are commonly found during necropsies of patients who die in *status asthmaticus* (Fig. 1). Aside from mucins, mucus plugs contain plasma proteins (e.g. serum albumin), DNA and proteoglycans [25,26]. Plasma exudates increase luminal liquid volume and trigger mucus secretion. In addition, albumin and DNA may become entangled with mucin polymers, leading to synergistic increases in mucus viscosity [27]. Lastly, newly released mucins often remain 'tethered' to goblet cells in fatal asthma [5,28]. This phenomenon is unique to asthma and may be attributed to its distinct inflammatory profile, with eosinophils the predominant cell type [28]. Eosinophil products are unlikely to cleave mucins, which is in contrast to proteases released by neutrophils in chronic bronchitis [28,29].

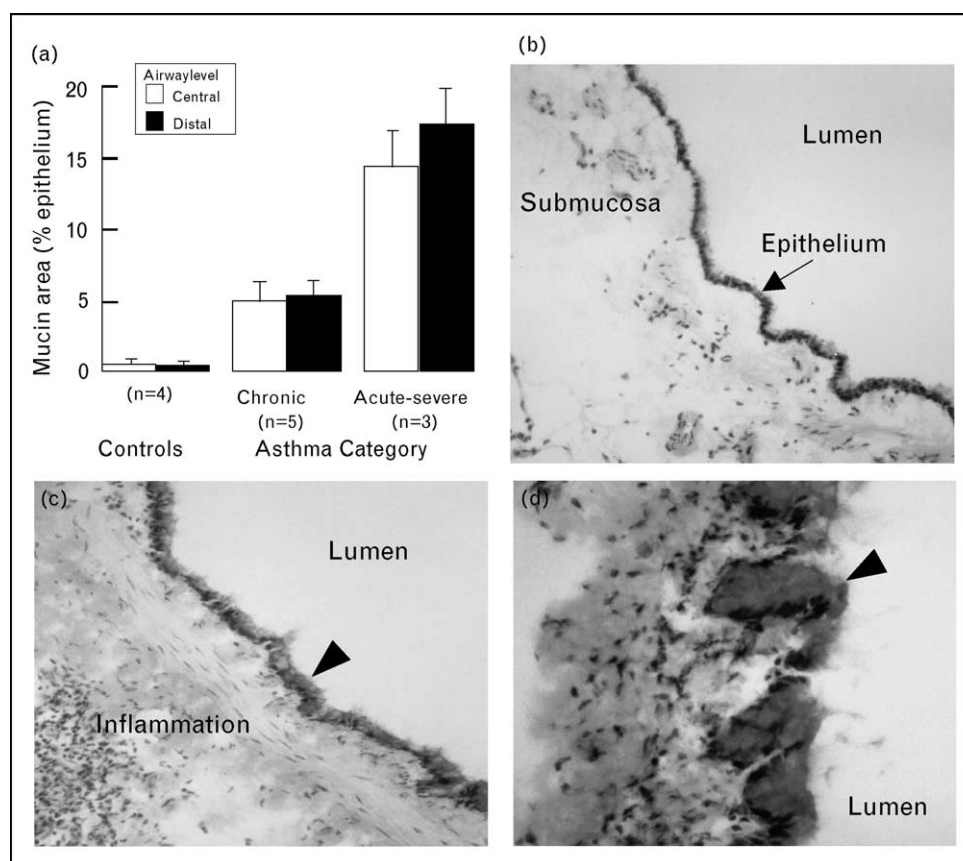
In addition to physically blocking airways, mucus can also contribute to airway hyper-responsiveness (Fig. 2). Hyper-responsiveness is a clinical feature of asthma and refers to the amplification of airway resistance during bronchoconstriction, part of which may be due to the presence of luminal mucus (Fig. 1) [4].

Inflammatory mediators signalling pathways in asthma and mucus hypersecretion

Mucin gene expression, with consequent increases in mucin synthesis, can be up-regulated by inflammatory mediators released during chronic asthma. The most relevant of these are the cytokines released by Th2 cells, namely IL-9 and IL-13 [30–32]. Other mediators discussed herein include TNF- α , IL-1 β and ligands of the epidermal growth factor receptor (EGF-R).

Th2 cytokine signalling

IL-9 and IL-13 are the 'classical' Th2 cytokines that up-regulate mucus production in asthmatic patients [32,33]. IL-13 is a crucial and potent mediator of mucus secretion, as neither IL-9 nor any factor produced by Th1 cells can induce production of mucus in the absence of IL-13

Figure 2 Goblet cell hyperplasia in asthma

(a) Quantification of airway goblet cell mucin in asthma. The area of stained goblet cell mucin was measured at necropsy in histological sections of lungs from asthmatic patients and controls without respiratory disease. The amount of mucin was expressed as the proportion of mucin to total epithelial layer. Redrawn using data in [22]. (b–d) Experimental airway goblet cell hyperplasia in rats. Brown Norway rats were sensitized to ovalbumin followed by an inhalation challenge with either saline (control: b) or ovalbumin (c and d) every third day for 21 days, after which lung sections were stained for mucin with periodic acid-Schiff. (b) Low-power image of control lung showing normal submucosa and thin, poorly stained epithelium. (c) Low-power image of lung from a sensitized and challenged rat showing submucosal inflammation (including eosinophilic infiltration) and goblet cell hyperplasia, as indicated by substantial epithelial staining (arrow head). (d) High-power image of part of c showing pronounced intracellular mucin.

[34,35]. Complete IL-13 blockade is required to abolish mucus production, with partial blockade only causing a minor reduction in mucin staining of mouse airway epithelial cells [34].

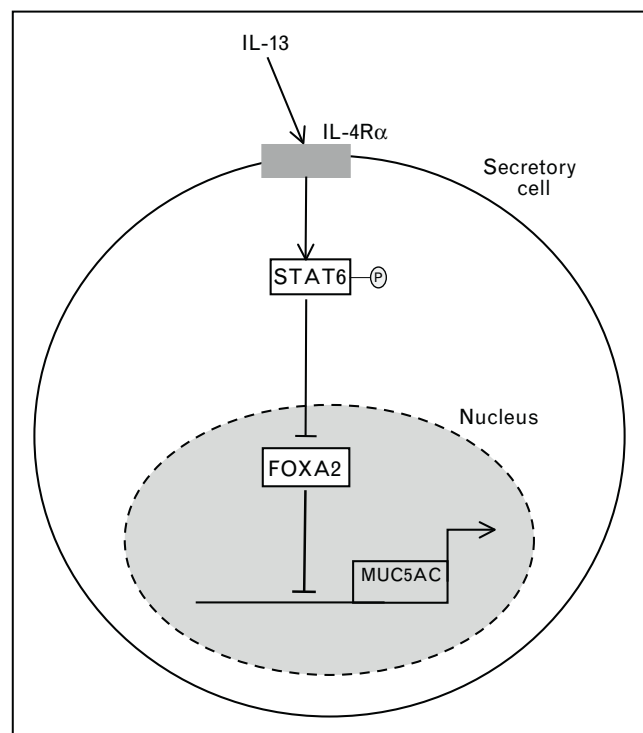
IL-13-mediated production of mucus is dependent on both the IL-4R α receptor and signal transducer and activator of transcription 6 (STAT6) [36]. Engagement of IL-13 with its receptor leads to phosphorylation of STAT6, with down-regulation of forkhead box A2 (FOXA2) (Fig. 3) [36]. In nonstimulated cells, FOXA2 inhibits MUC5AC transcription and its expression prevents development of goblet cell hyperplasia [37].

IL-13-mediated mucus production may occur partly through a mechanism involving transforming growth factor (TGF)- β 2. IL-13 increased release of TGF- β 2 by cultured epithelial cells from both asthmatic and control patients [38]. A neutralizing antibody against

TGF- β 2 partially suppressed IL-13-induced expression of mucin. Further studies are needed to clarify the link between the two, but TGF- β 2 is required for tissue repair during asthma and may, therefore, contribute to hypersecretion by promoting goblet cell metaplasia.

The SLC26A4 (PDS) gene encodes a multispanning transmembrane protein known as pendrin and was recently identified as an IL-13-inducible gene [39^{••}]. Pendrin is an anion transporter expressed on the apical membrane of bronchial epithelial cells and may contribute to mucus hypersecretion by regulating chloride transport. Enforced pendrin expression using a Sendai virus vector led to mucus hypersecretion in a mouse model of asthma [39^{••}].

IL-9 may contribute to mucus hypersecretion in asthma by up-regulating the human calcium-activated chloride channel hCLCA1 [40]. Thus, hCLCA1 may be partly

Figure 3 Regulation of MUC5AC gene transcription by IL-13

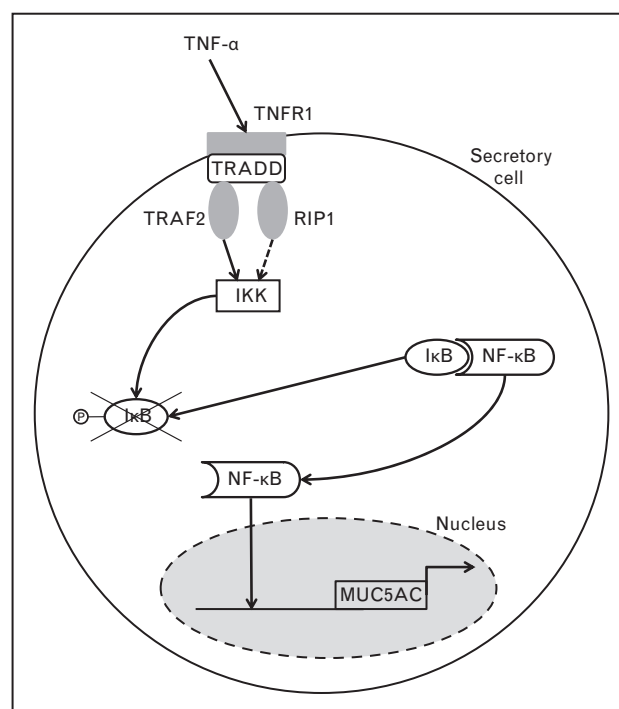
Interaction of IL-13 with IL-4R α causes phosphorylation (P) of STAT6. Expression of FoxA2, a transcriptional repressor of MUC5AC, is suppressed by STAT6, which allows IL-13 to increase MUC5AC expression and stimulate airway remodelling.

responsible for mucus overproduction in asthma, as well as regulating mucus volume by mediating chloride and water outflow. Mucus hydration may increase viscosity by facilitating osmotic movement of plasma exudates into the airway lumen [40].

TNF- α signalling

TNF- α is released by both Th2 cells and neutrophils and may, therefore, be relevant to mucus hypersecretion in severe asthma. Neutrophils are recruited to the airways by an IL-8-like chemoattractant synthesized by airway epithelial cells in response to IL-13 stimulation [41]. TNF- α stimulates a broad spectrum of responses and occasionally causes apoptosis by activating intracellular caspases [42]. However, ligation of TNF- α to its receptor usually leads to activation of the transcription factor nuclear factor (NF)- κ B [43].

TNF- α -mediated mucus production is dependent on I κ B kinase (IKK) and NF- κ B both *in vitro* and *in vivo* [30]. Exposure of epithelial cell cultures to TNF- α led to nuclear translocation of NF- κ B, followed by mucin synthesis (Fig. 4) [30,44]. NF- κ B is subject to additional regulation within the nucleus by other kinases, including

Figure 4 Signalling pathways involved in TNF- α -mediated mucin synthesis

The major receptor for TNF- α is TNFR1. In nonstimulated cells, the nuclear localization signal on NF- κ B is masked by I κ B. Binding of TNF- α induces receptor trimerization, followed by recruitment of multiple signalling proteins to the cytosolic domains of TNFR1. TRADD functions as a platform for recruitment of downstream signalling molecules, including RIP1 and TRAF2. Both RIP1 and TRAF2 initiate downstream signalling by activating I κ B kinase (IKK). IKK phosphorylates (P) I κ B, marking it for degradation (X) and allowing NF- κ B to enter the nucleus. The interaction between RIP1 and IKK has yet to be identified and is indicated by a dashed arrow. I κ B, inhibitor of NF- κ B; RIP1, receptor-interacting protein 1; TNFR1, TNF receptor 1; TRADD, TNFR1-associated death domain protein; TRAF2, TNF-receptor-associated factor 2.

the p38 subset of mitogen-activated protein kinases (MAPKs) [43].

TNF-receptor-associated factor 2 (TRAF2) appears to be required for IKK recruitment to TNFR1-associated death domain protein (TRADD) (Fig. 4). IKK comprises two catalytic subunits (IKK α and IKK β) and a single regulatory subunit (IKK γ) [43]. Phosphorylation of two serine residues within the IKK β activation loop [45] is needed for IKK activation. However, the mechanisms that link TNFR1 and IKK activation remain unclear. One possible mechanism may involve the transfer of ubiquitin between RIP1 and IKK γ , as IKK depends on ubiquitination for its activity [46].

Involvement of NF- κ B

NF- κ B regulates a variety of genes, including MUC genes. Sequence analyses of MUC2 and MUC5AC promoter clones revealed the presence of NF- κ B response

elements within them [47]. Mouse models of allergic lung inflammation have confirmed that NF- κ B is crucial for mucus production [48]. Events downstream of NF- κ B are likely to include acetylation of histones, followed by recruitment of general transcription factors and machinery required for mRNA transcription and processing (e.g. RNA polymerase and spliceosomes).

Signalling by IL-1 β and cyclooxygenase-2

IL-1 β released by the asthmatic bronchial epithelium [49] and activated macrophages contributes to mucus hypersecretion through indirect and direct mechanisms. Indirectly, IL-1 β induces mucin synthesis by activating CD4⁺ cells, and by promoting inflammatory cell recruitment via up-regulation of expression of cell surface adhesion molecules (e.g. ICAM-1, VCAM-1) on the vascular endothelium [50]. Conversely, IL-1 β increases MUC5AC in normal human tracheobronchial epithelial (NHTBE) cells via a direct mechanism involving cyclooxygenase (COX)-2 induction and prostaglandin (PG)E₂ release (Fig. 5) [51]. IL-1 β -stimulated COX-2

synthesis appears to be dependent on both ERK and p38 MAPK cascades. Inhibitors of these pathways suppress COX-2 expression and subsequent mucin synthesis [52].

Of the four prostaglandin E receptors (EP), only EP-2 and EP-4 are essential for IL-1 β /PGE₂-mediated mucus production by NHTBE cells. EP-2 and EP-4 are transmembrane G-protein-coupled receptors that activate adenylate cyclase following ligand engagement. Subsequent activation of cAMP-dependent protein kinases (e.g. protein kinase A) initiates signalling to downstream transcription factors (Fig. 5) [53]. IL-1 β - and PGE₂-induced MUC5AC synthesis can be abolished by inhibitors of PKA [51]. Thus, IL-1 β -induced expression of MUC5AC depends on COX-2-generated PGE₂ and triggering of cAMP-PKA-mediated signalling pathway via EP-2 and EP-4 receptors [51,52].

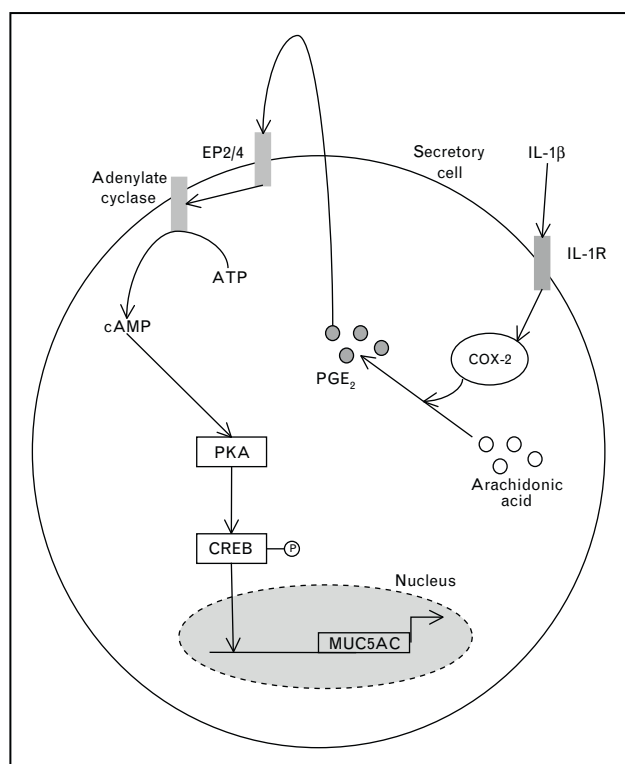
Additionally, IL-1 β regulates mucus volume and pH. IL-1 β stimulates secretion of chloride ions and subsequent mucus hydration by up-regulating chloride channels, including the cystic fibrosis transmembrane conductance regulator (CFTR) and hCLCA1 [54]. In parallel, water absorption from the airway lumen is suppressed by inhibiting epithelial sodium channel (ENaC)-mediated influx of Na⁺. IL-1 β encourages secretion of HCO₃⁻ ions as part of a homeostatic mechanism that attempts to correct acidification of mucus during inflammation [54]. Thus, IL-1 β simultaneously regulates three elements of mucus (i.e. volume, pH, mucin content) and thereby plays an important role in airway homeostasis by improving mucociliary clearance [54].

Epidermal growth factor receptor-mediated signalling

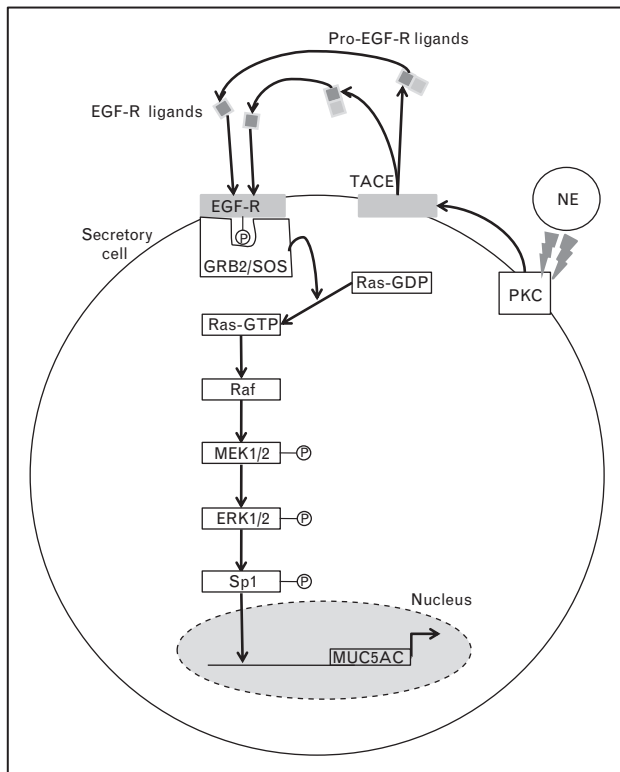
Epidermal growth factor receptor is a 170-kDa receptor tyrosine kinase expressed on the surface of many cell types. EGF-R and its ligands are up-regulated during inflammatory conditions such as asthma, with a positive correlation between EGF-R expression and goblet cell hyperplasia [55]. Activation of EGF-R tyrosine kinases *in vivo* increases MUC5AC expression and induces hyperplasia via a Ras-Raf, MEK, ERK pathway (Fig. 6) [56]. Additionally, EGF-R signalling down-regulates FOXA2 [57]. FOXA2 may, therefore, be a point of convergence for multiple pathways that regulate goblet cell differentiation. EGF-R may play a critical role in mucus hypersecretion during asthma, as tyrosine kinase inhibitors completely block MUC5AC expression and goblet cell increase in experimental models of asthma [58].

Neutrophilia occurs in severe asthma and contributes to hypersecretion by releasing inflammatory cytokines (e.g. TNF- α) and proteolytic enzymes (e.g. elastase). TNF- α directly stimulates mucin synthesis, and up-regulates

Figure 5 Molecular mechanisms involved in IL-1 β -mediated mucin expression



IL-1 β interaction with IL-1R leads to COX-2 induction and PGE₂ synthesis. COX-2 catalyses the conversion of arachidonic acid to the prostanoid precursor PGH₂ (not shown). PGE₂ is synthesized via the action of PGE synthase on PGH₂. PGE₂ activates MUC5AC transcription via a cAMP-PKA-mediated signalling pathway. CREB must be phosphorylated (P) by PKA before it can bind to DNA. CAMP, cyclic adenosine monophosphate; CREB, cyclic adenosine monophosphate response element binding protein; IL-1R, interleukin-1 receptor.

Figure 6 Up-regulation of MUC5AC synthesis by neutrophil elastase

Neutrophil elastase release in severe asthma triggers induction of membrane-bound PKC. Pro-EGF-R ligands are cleaved by TACE following activation by PKC. GRB2 is recruited to phosphotyrosine residues on EGF-R via its SH2 domain, and recruits SOS via SH3 domains. SOS exchanges GDP for GTP, activating Ras. Ras then activates (via phosphorylation, P) the MAPK cascade, triggering MUC5AC production. GBR2, growth factor receptor-bound protein 2; SOS, Son of Sevenless.

expression of EGF-R both *in vitro* and *in vivo* [58]. Neutrophil elastase initiates ligand-dependent receptor activation through a mechanism that involves protein kinase C (PKC) induction, followed by activation of

TNF- α -converting enzyme (TACE) and cleavage of pro-EGF-R ligands (e.g. TGF- α) (Fig. 6) [59]. TACE inhibitors (e.g. TAPI-1) and siRNA knockdown of TACE expression suppressed HNE-stimulated TGF- α production [59], suggesting that HNE may not act on TGF- α directly, as reported elsewhere [60].

Novel pharmacotherapy

The intracellular signalling pathways outlined above provide opportunities for targeted pharmacotherapy (Table 1, [61–66,67^{••},68,69[•]]). Calcium-activated chloride channels have previously attracted considerable interest, but do not appear to be essential for development of goblet cell hyperplasia [70]. At present, the most promising targets are those involved in EGF-R and Th2 cytokine signalling, and agents that act on these pathways are discussed below.

Targeting the epidermal growth factor receptor pathway

During asthma, activation of EGF-R tyrosine kinases appears central to induction of mucin synthesis and goblet cell hyperplasia [71]. As described above, tyrosine kinase inhibitors prevent activation of EGF-R and suppress mucin gene transcription in animal models. Administration of these compounds may, therefore, reduce morbidity caused by mucus plugging of asthmatic airways. Inhibitors such as gefitinib (Iressa) and erlotinib (Tarceva) are currently used as treatments for cancers that overexpress EGF-R [72]. Drugs that act on targets downstream of EGF-R have also been developed. Sorafenib (Nexavar) is a Raf inhibitor approved for use in patients with renal cell carcinoma [73]. However, the clinical benefits of these drugs in asthmatic patients have not yet been established. To that end, it should be noted that interference with EGF-R signalling to suppress airway mucus hypersecretion may have undesirable side effects on other off-target systems. For example, EGF-R signalling is central to airway epithelial repair in response to damage by viruses, allergens and

Table 1 Potential signalling targets for pharmacotherapy of mucus hypersecretion in asthma

Target	Location	Therapeutic agent
EGF-R tyrosine kinase	Cell membrane	Gefitinib (Iressa), erlotinib (Tarceva)
FOXA2	Nucleus	None reported
IL-4R α	Cell membrane	IL-4R α antisense oligonucleotide [61] and soluble decoy receptors (e.g. sIL-4R α) [62]
IL-13	Extracellular	Anti-IL-13 monoclonal antibodies (e.g. CAT-354, IMA-638) [63,64]
Neutrophil elastase	Extracellular	Elastase inhibitors (e.g. batimastat, suramin) [65]
NF- κ B	Cytosol	Cell-penetrating NF- κ B inhibitors [66,67 ^{••}]
Raf	Cytosol	Sorafenib (Nexavar)
STAT6	Cytosol	STAT6 inhibitory peptide [67 ^{••} ,68]
TNF- α ^a	Extracellular	Anti-TNF- α monoclonal antibodies (e.g. infliximab, adalimumab) [69 [•]] and soluble decoy receptors (e.g. etanercept) [69 [•]].

^a May not be effective for all phenotypes.

pollutants. Interference with this pathway has been proposed to divert repair towards an inflammatory and remodelling signalling pathway [74]. This is especially important because the airway epithelium in asthmatic patients, compared with nonasthmatic patients, has been shown *in vitro* to be inherently unable to successfully repair after wounding [75], whilst conversely displaying an increased capacity to undergo epithelial–mesenchymal transition [76]. The latter is associated with fibroblast proliferation. These combined observations suggest that, in asthma, suppression of mucus hypersecretion by EGF-R tyrosine kinase inhibitors might, in parallel, compromise the airway by inducing structural remodelling. This potential problem could be addressed by use of EGF-R inhibitors that are highly selective for the mucin synthesis pathway rather than the epithelial repair pathway.

Targeting components of Th2 cytokine signalling

Mucus hypersecretion in asthma is critically dependent on IL-13 and its associated signalling pathways. Consequently, there is considerable interest in development of agents that block IL-13 signalling. Compounds that abolish the function of signalling components at various stages along the pathway are currently being investigated. Most studies have focused on preventing engagement of IL-13 with IL-4R α [61–64]. The potential benefit of IL-13 antagonists has been shown in experimental models [63,64], and clinical development is currently underway. In addition, STAT6 inhibitory peptides (STAT6-IPs) have potential for clinical use in asthma, but further studies are needed to clarify the mechanisms by which they inhibit mucus production [67,68].

Conclusion

Acute mucus hypersecretion is a physiological mechanism that protects the airway epithelium against inhaled irritants. These irritants stimulate mucus production by triggering release of cytokines, leading to activation of signalling pathways involved in mucin up-regulation. During chronic inflammation in asthma, these normally redundant pathways can become problematic, as a constant barrage of mediators causes long-term hypersecretion of mucus, with airway obstruction by mucus a common feature of asthma. Identification of signalling pathways responsible for hypersecretion has driven pharmacotherapeutic development of targeted treatments, ranging from small-molecule inhibitors to monoclonal antibodies. The most promising of these are those that target EGF-R signalling and components of Th2 cytokine signalling, including inhibitors of IL-4R α and STAT6. The clinical value of these agents needs to be assessed in asthmatic patients in whom excessive airway mucus production contributes to morbidity and mortality.

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