Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jan 25; 10(F):215-223.
https://doi.org/10.3889/oamjms.2022.8060
eISSN: 1857-9655
**Category:** *F - Review Articles*
***Section:*** *Narrative Review Article*



# Distinct Secretion of MUC5AC and MUC5B in Upper and Lower Chronic Airway Diseases

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**Edited by:** Slavica Hristomanova-Mitkovska
**Citation:** Shah SA, Ishinaga H, Takeuchi K. Distinct Secretion of MUC5AC and MUC5B in Upper and Lower Chronic Airway Diseases. Open-Access Maced J Med Sci. 2022 Jan 25; 10(F):215-223. https://doi.org/10.3889/oamjms.2022.8060
**Keywords:** MUC5AC/MUC5B hypersecretion; Goblet cell hyperplasia; Submucosal gland hypertrophy; Chronic airway diseases; Mechanisms/pathways
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**Received:** 23-Nov-2021
**Revised:** 12-Jan-2022
**Accepted:** 15-Jan-2022

**Funding:** This research did not receive any financial support
**Competing Interest:** The authors have declared that no competing interests exists


**Abstract**

The human airway is protected by a defensive mucus barrier. The most prominent components of mucus are the mucin glycoproteins MUC5AC and MUC5B. They are produced by goblet cells and submucosal gland cells in the upper and lower airways. Hyperplasia of these cells and hypersecretion of MUC5AC and MUC5B characterize chronic inflammatory diseases of the upper and lower airways. Recent studies have revealed that MUC5AC and MUC5B are expressed at specific sites in the respiratory tract through different molecular mechanisms and have distinct functions. Morphometric and histochemical studies have also examined the roles of goblet cells, submucosal gland cells, MUC5AC, and MUC5B in different chronic airway diseases individually. The individual study of goblet cells, submucosal gland cells, MUC5AC, and MUC5B in airway diseases would be helpful for precisely diagnosing chronic inflammatory diseases of the airway and establishing optimal treatments. This review focuses on the distinct secretion of MUC5AC and MUC5B and their producing cells in chronic inflammatory diseases of the upper and lower airway.

## Introduction

Airway mucus is a hydrogel in which water and mucins are important components that provide lubrication and act as a molecular barrier at the epithelial surface [1]. The airway is exposed to various infectious agents, such as viruses, fungi, and bacteria, and to allergens, irritants, smoke, and other pollutants and pathogens that are potentially hazardous to airway health [2]. The mucus clearance system removes these agents from the human airway and protects its surface from their noxious effects [3]. However, dysfunction of this clearance system can cause the overproduction of mucus and failure of mucus transport, resulting in the accumulation of mucus that contributes to sputum production, airway obstruction, and the exacerbation of muco-obstructive airway diseases [4].

Many cell types are found throughout the airway epithelium, including mucous, basal, ciliated, and Clara cells, and type I and type II cells in the alveolar epithelium [5]. Several mucin genes have been discovered and classified into two structurally different groups according to their cellular localization: Secreted and membrane-bound mucins [6]. In the human airway, MUC5AC and MUC5B are the two major secreted gel-forming mucins [4], and they account for approximately 90% of the mucin content of mucus [7]. MUC5AC is secreted by goblet cells, while MUC5B is produced by goblet cells and submucosal glands [8]. MUC5B, the predominant mucin in the normal healthy airway [9], is essential for airway homeostasis and antibacterial defense [10].

Deletion of the *Muc5b* gene in mice results in a profound loss of mucociliary clearance, the accumulation of particulate debris in the lung, and a high death rate due to infection or airway obstruction [11]. On the other hand, deletion of the *Muc5ac* gene in mice leads to a deficiency of neutrophil trafficking following pulmonary edema during injurious ventilation, suggesting an important role for endogenous MUC5AC in pulmonary neutrophil recruitment during lung injury [12].

The synthesis of the peptide backbone of mucins starts on membrane-bound ribosomes of the rough endoplasmic reticulum with the formation of apomucin, which is cotranslationally inserted into the endoplasmic reticulum. Apomucin undergoes several post-translational modifications such as N-glycosylation, C-mannosylation, and dimerization [13]. Sugars are added subsequently, and mucins are fully glycosylated

as they move through the cell from the rough endoplasmic reticulum toward the Golgi apparatus [14]. They are packaged into large carrier vesicles, and new mucin granules fuse laterally to generate large secretory granules, which are released in response to intracellular messengers and extracellular signals. In the airway, the secretion rate of mucin can be low at baseline or high in response to secretory stimuli [15].

Mucin overproduction is associated with chronic airway diseases [3], [4], [16], in which many morphological and pathological changes occur in mucous cells and glands, including hypertrophy, hyperplasia, and metaplasia [3], [17], [18]. These changes can cause increased production of MUC5AC and MUC5B, with higher levels of both seen in asthma and chronic pulmonary obstructive disease (COPD) or in cystic fibrosis following disease exacerbation [3], [9], [19], [20]. In addition, hyperplasia of goblet and mucous cells is induced by several stimuli, such as pathogens, toxins, oxidants, particulates, and cigarette smoke [18], leading to hypersecretion of MUC5AC and MUC5B. The individual study of MUC5AC and MUC5B hypersecretion, mucus-producing cell hypertrophy, hyperplasia, and metaplasia, and the underlying mechanisms leading to these changes would be helpful for precisely diagnosing and treating chronic inflammatory diseases of the airway, and we focus on this issue in the present review. Figure 1 gives a general overview of normal and diseased airways and the synthesis of mucins.

## Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is an inflammatory condition of the nose and paranasal sinus mucosa [21]. In CRS, the nasal and paranasal sinuses undergo a remodeling process that includes goblet cell hyperplasia and mucous gland hypertrophy [22]. Immunohistochemical examination of paranasal sinus tissue from patients with CRS has revealed significant submucosal gland cell hyperplasia and a trend toward increased glandular MUC5B expression [23]. Submucosal gland cell hyperplasia and MUC5B secretion are considered characteristic phenotypes of CRS [24]. The results of enzyme-linked immunosorbent assays indicate that MUC5B secretion is significantly upregulated in mucus samples taken from the sinuses of CRS patients compared with those taken from control subjects [25].

Immunohistochemistry has also revealed that MUC5AC and MUC5B are highly expressed in type 2 inflammatory nasal polyps characterized by interleukin (IL)-5 expression [26]. A recent study reported high MUC5AC expression in mucosal tissue of the ostiomeatal complex of CRS patients without nasal polyps (CRSsNP) and nasal polyp tissue of CRS patients with nasal polyps (CRSwNP) compared with the inferior turbinate of control subjects [27]. Moreover, a significant increase in both *MUC5AC* and *MUC5B* mRNA levels is observed in tissue taken from the maxillary sinus of adult CRS patients [28].

In inflamed sinus mucosa, immunohistochemistry has detected MUC5AC in goblet cells and MUC5B in submucosal glands, whereas in normal sinus mucosa, MUC5AC and MUC5B are both expressed at low levels, suggesting the hyperactivity of goblet cells and submucosal glands in sinus inflammation [29]. On the other hand, a quantitative histological investigation revealed that the density of goblet cells in the maxillary sinus mucosa of adult patients is lower in chronic sinusitis than in the normal sinus, whereas the density of glands is 6-fold higher in chronic sinusitis than in the normal sinus. However, the increased production of mucus in chronic sinusitis is mainly derived from newly formed glands during disease progression because of basal cell hyperplasia [30].

Allergic fungal rhinosinusitis and eosinophilic CRS are characterized by type 2 inflammation, and they manifest with a thick, tenacious, and eosinophilic mucus [31], [32]. In immunohistochemical examinations of ethmoid sinus and nasal polyp tissue, there are more glands in CRSsNP and non-eosinophilic CRSwNP patients than in CRSwNP and eosinophilic CRSwNP patients. However, all types of CRS (CRSsNP, CRSwNP, and eosinophilic and non-eosinophilic CRSwNP) demonstrate a similar level of goblet cell hyperplasia [33]. Increased numbers of mucus-producing cells and increased MUC5AC and MUC5B production are pathological features of CRS. Thus, further evaluation, particularly of the molecular mechanisms of goblet cell and submucosal gland hyperplasia and hypertrophy, is needed to identify new characteristics and to develop novel treatments.

## Allergic Rhinitis (AR)

AR is characterized by episodes of sneezing, itching, rhinorrhea, and nasal obstruction [34]. It is caused by immunoglobin E-mediated reactions against inhaled allergens. Mucosal inflammation in AR is driven by T helper 2 (Th2) cells [35].

In AR, MUC5AC is primarily secreted from epithelial goblet cells, while MUC5B is secreted from goblet cells and submucosal glands [36]. Several studies have focused on mucin-producing cell hyperplasia including goblet cells in AR, but conflicting results have been reported. According to the previous studies, in a mouse model of AR, goblet cell hyperplasia develops only following stimulation with ovalbumin or tumor growth factor-β [37]. However, animal models of

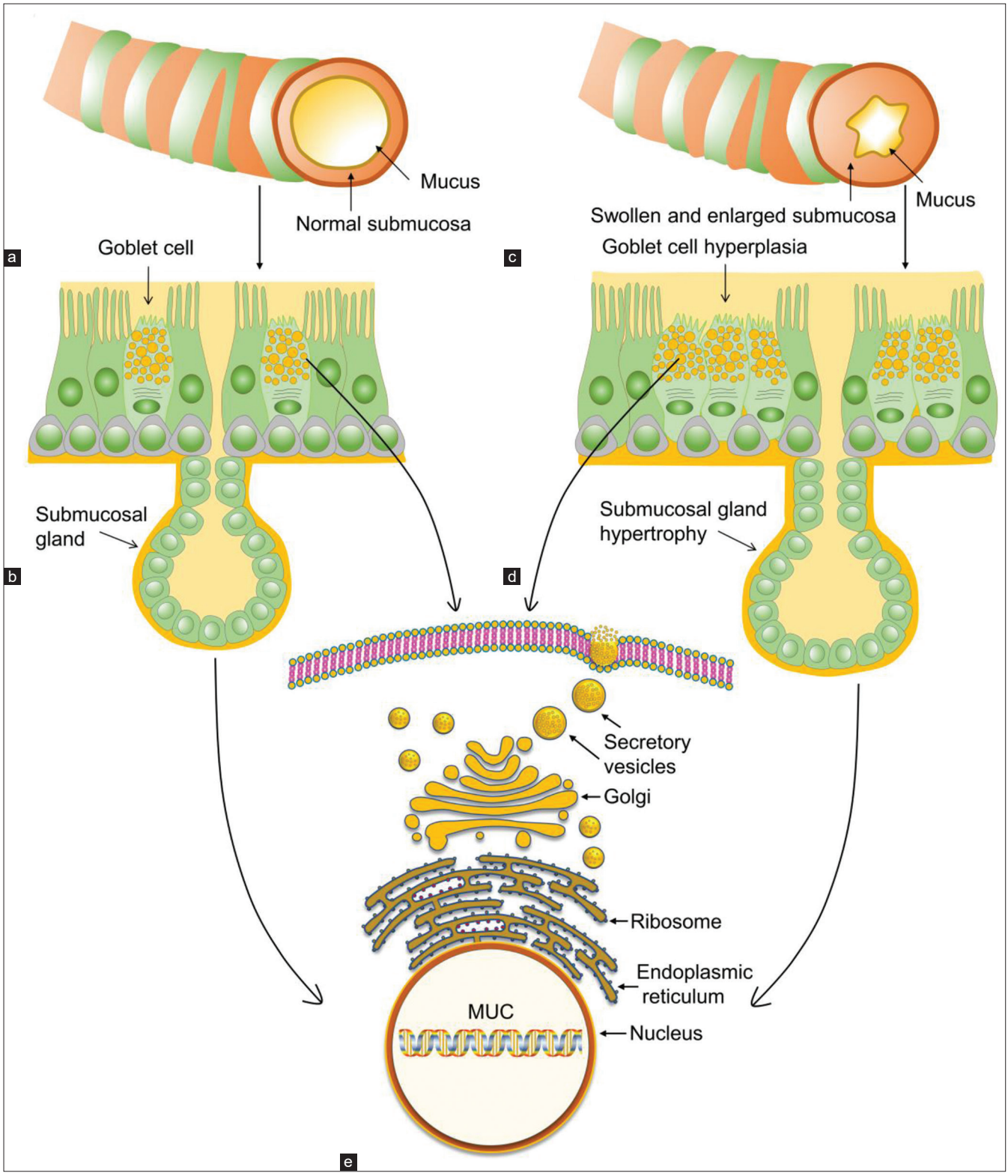


*Figure 1: Overview of normal and diseased airways and the synthesis of mucins. (a and b) Normal airway. (c and d) Airway with chronic inflammation that has signs of remodeling, including goblet cell hyperplasia, submucosal gland hypertrophy, and basement membrane thickening, and an increase in mucus production. (e) Synthesis of mucins including MUC5AC and MUC5B in mucus-producing cells*

AR may not be helpful for or may not apply to human disease, because the disease is induced by ovalbumin exposure [22]. Moreover, the results of nasal smears from schoolchildren have shown no significant association between clinically evident nasal allergy and goblet cells [38]. Furthermore, in perennial rhinitis, no significant difference was found in the number of goblet cells between patients with perennial rhinitis and control subjects [39]. Relevant to previous studies, Eifan *et al*. also revealed that there is no difference in the nasal mucosal glandular area between patients with persistent AR and healthy subjects, and they failed to

detect any evidence of remodeling in these patients compared with the controls, in pollen season compared with out of season or in seasonal disease compared with perennial disease [40].

The evidence for remodeling in AR, namely, changes in goblet cells and nasal mucosal glands as well as other structures, seems to be contradictory, suggesting that the remodeling process, which is well defined in asthma, does not occur or is not a prominent feature in AR [22]. Although the inflammation is similar in AR and asthma, remodeling is extensive and well explained in the asthmatic airway [22]. The clinical implications of mucin gene expression in the upper airway and the mechanism of remodeling in AR, including goblet cell and submucosal gland cell hyperplasia, appear to require more detailed studies that will assist in the treatment of AR.

## Asthma

Asthma is characterized by airway inflammation and structural changes in airway tissues, including epithelial goblet cell hyperplasia, subepithelial collagen deposition, and smooth muscle hypertrophy [41]. Goblet cell hyperplasia, as a key feature of remodeling, and mucin overproduction are prominent pathological findings in human patients and in animal models of asthma [41], [42]. In fatal asthma, a 30-fold increase in goblet cell number has been reported, and this increase resulted in increased mucus production and mucus plugging in the proximal and distal airways, which are the main causes of death in asthmatic patients [43].

In asthma, *MUC5AC* and *MUC5B* mRNA expression is altered, with *MUC5AC* expression increased significantly and consistently [42], [43]. The results of experiments in mice have also demonstrated that *Muc5ac* expression is dramatically increased within the epithelium after antigen challenge, although *Muc5b* mRNA levels remain at baseline [44].

A wide variety of stimulants causes goblet cell metaplasia and mucus hypersecretion through different mechanisms in asthma, including Th2 cytokines such as IL-4 and IL-13 [45]. IL-13 binding to its primary receptor chain (IL-13R) as well as IL-4 sharing its receptor with IL-13 have been demonstrated to increase goblet cell hyperplasia and mucus production through the phosphorylation of signal transducer and activator of transcription 6 [46].

Further, SAM pointed domain-containing ETS transcription factor (SPDEF) and Forkhead ortholog A3 (FOXA3) have been shown to increase the number of goblet cells [47], [48]. SPDEF and FOXA3 are induced following exposure to aeroallergens, rhinovirus, and Th2 cytokines, including IL-13 [47]. SPDEF is an important regulator of mucous cell differentiation, and SPDEF-deficient mice have no goblet cells [48]. SPDEF, IL-13, and epidermal growth factor receptor (EGFR) inhibit FOXA2, which represses mucous cell differentiation [49].

EGFR is activated by its ligands, including EGF, transforming growth factor-$\alpha$, heparin-binding EGF-like growth factor, betacellulin, amphiregulin, epiregulin, and epigen [50]. EGFR ligand binding activates the Ras–Raf–MEK1/2–ERK1/2 pathway, which eventually induces MUC5AC expression through the Sp1 transcription factor [51]. On the other hand, tyrosine kinase inhibitors inhibit EGFR kinase and prevent the induction of mucin expression by EGFR ligands [52].

A recent study revealed that Notch activation is important for the differentiation of basal or club cells toward goblet cells [53]. Notch is a transmembrane receptor that binds to cell surface ligands, including the Delta-like and Jagged families [49], [54]. This interaction activates $\gamma$-secretase-mediated proteolytic cleavage of the Notch intracellular domain, which enters the nucleus, associates with transcription factors, and drives the expression of downstream Notch genes [49], [54]. In the lung, the best-characterized Notch target is Hes family bHLH transcription factor 1 (Hes1), which appears to be crucial for the inhibition of mucous cell metaplasia and *MUC5AC* transcription [55]. Interestingly, an inhibitor of the Notch antagonist $\gamma$-secretase reduces the Notch-induced increase in the number of MUC5AC-containing mucous cells [54]. Further, Notch2 is located downstream from IL-13 and acts as a mediator of goblet cell metaplasia, whereas anti-Notch2 antibodies prevent IL-13- and allergen-driven goblet cell metaplasia [56], [57]. Anti-Notch2 antibodies inhibit the expression of goblet cell markers (MUC5AC, MUC5B, and FOXA3) while simultaneously increasing the expression of ciliated cell markers (FOXJ1 and dynein axonemal intermediate chain 2) and a basal cell marker (p63) [56], suggesting a role for Notch in goblet cell fate.

Th2 and type 2 innate lymphoid cells are particularly relevant for the coordination of remodeling, inflammation, and mucus hypersecretion in the airway of asthmatic patients [43], [58]. Type 2 innate lymphoid cells also secret Th2 cytokines, such as IL-13, which have important roles in goblet cell hyperplasia and mucus production [58]. Asthma has been divided into two distinct molecular phenotypes according to the degree of Th2 inflammation (Th2-high and Th2-low) [59]. Approximately 50% of asthmatic patients exhibit Th2-high asthma with increased levels of IL-4, IL-5, IL-13, and MUC5AC and severe mucus obstruction, although MUC5B levels are lower than those of MUC5AC [59], [60]. Mucin expression is detected in Th2-low asthma, but therapies targeting Th2 cytokines are effective in only a subset of patients [59].

Therefore, more detailed studies are needed, especially in patients exhibiting Th2-low asthma, to explore the mechanisms of mucus-producing cell hyperplasia and MUC5AC/MUC5B secretion and help in the development of an effective treatment. Figure 2 shows the signaling pathways involved in mucus production in asthma.

## COPD

COPD is a chronic inflammatory lung disease that causes breathing difficulty, coughing, and mucus hypersecretion. Chronic mucus hypersecretion is a prominent feature of COPD and contributes to disease progression [61]. Transient mucus hypersecretion occurs due to increased numbers of goblet cells or mucous cell hyperplasia in response to pathogens, oxidants, toxins, particles, and cigarette smoke, and normally disappears after the removal of the causative agent. However, in COPD, mucus overproduction persists, as manifested by increased sputum, and contributes to the worsening of the clinical symptoms [18].

Many studies emphasize the likely roles of cigarette smoke and rhinovirus infection as major risk factors in the increased numbers of goblet cells or mucous cell hyperplasia and mucus overproduction seen in COPD and have suggested several pathways involved in the promotion of mucous cell hyperplasia by

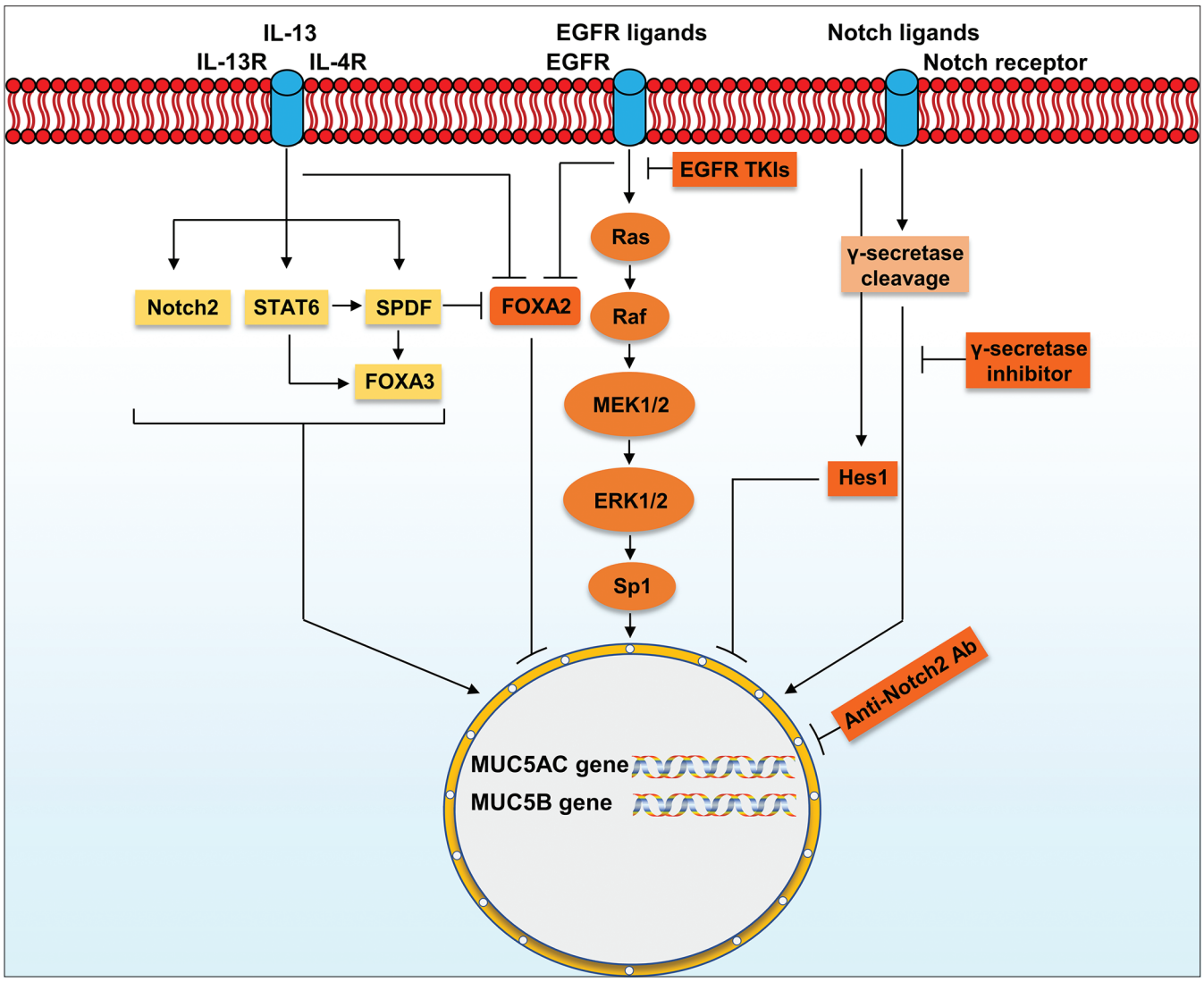


*Figure 2: Signaling pathways contributing to MUC5AC and MUC5B induction and mucin-producing cell differentiation in asthma. Interleukin (IL)-13 increases the number of mucin-producing cells and mucin production through its interactions with STAT6, SAM pointed domain-containing ETS transcription factor (SPDEF), and Notch. Forkhead ortholog A 2 inhibits MUC5AC, whereas this effect is repressed by IL-13, SPDEF, and epidermal growth factor receptor (EGFR). EGFR is activated by EGFR ligands, and the activation of EGFR kinase induces the Ras–Raf–MEK1/2–ERK1/2-Sp1 pathway, leading to MUC5AC transcription, whereas tyrosine kinase inhibitors inhibit EGFR phosphorylation. The interaction of Notch with its cell surface ligands activates γ-secretase-mediated proteolytic processes and the differentiation of mucin-producing cells. In contrast, an inhibitor of the Notch antagonist γ-secretase reduces the Notch-induced increase of mucin-producing cells. Hes1 also inhibits MUC5AC transcription. Furthermore, anti-Notch2 antibodies prevent goblet cell metaplasia and inhibit MUC5AC and MUC5B expression*

the modification of airway basal cells [62], [63]. The most common cause of COPD exacerbation is rhinovirus infection, through modification of the airway basal cells and promotion of a greater number of mucus-producing cells and *MUC5AC*/*MUC5B* expression [62], [63]. Rhinovirus infects basal cells by interacting with the highly expressed intercellular adhesion molecule 1 [64]. Rhinovirus suppresses junction barrier formation and prevents the normal renewal of injured and regenerating airway epithelium through the induction of epithelial-to-mesenchymal transition-like features, resulting in goblet cell hyperplasia [64]. This process is facilitated through the Notch signaling pathway. *Notch1*, *Notch3*, and Hes-related family bHLH transcription factor with YRPW motif 1 mRNA expression are increased in rhinovirus-infected COPD cells, whereas the inhibition of Notch signaling by a γ-secretase inhibitor abolishes rhinovirus-infected goblet cell hyperplasia and mucin gene expression; however, this effect is not seen with anti-IL-13 antibodies [63].

MUC5AC is produced by goblet cell hyperplasia in smokers, while MUC5B is produced by submucosal gland cells in COPD patients [4], [65]. In COPD patients, MUC5B is the prominent mucin in the bronchiolar lumen, while MUC5AC predominates in the bronchiolar epithelium [66]. MUC5AC levels are particularly high in smokers [65]. A recent study showed that the absolute concentrations of MUC5B are approximately 3 times higher in current or former smokers with severe COPD compared with controls who have never smoked, and MUC5AC levels are 10 times as high [4]. Further, analysis of the airway epithelium has revealed higher levels of EGFR in basal cells, whereas smoking induces its ligand EGF in ciliated cells, shifting the differentiation of basal cells from mucociliary to squamous and generating epithelial-to-mesenchymal transition-like phenotypes [62]. Smoking increases the number of goblet cells or promotes mucous cell hyperplasia by activating EGFR signaling in the airway basal cells, and this effect is independent of inflammation [67]. In addition, smoking has a detrimental effect on the function and structure of cilia [3], [68]. Thus, the cessation of smoking provides a protective effect against mucus production in the airway. Table 1 shows the characteristics of goblet cell hyperplasia, submucosal gland hypertrophy, and MUC5AC/MUC5B production in chronic diseases of the upper and lower airways.

**Table 1: Goblet cell hyperplasia, submucosal gland hypertrophy, and MUC5AC/MUC5B overproduction in chronic inflammatory diseases of the upper and lower airways**

| Disease | GCH | SGH | MUC5AC | MUC5B | References |
|---|---|---|---|---|---|
| Chronic rhinosinusitis | + | + | + | + | [24], [27], [28], [29] |
| Eosinophilic chronic rhinosinusitis | + | + | + | + | [33] |
| Allergic rhinitis | − | − | + | + | [22], [36],[40] |
| Asthma | + | + | + | + | [41], [42], [43] |
| COPD | + | + | + | + | [4], [65], [66] |

COPD: Chronic obstructive pulmonary disease, GCH: Goblet cell hyperplasia, SGH: Submucosal gland hypertrophy, +: Present, −: Absent.

## Cystic Fibrosis

Cystic fibrosis is a progressive disease of the airway caused by variants in the gene encoding the chloride-conducting transmembrane channel, called the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates salt and fluid transport [69]. CFTR is involved in mucociliary clearance in the airway and its functional failure results in mucus retention and chronic infection, and eventually inflammation [70].

It is believed that cystic fibrosis is associated with mucus hypersecretion, and so, the major gel-forming mucins MUC5AC and MUC5B are expected to be increased in cystic fibrosis. However, studies have shown that MUC5AC and MUC5B levels are not increased during stable cystic fibrosis but are increased during disease exacerbation in response to infection or inflammatory stimuli [71]. Exposure of the cystic fibrosis airway to persistent bacterial infection and inflammation results in airway epithelium remodeling, goblet cell hyperplasia, and increased mucin gene transcription [72]. Significant CFTR expression and its direct impact on the fundamental process of mucin production have not been observed in goblet cells [73]. It is believed that CFTR expression and activity are mainly localized to the epithelial cells neighboring goblet cells and abnormalities lead to inappropriate ion composition and fluid volume and consequently abnormal mucus production [73]. Furthermore, an increase in goblet cell size in cystic fibrosis tissue and a 4-fold increase in submucosal gland volume have been observed [16].

In cystic fibrosis, epithelial sodium channel activity and sodium transport are increased, leading to dehydration of the airway surface liquid and mucus and a reduction in the height of periciliary liquid [74]. Disrupted anion secretion alters the morphology of MUC5AC and MUC5B, resulting in impaired mucociliary clearance [69], [75]. Disrupted mucociliary clearance causes mucus obstruction, neutrophil infiltration, chronic bacterial infection, and inflammation, which are detrimental to airway health [70], [74]. Further detailed studies are required to elucidate the molecular mechanism and role of CFTR in goblet cells and mucous glands to establish proper management.

## Conclusion

It is important to detect the molecular mechanisms and pathways involved in mucus-producing cell hyperplasia, mucin hypersecretion, and control of mucin production. The heterogeneous structure of mucin molecules and their producing cells

makes it challenging to acquire meaningful information. Therefore, focusing on and understanding the roles of individual mucins and their producing cells in different diseases of the airway will contribute to elucidating the underlying mechanisms and developing optimal medications.

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