Review

Airway Mucus and Asthma: The Role of MUC5AC and MUC5B

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Abstract: Asthma is characterized by mucus abnormalities. Airway epithelial metaplasia results in changes in stored and secreted mucin and the production of a pathologic mucus gel. Mucus transport is impaired culminating in mucus plugging and airway obstruction, a major cause of morbidity in asthma. The polymeric mucins MUC5AC and MUC5B are integral components of airway mucus. MUC5AC and MUC5B gene expression is altered in asthma and recent work sheds light on their contribution to asthma pathogenesis. Herein we review our current understanding of the role of MUC5AC and MUC5B in mucus dysfunction in asthma.

Keywords: MUC5AC; MUC5B; asthma

1. Asthma

Asthma is a common, chronic, non-communicable disease that affects ~334 million people of all ages, races and ethnicities worldwide [1]. Dramatic increases in the prevalence of atopy and asthma have occurred in Westernized countries, and incidence is rising in less-developed countries [2]. Asthma causes approximately 250 000 deaths annually, is a major cause of lost school and work days, and imposes a substantial economic burden, particularly in low- to middle-income countries [3,4]. Asthma symptoms include wheezing, breathlessness (dyspnea), chest tightness and cough; all result from obstruction in airflow arising from a combination of inflammation induced airway smooth muscle constriction and impaired mucociliary clearance [5].

2. Mucociliary clearance

The conducting airways of the lung are lined by a pseudostratified columnar epithelium extending from the nasal cavity to the lower airway [6]. The epithelium is populated by several cell types. Ciliated cells are interspersed with secretory cells [6], which include club and goblet cells, and contribute secretions to the apical mucus gel [7]. In larger airways, the surface epithelium is contiguous with submucosal glands, which are situated between smooth muscle and cartilage plates [7]. Mucous cells within gland acini are a major mucus source [7] and mucous cells are also found within ducts which deliver gland secretions to the airway lumen. Basal cells anchor the epithelium to the underlying matrix and function as stem/progenitor cells for other airway cell types during natural turnover and in response to injury [8].

Together, the ciliated epithelium, periciliary layer and airway mucus gel form the mucociliary escalator [9]. Individual cilia atop ciliated cells beat in concert within the periciliary layer to propel airway mucus up and out of the lung [10]. In addition to providing a favorable environment for ciliary activity, the periciliary layer prevents compression from the overlying mucus gel layer, and provides a water reservoir to control water distribution [11]. Airway mucus is a hydrogel that functions as molecular flypaper, protecting the underlying epithelium by trapping potentially harmful inhaled particles, pathogens and dissolved chemicals within it [12].
Effective mucociliary clearance is essential for maintaining an uninfected and unobstructed airway, and relies on ciliary activity and the physiochemical properties of the periciliary layer and mucus gel [9,12]. Failure of any component of the mucociliary apparatus can render clearance defective and lead to obstruction. For example, in primary ciliary dyskinesia (PCD), cilia absence and/or immotility impair mucociliary clearance, while in cystic fibrosis (CF) periciliary liquid depletion manifests as mucostasis [11]. In asthma, ‘pathologically the outstanding feature of the asthmatic lung lies in the failure of clearance of the bronchial secretions’ [13]. In fact, the principal cause of death in asthma is asphyxiation from intraluminal airway obstruction by mucus plugs [14–16]. Defective mucociliary clearance is observed even in mild stable asthma [17–19] and is also significantly impaired during acute exacerbation [20].

3. Polymeric mucins

Mucins are the products of secretory cells and the primary macromolecular components of mucus. Mucins are heterogeneous, densely glycosylated high molecular weight molecules [21]. To date ~20 mucin-like genes have been identified and fall into 2 broad classes: membrane-bound or cell surface mucins, and secreted mucins. Secreted mucins are further subdivided into polymeric and non-polymeric glycoconjugates [22]. 4 polymeric MUC genes, MUC2, MUC5AC, MUC5B and MUC6, are present in tandem on a conserved cluster of human chromosome 11p15 and likely arose by gene duplication [23]; the fifth, MUC19, is found on 12q12 [21,24].

Polymeric mucin gene products have complex, multidomain polypeptide structures important to their function [21]. They possess cysteine-rich von Willebrand factor (vWF) -like D-domains including 3 D-domains (D1,2 and 3) at the N terminus and a fourth at the C terminus (D4); a partial D domain (D') lies between the D2 and D3 domain [21,25]. Additional cysteine rich vWF-like domains (B, C, CK) are located at the C terminus. These domains are sites of mucin dimerization and polymerization, with mucin monomers forming disulfide-bonded polymers in both mass (2-50 mDa) and length (0.5-10 um) [9]. The capacity of polymeric mucins to polymerize is crucial to their gel-forming properties.

The hallmark of these proteins are the tandem repeat domains, encoded by a single large central exon and rich in proline, serine and threonine residues [9]. These regions are the site of O-glycosylation; the repetitive sequences create a dense array of glycan structures which contribute 50-90% weight by mass of the glycoprotein [21]. The extensive glycosylation extends and stiffens the mucin polypeptide chain. Terminal sulfation and sialylation of the O-glycans results in charge repulsion between neighboring oligosaccharide groups. Mucins therefore have a large hydrodynamic volume in solution, which is important for gel formation [21]. Charged polymers like mucins are also very effective lubricants in aqueous environments [26].

As aforementioned, mucins share sequence similarity with vWF, which also polymerizes through N and C-terminal disulfide linkages [25]. Studies on intact mucins, recombinant N and C terminal domains, as well as studies on porcine submaxillary mucin (PSM) have shown that polymeric mucins also share some basic pattern of polymer assembly with vWF [27–30]. The latter stages of assembly involving multimerization and packaging into secretory granules are less clearly resolved. Polymeric mucins are packaged highly condensed and dehydrated into secretory granules; calcium ions enable this through shielding charge on the polyanionic mucins [31,32]. A recent study characterized an additional association between MUC5B N-terminal D3 domains that enables secretory granule storage; uncoupling of the D3-mediated results in expansion during exocytosis [33]. As all polymeric mucins share sequence identity it is possible that the assembly mechanism is also shared.

Additionally, the mechanisms leading to mucus formation post-exocytosis are poorly understood. A 2-phase model has been proposed to explain the rapid and massive mucin expansion that occurs on secretion [34]. Following secretory granule fusion with the plasma membrane, calcium ions are exchanged by monovalent cations such as sodium and potassium and/or sequestered by bicarbonate [35,36]. This exposes the negatively charged terminal sugars on adjacent mucins, leading to their mutual repulsion and further expansion [36]. This process is followed by
changes in mucin morphology, the molecules unfurling to attain a linear polymeric form in a
process coined ‘maturation’ [34].

4. MUC5AC and MUC5B

In the airway, MUC5AC and MUC5B predominate, with little MUC2 detected and low
level MUC19 expression reported; MUC6 is the only polymeric mucin not expressed [21,37].
MUC5B is produced by mucous cells in submucosal glands, and to a lesser extent secretory cells
within the surface airway epithelium [38–40]. MUC5AC is produced by specialized secretory cells
in the surface epithelium called goblet cells; MUC5AC staining can also be observed in the terminal
secretory ducts of submucosal glands [38–40]. MUC5AC and MUC5B are secreted from different
cells, or from different granules within the same cell, and remain largely segregated after secretion
into the lumen [41,42]. They may also form distinct morphologic structures: lectins preferentially
recognizing each mucin suggest MUC5B forms strands and MUC5AC threads and sheets in a
porcine model.

As the major matrix-forming macromolecules in airway mucus, the viscoelastic properties
of airway mucus depend on MUC5AC and MUC5B [9]. Electron microscopy revealed that
MUC5AC and MUC5B polymers are long, flexible linear threads [43,44]. However, MUC5AC and
MUC5B differ in charge and shape [45]. MUC5B exists as 2 glycoforms, differing in charge due to
glycosylation [46]. The high charge MUC5B variant has been identified in a subpopulation of
submucosal gland cells suggesting a distinct cellular origin and glycosyltransferase repertoire [40].
MUC5AC has a lower sedimentation rate than MUC5B. As both form polymers of similar size, the
difference in sedimentation is likely determined by the shape of the molecules: MUC5AC behaves
more rod-like or extended in solution compared to MUC5B [44]. This characteristic of MUC5AC
likely explains why MUC5AC polymers appear less polydisperse than MUC5B polymers as the
extended structure gives poorer separation by sedimentation rate [40,44].

Targeting mouse mucin genes has provided insights into the roles of MUC5AC and
MUC5B in the airway. MUC5B is critical for mucociliary clearance and airway defense [47].
MUC5B-deficient mice accumulate aspirated materials in the airway and develop chronic bacterial
infections, severe inflammation, and airway obstruction [47]. Loss of MUC5B also inhibits innate
inflammatory responses suppressing IL-23 that results in accumulation of alveolar macrophages
whose phagocytosis and clearance of Staphylococcus aureus was impaired [47]. The role of MUC5B
was also explored by crossing MUC5B-deficient mice with Scnn1b-Tg mice, which exhibit mucus
hyperconcentration and airway surface adhesion due to overexpression of the epithelial sodium
channel (ENAC) [48]. The magnitude of mucus obstruction in Scnn1b-Tg mice was significantly
reduced in the absence of MUC5B, however mucus adhesion persisted and MUC5B deletion did not
alleviate bacterial burden. Absence of MUC5B in Scnn1b-Tg mice was associated with increased
airway inflammation suggesting that MUC5B is required to maintain immune homeostasis and is
important in anti-bacterial defense.

MUC5AC-deficient mice have normal mucociliary transport and anti-bacterial defense and
are protected from mucus plugging in an allergic asthma model [47,49]. Overexpression of
MUC5AC confers resistance to viral infection but does not cause metaplasia or obstruction
suggesting mucus hypersecretion alone is insufficient to trigger plugging [50]. However, MUC5AC
appears to be detrimental in acute lung injury, enhancing neutrophil trafficking and inflammation
[51].

Whether the polymeric mucins function similarly in humans has yet to be established. As
aforementioned, the airways of normal mice more resemble human distal airways in respect to their
diameter [52]. Additionally, the distribution of secretory cells differs between human and mice;
submucosal glands are limited to the laryngeal region of trachea in mice [53]. Based on these cross-
species anatomical differences one could hypothesize that MUC5B may perform baseline barrier
and clearance functions in human distal airways, but its function may be augmented by MUC5AC
in the proximal airways where MUC5AC production is greater. Notably, the proportion of
MUC5AC and MUC5B varies with the state of health and the effects of this in asthma are discussed below.

5. Regulation of MUC5AC and MUC5B expression in asthma

Variants in the 11p15 MUC5B and MUC5AC locus have been associated with AHR in asthma (6). Many individuals with asthma have increased MUC5AC mRNA levels but decreased MUC5B mRNA levels [54]. MUC5AC and MUC5B expression is sensitive to a wide variety of stimulants and developmental cues. Of particular pertinence to asthma are type 2 immune cells, including type 2 T helper (Th2) cells and innate lymphoid cells (iLC2s), which orchestrate allergic airway remodeling in asthma. IL-13 is produced by these cells during allergic inflammation, inducing characteristic changes in airway epithelial mRNA [55–57] and miRNA expression [58] in airway epithelial cells. The IL-13 transcriptional signature can be used to identify individuals with Th2 high and Th2 low asthma; approximately 50% of people with asthma are Th2 high [54,56].

Individuals with Th2 asthma have elevated levels of MUC5AC compared with healthy controls or individuals with Th2 low asthma; a substantial decrease in MUC5B expression is also observed in Th2 high asthma [54,59]. IL-13 significantly and consistently increases expression of MUC5AC in human airway epithelial cells in vitro and expression of Muc5ac in murine models [41,55,57,60,61]. The effect of IL-13 on MUC5B is more variable. IL-13 (and allergen challenge) induces Muc5b in mouse models but IL-13 frequently decreases MUC5B in cultured human airway epithelial cells [41,59].

The link between type 2 inflammation and airway structural cell dysfunction is incompletely understood. A recent study has suggested that Th2 inflammation is necessary but not sufficient for allergic asthma, and that the airway epithelium is more responsive to Th2 inflammation in people with asthma as measured by MUC5AC [62]. Whether this is because asthma cells are intrinsically more sensitive to type 2 inflammation or develop altered responses in a chronic inflammation environment remains undetermined [62].

Epidermal growth factor receptor (EGFR) signaling is also required for mucus production in vitro and in vivo [57,63,64]. EGFR levels are increased in individuals with asthma and expression correlates with disease severity [65]. Various stimuli (bacterial products, viruses, cigarette smoke and inflammatory cell products) and various ligands (EGF, TGF-α, amphiregulin) can trigger EGFR signaling in airway epithelial cells. EGFR signaling induces MUC5AC expression while EGFR tyrosine kinase inhibition blocked MUC5AC expression [63].

Recently, a murine inbred strain study revealed that a large fraction of the variation in secreted MUC5AC and MUC5B was attributable to strain specific genetic differences indicating heritability [66]. Although MUC5AC and MUC5B mRNA levels were strongly correlated, likely due to shared transcriptional regulation, neither mRNA correlated with protein production suggesting post-transcriptional events were important in mucin regulation [66]. Quantitative trait locus (QTL) mapping identified distinct, trans protein QTL for MUC5AC (chromosome 13) and MUC5B (chromosome 2) explaining 18% and 20% of phenotypic variance, respectively, indicating separate distal regulatory control [66]. Identifying additional QTL loci will inform mucin regulation further.

6. Goblet cell fate in asthma

A key feature of airway epithelial remodeling in asthma is increased goblet cell number, which accompanies the aforementioned increase in MUC5AC copy number. In fatal asthma a 30-fold increase in goblet cell number was reported [67]; increased goblet cell number is readily observed in mild to moderate disease too [68]. The mechanisms mediating goblet cell differentiation are incompletely understood with both hyperplasia and metaplasia proposed. In the human airways, understanding of secretory cell fate is limited and much of our knowledge derives from mouse models. During normal development, epithelial cells are thought to differentiate into ciliated and secretory lineages from basal and club cells that are considered to function as progenitor/stem cells. In the proximal airways, basal cells are the progenitors of ciliated and secretory cells [8]. The proportion of basal cells in the airway is highest in the large airways and progressively decreases
down the tracheobronchial tree, where club cells likely act as progenitors [69]. In murine models, where airways more resemble human distal airways, transition from both ciliated and club cells has been evidenced suggesting variable lineage [70,71].

Pathologic remodeling is caused by dysregulation of signaling cascades that govern normal differentiation. Notch signaling is an evolutionary conserved pathway that regulates cell fate decisions during development. Notch recently emerged as a pivotal regulator of basal cell differentiation in conducting airways with activation of secretory over ciliated lineages [72]. Notch2 is a common node downstream of IL-13 and is absolutely required for goblet cell metaplasia in vitro and in vivo [73]. Inhibition of Notch2 inhibits IL-13 and allergen driven goblet cell metaplasia in vivo [73]. In a mouse model of respiratory disease, inhibition of JAG, a ligand for the transmembrane Notch receptor, reduced goblet cell metaplasia when administered prior to an inflammatory stimulus, and reversed goblet cell metaplasia when administered post-stimulus (i.e. once metaplasia was established) [74].

At the transcriptional level, a number of transcription factors are thought to be involved in increased MUC5AC expression and mucous metaplasia. Sam pointed domain-containing ETS transcription factor (SPDEF) is sufficient and necessary for goblet cell metaplasia and for increasing MUC5AC and MUC5B expression [75]. SPDEF expression is increased in airway epithelial cells of patients with asthma compared to healthy controls [76], remains increased in spite of anti-inflammatory treatment, and is upregulated following IL-13 stimulation [77]. SPDEF induction following IL-13 stimulation was accompanied by DNA hypomethylation of several CpG sites within the SPDEF promoter [78]. Epigenetic editing of SPDEF suppressed MUC5AC expression in human airway epithelial cells [79]. In SPDEF deficient mice, goblet cells are absent, whilst overexpression of SPDEF causes goblet cell metaplasia [80].

Several forkhead box family members have also been implicated in airway polymeric mucin expression and mucous metaplasia. Forkhead box protein A2 (FOXA2) is negatively regulated by SPDEF and MUC5AC expression, and is a potent inhibitor of goblet cell differentiation [81]. FOXA2 is also regulated by DNA methylation [78]. Interestingly, both IL-13 and EGFR signaling cascades converge on FOXA2 inhibition, perhaps representing a common pathway for IL-13 and EGFR-induced mucous metaplasia [10]. Another family member, FOXA3, also functions as a goblet cell metaplasia regulator: it is highly expressed in patients with asthma, and is IL-13 and rhinovirus inducible [76]. HIF-1 is also downstream of IL-13 and EGF stimulation, plus a HIF-1 binding motif is conserved in mammalian MUC5AC promoters [82].

7. Altered MUC5AC and MUC5B properties

Abnormalities in goblet cell number are accompanied by changes in stored and secreted mucin. In asthma as in health, MUC5AC is produced in goblet cells from the surface epithelium, while MUC5B is largely produced in the submucosal glands. However, changes in the relative proportion of MUC5AC and MUC5B are observed in asthma (Figure 1). As at the gene expression level, elevated MUC5AC production is consistently reported, but there are conflicting reports regarding MUC5B. Increased MUC5AC and MUC5B protein have been reported in sputum from individuals with asthma [83]. Another study identified MUC5B as the predominant mucin in healthy secretions, while MUC5AC concentration increased and MUC5B decreased in individuals with asthma, including those in exacerbation [42]. Interestingly, within the asthma cohort, a higher ratio of MUC5AC to MUC5B correlated with type 2 inflammation (>2% eosinophils) [42]. in pediatric asthma, similar observations were made: increased MUC5AC was reported in children with both stable and acute asthma vs healthy controls. Median MUC5B concentration was non-significantly reduced, however, overrepresentation of a low-charge glycoform of MUC5B was observed [84]. A study on viscous mucus exudate from a patient who died in status asthmaticus demonstrated that the MUC5B low charge glycoform was the major constituent suggesting mucin glycosylation status may also be important in asthma [85]. Additionally, in mild asthmatics, large amounts of glandular MUC5B extracellular mucus was observed [86]. The contribution of glandular MUC5B to mucus dysfunction in asthma requires further exploration.
It has been noted that asthmatic sputum is abnormally viscous [87]. Rheological measurements of sputum from patients with asthma during acute exacerbation demonstrated increased elastic and viscous moduli; the increased elastic response dominated suggesting increased crosslinking of mucin polymers as demonstrated recently in CF [88,89]. These differences are most visible in the form of mucus plugs, which occlude airways and prevent mucociliary clearance. Although mucins are primarily responsible for the biophysical properties of the gel, other constituents including DNA and albumin may also contribute to the increased viscoelasticity reported in asthma [87,88]. Several studies have compared the size distribution of MUC5AC and MUC5B in sputum from patients with asthma yet no discernible difference has been observed [84,88]. It has been suggested that mucin degradation is inhibited in asthma: protease dependent mucin degradation was inhibited at the height of exacerbation but restored during recovery [88]. Alterations in protease and antiprotease expression has been reported in asthma suggesting imbalance could affect mucus clearance and contribute to tethering and plugging.

Despite substantial plugging observed in the majority of patients with fatal asthma, the biochemical and biophysical mechanisms by which secreted mucus occludes airways is not fully understood. An autopsy study demonstrated a large increase in the frequency of goblet cells in continuity with intraluminal mucus in individuals with asthma [90]. We found that extracellular domains of MUC5AC-rich mucus were intimately associated or tethered to epithelial mucous cells, markedly impairing mucociliary transport [41]. Images from allergic mouse airways [49] are also consistent with tethering. MUC5AC-tethering probably leads to progressive luminal accumulation of mucus and airway plugging (Figure 1). The mechanism by which MUC5AC is tethered requires further investigation. It is possible that exocytosed MUC5AC is not fully released or expanded from goblet cells leading to tethering of mucus to the epithelium.

Figure 1. Alterations in MUC5AC and MUC5B contribute to mucus dysfunction in asthma. In health (left), MUC5B (red) is the predominant mucin expressed and the principal component of the airway mucus gel. The MUC5B-rich gel is readily transported by the ciliated epithelium (purple) maintaining an unobstructed and uninfected airway. In asthma (right), mucin expression is altered: MUC5AC (green) expression is upregulated, while MUC5B expression is reduced. This leads to the production of a heterogeneous airway mucus gel comprising distinct MUC5AC and MUC5B domains. Extracellular MUC5AC-domains remain tethered to MUC5AC-producing cells (orange box) compromising mucociliary clearance. Mucus accumulates forming mucus plugs which occlude the airway. Airway obstruction manifests clinically as breathlessness and wheeze; in some patients, intraluminal occlusion by mucus plugging can lead to asphyxiation.
Interestingly, mucins from a viscous mucus plug appeared as ‘tangled masses condensed around nodes from which many chains emanate’, contrasting with the classic view of polymeric mucins as linear threadlike molecules [85]. These mucins resembled freshly secreted mucins implicating improper unpackaging of mucins post-secretion as a contributor to tethering [34]. Defective postsecretory maturation of MUC5B has been reported in CF [91]. Altered luminal pH could also contribute since sputum samples collected during asthma exacerbation have been shown to be more acidic compared with samples from people with stable asthma or with other respiratory diseases [90,92]. As aforementioned, a plethora of transcriptional alterations are observed in asthma which likely alter ciliary transport and ion transport and could impact airway surface pH, mucus adhesivity and mucociliary transport. The implications of altered pH on mucociliary transport is adequately demonstrated in cystic fibrosis [11].

We also demonstrated that MUC5AC and MUC5B form distinct extracellular domains and that IL-13 induces a heterogeneous gel, which could have implications for mucociliary clearance in asthma [41]. Differences in the biophysical properties of extracellular MUC5AC- and MUC5B-containing domains could be attributable to intrinsic properties of the MUC5AC and MUC5B core proteins. Other potentially important factors include posttranslational mucin modifications including glycosylation (low-charge MUC5B [84]) or disulfide cross-linking, hydration- and bicarbonate-mediated mucin expansion, non-mucin mucus constituents (e.g. intelectin-1 [93]), or other differences in the secretory cell or the luminal environment. Additionally, differences in airway mucus may be caused by differences in the clinical features of asthma, including exacerbation, severity, duration, smoking, and treatment.

8. Therapeutics

Together with smooth muscle contraction, mucus obstruction is a major cause of airway obstruction in asthma [10]. A mucoactive drug is an agent capable of modifying mucus production, secretion, properties, or its interactions with the mucociliary epithelium [94]. Mucoactive agents facilitate mucus clearance (mucolytics) or inhibit mucus production or secretion (mucoregulators) [95,96].

No effective mucolytic treatments for asthma exist. Hypertonic saline is associated with mucus clearance but modest improvements in airflow [97]. The reducing agent N-acetylcysteine (NAC) is sometimes used as a mucolytic therapy but exhibits low efficacy (low mucolytic activity at high mucus concentrations and neutral pH) and tolerability: N-acetylcysteine can irritate the airways and cause bronchospasm in hyperreactive patients [98–103]. Thiol-modified carbohydrates have been proposed as novel mucolytics for CF and other lung diseases [89]. Pulmozyme, a human DNAse, improves pulmonary function and reduces pulmonary exacerbation in CF [104,105], but there is no evidence it is effective in other diseases, presumably since it does not target the mucins themselves. Recent evidence suggests mucin-specific approaches could be of benefit: complete MUC5B removal from the airway may be detrimental [48], whilst the identification of MUC5AC as an essential non-contractile mediator of AHR [49] and the role of MUC5AC in tethering [41] suggest MUC5AC-specific therapies could be of benefit in asthma.

There is rationale for development of cytokine specific antibodies as mucoregulators. For example, a recent trial with anti-IL-13 (lebrikizumab) demonstrated improved airflow (prebronchodilator FEV1) in patients with Th2 asthma. However anti-IL-13 only met its primary endpoint of significantly reducing exacerbation rates in one of two parallel Phase III studies, despite significantly improving FEV1 in both [106,107]. Although other mechanisms likely contribute, improved FEV1 could represent reduced mucus obstruction. An agent that inhibits a common subunit of IL-13 and IL-4 receptors also had beneficial effects in a clinical trial. Agents that reduce production of IL-13, including corticosteroids and antibodies against the epithelial-derived type 2-promoting cytokine TSLP likely act in part by inhibiting production of pathologic mucins [59,108].

Other approaches to regulating mucus obstruction might include specific targeting of mucin (especially MUC5AC) gene transcription or protein processing or blocking the differentiation of mucus-producing goblet cells. For example, targeting Notch through Jagged antagonism
reversed goblet cell metaplasia in a preclinical model [74]. Although controlling mucus hypersecretion is attractive therapeutically, a therapy which completely disrupts secretion and inhibits MUC5B may be detrimental. Overall, it is unclear which mucoactive drugs would offer optimal benefit [109] and further research is required.

9. Conclusions

MUC5AC and MUC5B are principal components of airway mucus. In the airway, their production is spatially separated, and they serve different functions (at least in mice). Altered MUC5AC and MUC5B gene expression is consistently observed in both asthma models and individuals with disease. Increases in goblet cell number accompany changes in mucin gene expression, which result in altered mucus composition and organization. These changes are associated with increased gel viscoelasticity, and are sufficient to impair mucus transport through MUC5AC-tethering, likely contributing to airway obstruction and mucus plugging. Continued research to understand the mechanisms underlying goblet cell fate and MUC5AC-tethering are crucial for the development of effective mucoactive agents.

Acknowledgments: This work was supported by NIH grants AI077439, HL138424 and HL099101, the Cystic Fibrosis Cell Models Core (funded by NIH grant DK072517 and Cystic Fibrosis Foundation grant DR613-CR11) and the UCSF Program for Breakthrough Biomedical Research Postdoctoral Independent Research Project Award.

Author Contributions: L.R.B and D.J.E wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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