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REVIEW

Research Progress on the Mechanisms of High Mucus Secretion in the Airway: A Scoping Review

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Background: Excessive mucus production in the airways is a key pathogenic characteristic of chronic respiratory conditions, including bronchial asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). The etiology is intricate, encompassing various factors such as aberrant activation of inflammatory signaling pathways, deregulation of mucin gene expression, modified rheological characteristics of mucus, and impairment of the ciliary clearance mechanism. Nonetheless, the current evidence is disjointed, and a thorough and systematic synthesis is still absent.

Objective: This scoping review sought to systematically summarize and delineate the mechanisms of airway mucus hypersecretion, identify predominant research themes, and underscore significant knowledge gaps in existing studies.

Methods: This research was performed as a scoping review using the PRISMA principles. A thorough literature search was conducted in PubMed and the China National Knowledge Infrastructure (CNKI) databases using predefined keywords, encompassing papers from January 2005 to September 2025. Studies employing various experimental models to examine the mechanisms of airway mucus hypersecretion were included. Data were obtained from all qualifying papers for further synthesis.

Results: A total of 31 studies were incorporated. This paper methodically examines recent research developments in this domain, emphasizing fundamental inflammatory pathways exemplified by NF-κB, IL-13/STAT6, and EGFR; the function of transcription regulatory networks illustrated by SPDEF, Notch, and Wnt; modifications in mucus rheological characteristics, including hydration dysfunction and polymer surplus; and clearance deficiencies primarily driven by ciliary dysfunction in excessive mucus production.

Conclusion: Airway mucus hypersecretion is regulated by multiple mechanisms at various levels. This review systematically integrates contemporary evidence to establish a conceptual framework and translational perspective for developing targeted therapeutic strategies. These strategies include interventions aimed at IL-13–related pathways, transcriptional networks like Notch, water transport channels and regulatory factors, and genes linked to ciliary dysfunction, thereby facilitating the progression of personalized precision medicine in chronic airway diseases.

Keywords: respiratory diseases, hypermucus secretion in airways, bronchial asthma, COPD, CF, MUC5AC

Introduction

Chronic respiratory disorders impact 500 million individuals globally,[1] resulting in 4 million fatalities per year[2] and putting a considerable health burden on society. Approximately 50% of chronic obstructive pulmonary disease (COPD) patients, 20%–40% of asthma patients,[3] and nearly all cystic fibrosis (CF) patients experience symptoms of heightened airway mucus secretion, including coughing and excessive phlegm formation. Although clinical presentations are analogous, the underlying mechanisms vary significantly among disorders. Asthma is generally associated with Th2-driven inflammation, COPD is significantly connected with EGFR signaling and tobacco smoke exposure, whereas CF arises primarily from mutations in the CFTR gene. These mechanistic disparities suggest that a singular therapy approach is improbable to be universally efficacious for all patients.

The mucus layer on the airway surface functions as an essential barrier in the respiratory system and is integral to the body's defense processes. Normal airway surface mucus comprises 98% water, 0.9% ions, 0.8% globular proteins, and 0.3% high-molecular-weight mucoprotein polymers.[4] The mucus covering the airway surfaces moistens the airways and

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secretes diverse antibacterial and immunomodulatory chemicals to protect against bacterial invasion.[5] Excessive mucus production results in mucus buildup and airway blockage, simultaneously diminishing ciliary clearance. This fosters an environment conducive to harmful microbes, aggravating respiratory infections and inflammation.

Airway obstruction and bacterial accumulation due to mucus hypersecretion facilitate recurring infections and acute disease exacerbations of illness, thereby elevating the risk of hospitalization. Furthermore, hypoxemia and respiratory failure resulting from mucus-induced airway blockage are significant factors contributing to elevated death rates.[6] Concurrently, symptoms resulting from excessive mucus production, such as persistent cough, sputum expectoration, and dyspnea, significantly diminish patients' quality of life. Contemporary therapeutic methodologies demonstrate considerable constraints. The prolonged administration of corticosteroids correlates with a heightened risk of immunosuppression; mucolytic agents, such as N-acetylcysteine, can alter the physicochemical characteristics of sputum but have not definitively demonstrated efficacy in decelerating lung function deterioration; and biologic therapies are constrained by inconsistent response rates and restricted target demographics. These constraints collectively highlight the pressing necessity for innovative treatment strategies. Furthermore, significant variation is present even within the same airway pathology. Asthma can be classified into Th2-high and non–Th2 endotypes, while COPD comprises distinct phenotypes, including neutrophilic and eosinophilic subtypes. Consequently, attaining precision medicine necessitates the identification of disease-specific biomarkers and the exact alignment of therapeutic methods with the predominant pathogenic pathways in individual patients.

The mechanisms governing airway mucus formation are intricate, encompassing various factors including aberrant activation of inflammatory signaling pathways, deregulation of mucin gene expression, modified rheological properties of mucus, and impairment of the ciliary clearance system.[7] Despite comprehensive research clarifying the roles of inflammatory signaling pathways, transcriptional expression, mucus characteristics, and ciliary function in hypersecretory mucus, a systematic analysis of the interplay between these mechanisms, their relative significance across various diseases, and the obstacles in translating fundamental discoveries into clinical applications is still absent. This work seeks to bridge this gap by carefully examining advancements in this field, clarifying the inherent relationships among various levels, and concentrating specifically on promising novel therapeutic targets. This methodology offers a distinct theoretical framework and translational viewpoint for formulating precision-targeted therapy methods.

Materials and Methods

Study Design

This research was executed as a scoping review adhering to the methodological framework established by Arksey and O'Malley[8] and reported in compliance with the PRISMA Extension for Scoping Reviews (PRISMA) guidelines. This scoping review was not prospectively registered.

Identification of the Research Questions

The review aimed to clarify the mechanisms responsible for airway mucus hypersecretion. The subsequent research questions were established:

(1) Which primary mechanistic domains are most commonly examined in research on airway mucus hypersecretion, and what particular mechanisms have been identified within each domain?

(2) How do different signaling pathways and biological mechanisms converge to induce aberrant mucus production?

(3) What processes may possess translational significance for therapeutic advancement?

Identification of Relevant Studies

Based on the predefined research questions, a systematic literature search was performed in the PubMed and China National Knowledge Infrastructure (CNKI) databases. The search encompassed studies published from January 2005 to September 2025. The search phrases encompassed "mucus", "asthma", "COPD", "CF", "MUC5AC", "airway mucus hypersecretion", "mechanism", "goblet cell", "inflammation", "NF-κB", "IL-13", "EGFR", "SPDEF", "Notch" and "Wnt", along with their synonyms. The phrases were amalgamated via Boolean operators ("AND"/"OR") to extract pertinent entries.

Study Selection

All acquired records were imported into Covidence software for deduplication. Two authors (WY and XJ) independently evaluated eligible studies based on the established inclusion and exclusion criteria. All differences were addressed through dialogue with a third author (LC) until an agreement was achieved.

The inclusion criteria were as follows:

(1) Research examining the mechanisms that contribute to airway mucus hypersecretion;
(2) Research employing in vivo, in vitro, or clinical research models;
(3) Research presenting novel results;
(4) Publications authored in English or Chinese.

The exclusion criteria comprised:

(1) Review articles, consensus statements, and methodological studies;
(2) Studies not directly pertinent to the mechanisms of airway mucus hypersecretion;
(3) Articles lacking accessible full texts;
(4) Publications in languages other than English or Chinese.

Data Extraction

Two authors (JZ and LY) independently performed comprehensive evaluations of all included studies and retrieved essential information with a standardized data extraction form. The extracted data comprised author names and year of publication, study design, examined processes or signaling pathways, and principal findings concerning airway mucus hypersecretion. Disagreements were handled by consulting a third author (LC) to reach consensus.

Results

The literature search produced a total of 1510 documents, comprising 1,309 from PubMed and 201 from CNKI. Following the elimination of 32 duplicate records, 1478 studies were evaluated at the title and abstract level. After the preliminary screening, 1007 records deemed inappropriate to the research topic were eliminated, resulting in 471 studies selected for full-text retrieval. In the full-text retrieval process, 133 research were discarded due to inaccessible full texts, and 338 publications were evaluated for eligibility. According to the established inclusion and exclusion criteria, other papers were omitted, including review articles, studies not directly pertinent to mechanisms of airway mucus hypersecretion, and non-English or non-Chinese publications. A total of 31 original studies were incorporated into this scoping review. The process of research selection is depicted in the PRISMA flow diagram (Figure 1).

The 31 investigations encompassed in vitro cell-based experiments, animal research, and clinical observational or interventional studies, collectively offering a thorough examination of the mechanisms driving airway mucus hypersecretion. These studies clarified the pathological foundation of mucus hypersecretion at various levels, including abnormal activation of inflammatory signaling pathways, transcriptional regulation of mucin expression, modifications in mucus physicochemical properties, disruption of airway surface liquid homeostasis, and dysfunction of mucociliary clearance. The specific attributes of the included research are encapsulated in Table 1.

Abnormal Activation of Inflammatory Signaling Pathways

Elevated mucus production in the airways is intricately linked to chronic inflammation. Various stimuli (including viruses, allergens, and pollutants) activate immune cells (such as neutrophils, eosinophils, and lymphocytes), prompting the release of inflammatory mediators and establishing a complex regulatory network. This network conveys inflammatory signals to airway epithelial cells via multiple fundamental signaling pathways, triggering mucin gene expression and facilitating goblet cell metaplasia and proliferation. The NF-κB, IL-13/STAT6, and EGFR pathways are the principal signaling axes that govern excessive mucus secretion.

Core Inflammatory Signaling Pathways

NF-κB Pathway (Inflammatory Response Hub)

The NF-κB pathway functions as a crucial center in host defense and chronic inflammation, holding a primary upstream

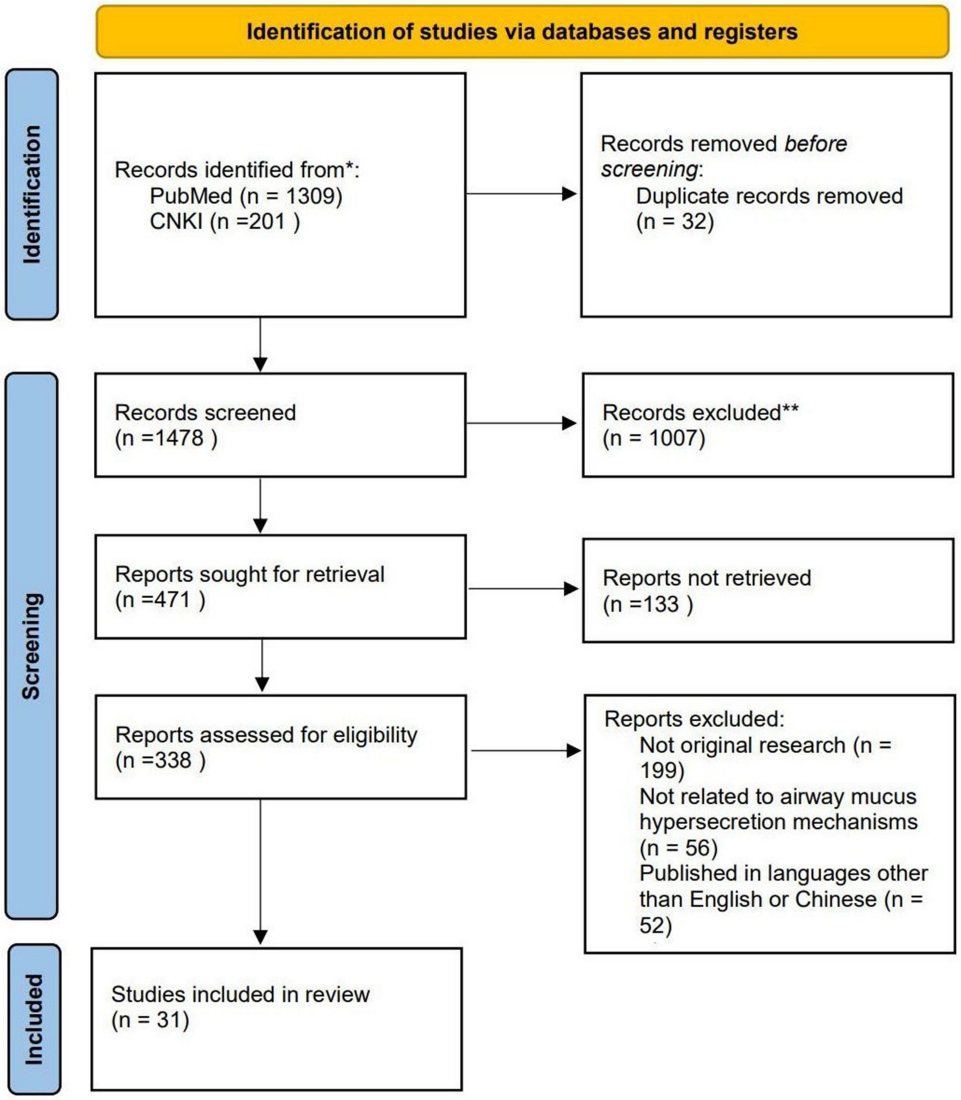

Figure 1 PRISMA flow diagram.

role within the inflammatory network. Viruses, bacteria, and different inflammatory mediators (such as TNF-α) attach to their specific receptors, swiftly activating the IKK complex. This results in the phosphorylation of the IκBα protein, prompting its dissociation from NF-κB. NF-κB is subsequently liberated and translocates into the nucleus. Upon nuclear translocation, NF-κB activates the expression of inflammatory and mucin genes[9] (Figure 2). In the non-canonical NF-κB pathway,[40] ligands such as CD40 and lymphotoxin-β receptor (LTβR) interact with their respective cell surface receptors, resulting in the activation of NF-κB–inducing kinase (NIK). Activated NIK subsequently phosphorylates the IKKα complex, leading to the processing of NF-κB precursor proteins and nuclear translocation of the active subunits, thereby activating the transcription of certain target genes. This route largely governs lymphoid organogenesis and the growth and maturation of lymphocytes. The NF-κB pathway functions in conjunction with various other signaling pathways, including MAPK and Wnt, to collaboratively govern cellular proliferation, inflammation, immunological responses, and differentiation.[41] Moreover, NF-κB signaling functions as a pivotal downstream component activated by other pathways, such as EGFR signaling. Yao Li et al[42] found that influenza A and B viruses enhance MUC5AC gene expression and promote mucus production via facilitating NF-κB nuclear translocation and p38 phosphorylation in the mitogen-activated protein kinase (MAPK) pathway. Although NF-κB signaling is traditionally linked to pro-inflammatory responses,

Table 1 Study Characteristics

Author (Year)	Study Type	Mechanism	Main Findings
Bae et al., 2019[9]	In vitro mechanistic study	Caveolin-1–dependent cytokine receptor clustering and NF-κB activation	Caveolin-1 upregulation enhanced cytokine-induced NF-κB activation and cellular injury, whereas caveolin-1 inhibition attenuated inflammatory responses.
Liu et al., 2018[10]	In vivo animal study	IL-13/STAT6–mediated mucus regulation	Curcumin suppressed IL-13/STAT6 signaling and reduced airway mucus hypersecretion in an asthmatic rat model.
Symowski et al., 2019[11]	In vivo animal study	IL-4/IL-13–STAT6–mediated type 2 inflammation	Th2 cell–derived IL-4 and IL-13 promoted ILC2 accumulation in the lung through STAT6-dependent signaling.
Dai et al., 2021[12]	In vitro and in vivo mechanistic study	MCPIP1 regulation of IL-13–induced airway mucus hypersecretion via GABAAR receptor signaling	Upregulation of MCPIP1 attenuated OVA- and IL-13-induced airway inflammation and mucus hypersecretion, reduced MUC5AC expression, and suppressed GABA_A receptor β2 subunit signaling in murine asthma models and bronchial epithelial cells.
Shin et al., 2014[13]	In vitro and in vivo mechanistic study	MAPK signaling–mediated regulation of MUC5AC expression	Melatonin significantly reduced EGF- and OVA-induced MUC5AC expression by inhibiting MAPK phosphorylation (ERK, JNK, and p38), accompanied by decreased airway inflammation and mucus production, indicating its inhibitory effect on airway mucus hypersecretion.
Roy et al., 2014[14]	In vivo animal study	Functional role of MUC5B in mucociliary clearance and airway host defense	Genetic deletion of Muc5b in mice caused severe impairment of mucociliary clearance, mucus accumulation, chronic airway infection, and unresolved inflammation, whereas Muc5ac deficiency did not compromise airway defense. These findings demonstrate that MUC5B is essential for maintaining airway mucus transport and immune homeostasis.
Kesimer et al., 2017[15]	Clinical observational study	Airway mucin hyperconcentration as a biophysical mechanism underlying chronic bronchitis	Total airway mucin concentrations were significantly increased in patients with chronic bronchitis and severe COPD, correlated with sputum production, airflow obstruction, and exacerbation frequency, supporting mucin hyperconcentration as a key pathogenic mechanism in muco-obstructive airway disease.
Wu et al., 2024[16]	In vitro mechanistic study	ROS/IP3R/Ca2+ signaling pathway in CSE-induced MUC5AC overexpression	Cigarette smoke extract (CSE) induced MUC5AC overexpression in Calu-3 cells by activating ROS production, IP3R/Ca2+ signaling, and the unfolded protein response (UPR). Knockdown of IP3R or treatment with NAC (N-acetyl-cysteine) alleviated these effects, indicating that ROS and IP3R/Ca2+ signaling contribute significantly to MUC5AC overexpression.
Baginski et al., 2006[17]	In vitro and in vivo mechanistic study	Synergistic enhancement of MUC5AC mucin production induced by cigarette smoke and proinflammatory stimuli (LPS, TNF-α)	Cigarette smoke extract (CSE) significantly enhanced MUC5AC mucin production induced by LPS and TNF-α in NCI-H292 cells. This effect was dose-dependent and involved the activation of EGFR signaling and oxidative stress. In vivo, CSE exposure amplified LPS-induced mucin production in rat airways and increased mucous-cell metaplasia. Co-exposure with CSE and LPS also raised total mucin content in bronchoalveolar lavage fluid.
Decramer et al., 2005[18]	Randomized controlled trial	Antioxidant therapy in COPD	N-acetylcysteine did not significantly reduce FEV1 decline or exacerbation rates in COPD patients.
Nagashima et al., 2016[19]	In vitro mechanistic study	Clarithromycin effects on IL-13-induced goblet cell hyperplasia	Clarithromycin inhibited IL-13-induced goblet cell hyperplasia and MUC5AC production by suppressing SPDEF and CLCA1 expression, without affecting STAT6 phosphorylation.

(*Continued*)

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Table 1 (Continued).

Author (Year)	Study Type	Mechanism	Main Findings
Siddiqui et al., 2021[20]	In vitro and in vivo mechanistic study	miR-141 regulation of IL-13–induced mucus production	miR-141 promoted IL-13–induced goblet cell differentiation and MUC5AC production, while miR-141 inhibition reduced airway mucus secretion.
Hu et al., 2023[21]	In vivo animal study	Midkine/Notch2/Hey1 signaling pathway in inflammation modulation	Erchen Decoction reduced airway inflammation in COPD rats through the Midkine/Notch2/Hey1 signaling pathway, decreasing inflammatory markers and improving lung function.
Kim et al., 2019[22]	In vivo animal study	WNT/RYK signaling in goblet cell differentiation	Loss of RYK impaired WNT/β-catenin signaling and induced goblet cell hyperplasia and mucus hypersecretion in the airway epithelium.
Li et al., 2021[23]	In vitro mechanistic study	miR-34b/c regulation of MUC5AC overexpression in RSV-infected airway epithelial cells	miR-34b/c inhibited MUC5AC overexpression in RSV-infected cells by targeting FGFR1 and regulating c-Jun/AP-1 signaling.
Tasena et al., 2018[24]	In vitro mechanistic study	miRNA regulation in chronic mucus hypersecretion (CMH) in COPD	miRNA-mediated regulation of mucus secretion, with miR-34b/c showing significant roles in modulating mucus production and inflammation in COPD cells.
Nishida et al., 2023[25]	In vitro mechanistic study	Mitochondrial damage and STING pathway in oxidative stress-induced MUC5AC expression	Oxidative stress-induced mitochondrial damage releases mtDNA, activating the STING pathway, which increases MUC5AC expression in airway epithelial cells.
Hauber et al., 2005[26]	In vitro and ex vivo experimental study	hCLCA1-mediated mucin production and inhibition by niflumic acid and MSI-2216	Inhibition of hCLCA1 using niflumic acid and MSI-2216 significantly reduced MUC5AC mRNA and mucus production in TNF-α-stimulated human airway mucosa explants.
Keeler et al., 2022[27]	In vivo animal study	CLCA1 regulation of MUC5AC-dependent mucus production	CLCA1 knockout in pigs selectively abolished MUC5AC-expressing mucous cells in airway epithelium without affecting MUC5B or MUC2, demonstrating an essential role of CLCA1 in airway mucus production in vivo.
Simonin et al., 2019[28]	Ex vivo human study	Airway surface liquid (ASL) acidification and CFTR-dependent bicarbonate transport	Reduced ASL pH in CF airways impaired bacterial clearance through defective CFTR/pendrin-dependent bicarbonate secretion and persistent ATP12A-mediated proton secretion.
Clunes et al., 2012[29]	In vitro and in vivo translational study	Cigarette smoke–induced CFTR dysfunction and airway surface liquid dehydration	Cigarette smoke induced CFTR internalization and loss of function, leading to airway surface liquid dehydration, mucus stasis, and impaired mucociliary clearance.
Liu et al., 2022[30]	In vitro mechanistic study	Particulate matter– and cold stimulation–induced MUC5AC expression	Fine particulate matter and cold exposure induced MUC5AC expression in airway epithelial cells, indicating that environmental stimuli directly promote airway mucus hypersecretion.
Lv et al., 2019[31]	In vivo animal study	AQP1/AQP5 dysregulation and ER stress in allergic airway inflammation	Sevoflurane attenuated airway inflammation and mucus hypersecretion by restoring AQP1/AQP5 expression and inhibiting ER stress markers (BiP, CHOP) in OVA-induced allergic mice.
Yang et al., 2016[32]	In vitro mechanistic study	NF-κB–mediated regulation of MUC5AC and AQP5 in COPD	S-allylmercapto-L-cysteine reduced LPS-induced MUC5AC expression and restored AQP5 levels by inhibiting NF-κB activation in airway epithelial cells.
Sidhaye et al., 2005[33]	In vitro mechanistic study	cAMP/PKA regulation of AQP5 trafficking and abundance	cAMP exerted biphasic effects on AQP5 in lung epithelial cells, causing short-term internalization and degradation but long-term membrane accumulation and increased expression via PKA-dependent signaling.
Delfino et al., 2021[34]	In vitro mechanistic study	DNase1L2-mediated degradation of DNA-rich mucus in cystic fibrosis	DNase1L2 rapidly reduced the viscosity of actin-rich cystic fibrosis mucus and showed strong resistance to actin inhibition, indicating its potential as an alternative mucolytic therapy for CF lung disease.

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Takabayashi et al., 2017[35]	Ex vivo and clinical sample–based experimental study	Fibrin degradation–mediated reduction of mucus viscosity	Nattokinase degraded fibrin in nasal polyp tissue and significantly reduced the viscosity of nasal discharge and sputum from patients with chronic rhinosinusitis and asthma.
Abou Alaiwa et al., 2024[36]	In vivo animal study	DNAI1 mutation–induced ciliary dysfunction and impaired mucociliary transport	DNAI1-mutant pigs exhibited defective ciliary motility, severely impaired mucociliary transport, airway mucus obstruction, and progressive airway inflammation, closely recapitulating primary ciliary dyskinesia lung disease.
Bonnefoy et al., 2018[37]	Human genetic and mechanistic study	LRRC56-dependent intraflagellar transport and dynein arm assembly	Biallelic LRRC56 mutations disrupted intraflagellar transport–mediated dynein arm assembly, causing ciliary dyskinesia, impaired mucociliary clearance, and chronic airway disease.
Mata et al., 2012[38]	In vitro mechanistic study	RSV-induced oxidative stress, ciliagenesis impairment, and mucus hypersecretion	RSV impaired ciliagenesis and induced MUC5AC expression, which were reversed by N-acetylcysteine through antioxidant mechanisms.
Leopold et al., 2009[39]	Clinical observational study	Smoking-associated cilia shortening and impaired mucociliary clearance	Airway epithelial cilia were significantly shorter in smokers than in nonsmokers, which was predicted to reduce effective mucociliary clearance and contribute to smoking-related airway disease.

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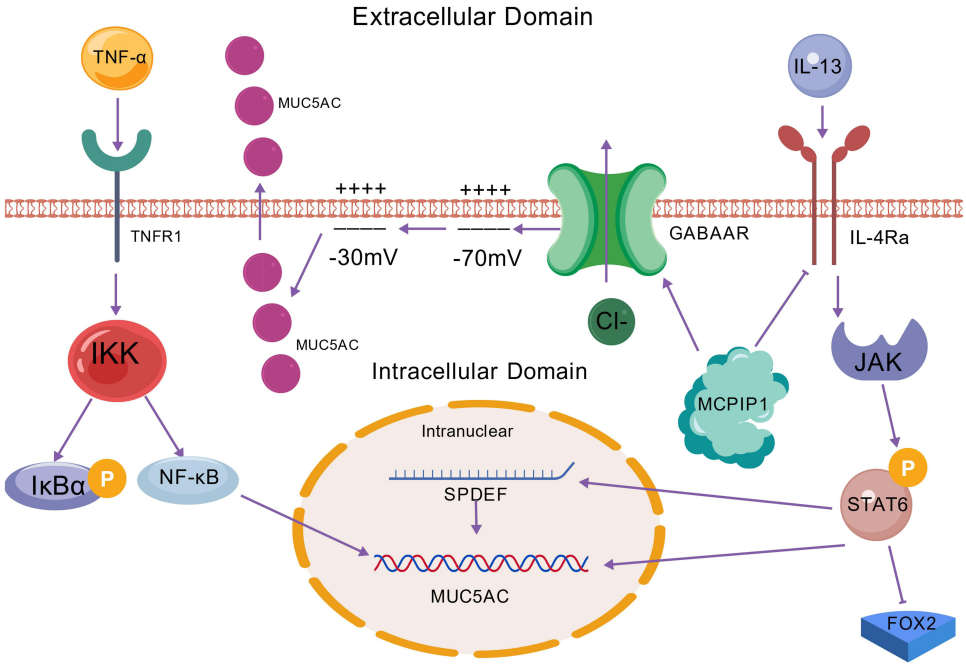

Figure 2 Schematic diagram of NF-KB, IL-13/STAT6, and GABAAR signaling pathways.

emerging evidence indicates that it may also have context-dependent anti-inflammatory effects by inhibiting the production of the pro-inflammatory cytokine interleukin-1β (IL-1β) and restricting its biological activity.[43]

Inhaled corticosteroids inhibit the active NF-κB pathway, effectively reducing airway inflammation and mucus production. They function as primary pharmacological agents for individuals with asthma and COPD. Nonetheless, prolonged use is linked to a heightened risk of immunosuppression, osteoporosis, and metabolic disorders, significantly constraining the clinical utility of corticosteroids. Macrolide antibiotics have been shown to suppress NF-κB pathway activation and inflammatory mediators.[44] Nonetheless, their use is linked to the hazards of bacterial resistance, cardiotoxicity, and ototoxicity, especially with prolonged use, potentially resulting in severe clinical ramifications. Consequently, while macrolides may offer therapeutic advantages in specific clinical situations, apprehensions about adverse effects and antimicrobial resistance cast doubt on their long-term efficacy and viability in clinical practice. Currently, there are nearly no agents that can directly and very selectively inhibit the NF-κB pathway.

The direct suppression of NF-κB, as a crucial component of the inflammatory network, undermines host defense and results in immunodeficiency. Future advancements depend on formulating focused regulation strategies for airway inflammatory cells, facilitating specific anti-inflammatory actions without causing immunosuppression.

IL-13/STAT6 Pathway (Core Axis of Th2-Type Inflammation)

IL-13 is a crucial pathogenic factor that triggers the Th2-type immune response in asthma. Signal Transduction and Activation of Transcription 6 (STAT6) functions as an essential element in intracellular signaling. Related investigations have demonstrated that STAT6 is also involved in the mechanism of airway mucus secretion in asthma. IL-13 functions as an upstream stimulatory factor within the STAT6 signaling pathway.[10] Th2 immune cells release IL-13, which attaches to the IL-4 receptor antagonist (IL-4Ra) on the cell membrane. This initiates the intracellular JAK-STAT6 pathway, resulting in the phosphorylation of STAT6. Phosphorylated STAT6 migrates to the nucleus, where it enhances the expression of the MUC5AC gene.[45] Furthermore, STAT6 can directly inhibit the expression of FOXA2, a negative regulator of goblet cell development and mucin production, thus creating negative feedback and alleviating the restriction. This stimulates goblet cell proliferation[46] and the expression of the MUC5AC gene[11] (Figure 2). A study revealed that FOXA2 is essential for controlling airway mucus secretion in lung tissues of asthma patients. The downregulation of FOXA2 was significantly and inversely associated with elevated MUC5AC expression

and goblet cell hyperplasia, a condition particularly evident in individuals with severe or fatal asthma accompanied by pronounced airway limitation.[47]

In asthma, the Th2 cytokine signaling pathway is highly reliant on IL-13 and its associated signaling pathways, which are crucial for promoting significant mucus secretion. Consequently, substantial resources are allocated to the advancement of therapeutics that inhibit IL-13 signaling. Compounds that inhibit the action of signaling components at different stages of this route are presently being studied. The majority of research has been on inhibiting the interaction between IL-13 and IL-4Ra. IL-13 antagonists have been clinically developed and utilized,[48] including specific therapeutic therapeutics such as omalizumab, mepolizumab, reslizumab, and dupilumab.[49] These biologic medicines have significantly altered the treatment paradigm of asthma; nevertheless, their exorbitant cost and the limited clinical efficacy shown in just a fraction of patients limit their widespread application. Their efficacy requires additional observation. STAT6 inhibitory peptides demonstrate potential for clinical application in asthma; however, further research is necessary to determine the exact mechanism by which these peptides suppress mucus production.[50]

Recent investigations have uncovered an additional mechanism for IL-13-mediated mucus secretion. GABAAR, a chloride channel, has been shown to stimulate prolonged mucus production by facilitating chloride efflux, leading to depolarization of the airway epithelium. IL-13 activates GABAAR, resulting in chloride efflux and cell depolarization by blocking the negative inflammatory regulator MCPIP1, therefore directly promoting prolonged mucin secretion independently of STAT6[12] (Figure 2).

While IL-13 antagonists exhibit effectiveness in certain asthma patients, their response rates are ambiguous, highlighting the need for the exploration of alternate routes. Subsequent investigations ought to incorporate biomarkers to discern groups most predisposed to benefit from this therapy and examine innovative intervention tactics aimed at downstream effector pathways of STAT6 or non-canonical pathways such as GABAAR, thereby facilitating more precise stratified treatment.

Downstream Effect Pathway: EGFR Pathway

The signalling of the epidermal growth factor receptor (EGFR) is marked by the participation of many cell surface receptor proteins, including EGFR (ErbB1), ErbB2, ErbB3, and ErbB4.[51] The EGFR pathway is involved in almost all facets of airway mucus hypersecretion in COPD. The EGFR pathway does not elicit inflammatory responses; rather, it acts as an integrative hub, converging many upstream signals like inflammation, oxidative stress, and environmental pollutants.[52]

The NF-κB pathway promotes the production of certain ligands, such as amphotericin B receptor-like protein (AREG). Upon ligand interaction, EGFR experiences conformational alterations and dimerizes with ErbB2, thereby activating its intrinsic tyrosine kinase (TK) activity. This subsequently activates the downstream phosphoinositide-3-kinase (PI3K) and serine/threonine protein kinase (AKT) pathways. This mechanism can collaborate with the IL-13 pathway to enhance MUC5AC gene transcription, resulting in increased mucus secretion and decreased clearance in COPD patients, thereby clogging the airways[53] (Figure 3). Further research suggests that in conditions like oxidative

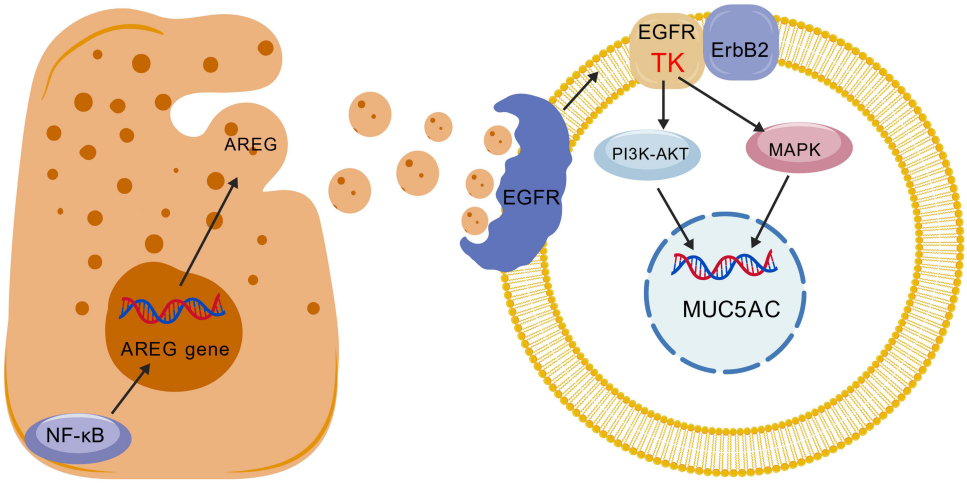

Figure 3 Schematic diagram of the EGFR signaling pathway.

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stress and bacterial products, EGFR tyrosine phosphorylation may transpire through a non-ligand-dependent mechanism. This subsequently activates a MAPK cascade, leading to the production of the MUC5AC gene.[13]

The EGFR pathway is essential for MUC5AC production and mucinous metaplasia triggered by allergens, allergic cytokines, bacterial exotoxins, viruses, cigarette smoke, and chemical agents. Consequently, employing EGFR TK inhibitors (such as afatinib, gefitinib, and erlotinib) presents a promising therapeutic approach to mitigate excessive mucus secretion in diverse pulmonary diseases. Currently, EGFR TK inhibitors are predominantly utilized for lung tumors, with third-generation inhibitors providing enhanced survival outcomes for individuals with non-small cell lung cancer.[54] Despite EGFR being a crucial signaling pathway, its efficacy in mitigating airway mucus hypersecretion is constrained, mostly due to apprehensions about systemic toxicity linked to EGFR-targeted treatments. Consequently, the development of inhaled EGFR inhibitors for localized delivery and minimized systemic effects is a crucial strategy for effectively converting them into therapies that mitigate excessive mucus secretion in the airways.

Dysregulation of Mucin Gene Expression

MUC5AC and MUC5B are recognized as the predominant mucins in the airway. In healthy conditions, MUC5B is the predominant mucin in the airways, crucial for mucociliary clearance, whereas MUC5AC is the secondary mucin in healthy airways.[14] Using stable isotope dilution mass spectrometry, one study quantitatively assessed sputum MUC5AC levels in a cohort of 148 individuals with COPD. Research indicates that MUC5AC levels in individuals with severe COPD markedly elevate with disease progression, attaining 108 ± 31 pmol/mL (exceeding tenfold). MUC5AC levels significantly increase with disease severity in individuals with mild to moderate COPD. Thus, elevated MUC5AC production is regarded as a primary pathogenic mechanism in COPD patients.[15] MUC5AC is predominantly synthesized by goblet epithelial cells and is affected by external stimuli, including smoking and air pollution. Smoking is a significant risk factor for individuals with COPD. In vitro investigations have demonstrated that cigarette smoke extract (CSE) can provoke the overexpression of MUC5AC in cells via oxidative stress, the IP3R/Ca^{2+} ratio (with IP3R referring to the inositol trisphosphate receptor), and the unfolded protein response.[16] In a rat model of airway inflammation, CSE was seen to synergistically augment LPS- and TNF-α-induced MUC5AC synthesis, with MUC5AC levels closely correlating with CSE concentration.[17] Excessive MUC5AC synthesis elevates airway mucus viscosity, complicating clearance and heightening the risk of airway blockage. N-acetylcysteine functions primarily as a mucolytic and antioxidant agent by disrupting disulfide bonds in mucin. Clinical investigations, however, have demonstrated that it has no substantial impact on stopping the decline of lung function in COPD patients. Consequently, the present research emphasis is on the formulation of a novel mucolytic agent.[18]

The dysregulation of mucin gene expression serves as the direct molecular foundation for excessive mucus release in the airways. Regulation can be classified into three tiers: direct transcriptional control within the cell nucleus, epigenetic regulation that influences gene expression without modifying DNA sequences, and cellular stress responses to both internal and external environmental alterations.

Transcriptional Regulation: The Core Mechanism of Mucin Gene Expression

SPDEF

SPDEF, also known as the prostate-derived ETS factor, functions as the principal regulator of secretory cell differentiation and functional preservation. Recent findings demonstrate that SPDEF is produced in airway epithelial cells and facilitates mucus production via many mechanisms, including control by the upstream IL-13/STAT6 pathway, where phosphorylated STAT6 promotes SPDEF transcription. SPDEF is involved in Th2-mediated airway inflammation and facilitates goblet cell metaplasia,[19] directly triggering the expression of many mucin-related genes, including MUC5AC. Agents aimed at SPDEF effectively inhibit its transcription and diminish excessive mucus production. Novel forkhead box M1 protein inhibitors can downregulate SPDEF expression and reduce goblet cell metaplasia.[20]

SPDEF, as the principal regulator of cup cell metaplasia, is a compelling therapeutic target. Nonetheless, its complexity as a transcription factor for pharmacological development presents considerable obstacles. Future endeavors should concentrate on its upstream regulators (eg, STAT6) or downstream effector networks to indirectly influence its function.

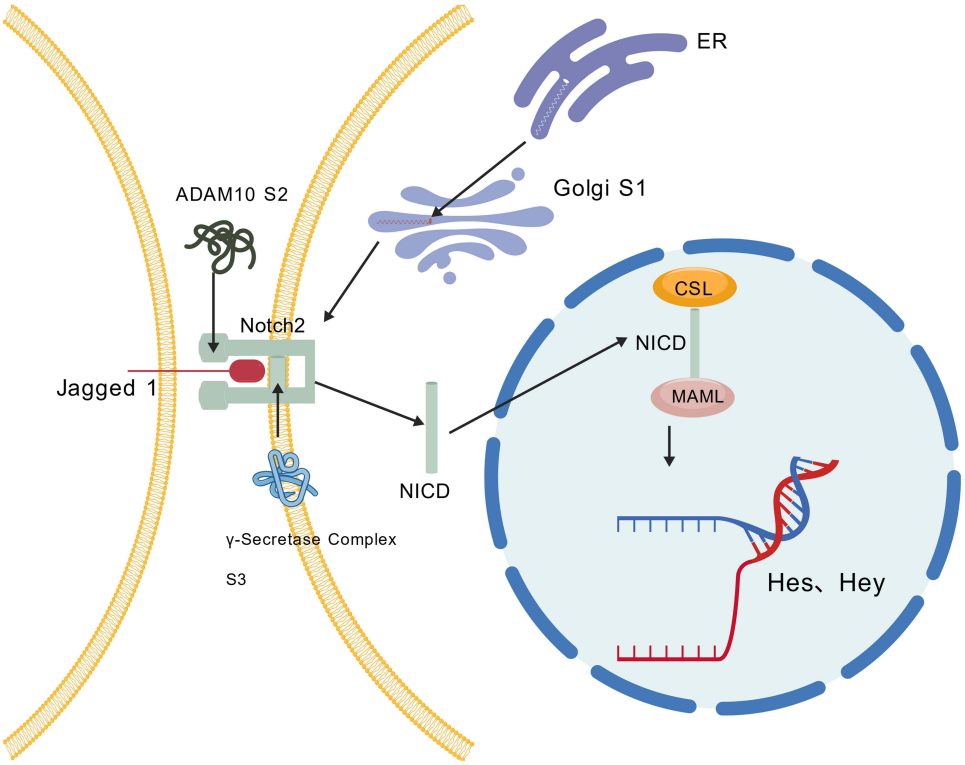

Figure 4 Schematic diagram of the Notch signaling pathway.

Notch Pathway

The Notch signaling pathway is an evolutionarily conserved signaling mechanism identified as a crucial regulator of airway basal cell development within the ciliated lineage, largely responsible for maintaining the balance between goblet cells and ciliated cells. The Notch family consists of four transmembrane receptor proteins, with Notch2 serving as one of the transcription factors downstream of IL-13.[21] Inhibiting Notch2 attenuates IL-13- and allergen-induced goblet cell metaplasia. In murine models of respiratory illnesses, pretreatment with Notch receptor ligand inhibitors before inflammatory stimulation diminishes goblet cell metaplasia. Moreover, Notch1 and Notch3 can elicit goblet cell metaplasia even in routes devoid of inflammatory cell participation.[55] The traditional Notch signaling pathway (Figure 4): The Notch2 receptor is produced in the endoplasmic reticulum and undergoes enzymatic processing (S1 cleavage) in the Golgi apparatus prior to interacting with its ligand (Jagged1) on the cell surface. The extracellular domain of Notch2 undergoes initial cleavage by ADAM metalloproteinases (S2 cleavage), subsequently followed by transmembrane cleavage by the γ-secretase complex (S3 cleavage). The intracellular domain (NICD) of Notch2 is translocated into the nucleus, where it associates with CSL and MAML to activate the transcription of downstream target genes Hes and Hey. Hes1 is the effector molecule downstream of the process. Elevated Hes1 activity inhibits Notch signaling, hence obstructing ciliocyte differentiation and facilitating goblet cell differentiation. Reduced Hes1 levels impede Notch signaling and alleviate the inhibition of ciliocyte differentiation.[56]

Due to the ubiquitous presence of the Notch pathway in multiple organs, its inhibition may elicit systemic responses. As a result, it is predominantly employed in tumor research.[57] To mitigate systemic adverse effects, the development of a locally inhalable medication that can inhibit the Notch pathway has emerged as a focal point of research for numerous scientists. This field is still in a phase of theoretical investigation and preliminary research.

Wnt/β-Catenin Pathway

The Wnt pathway is an evolutionarily conserved cell signaling system that is crucial for lung development, homeostasis, and goblet cell differentiation.[58] RYK (receptor TK) operates as a pseudokinase and serves as a Wnt co-receptor.[59]

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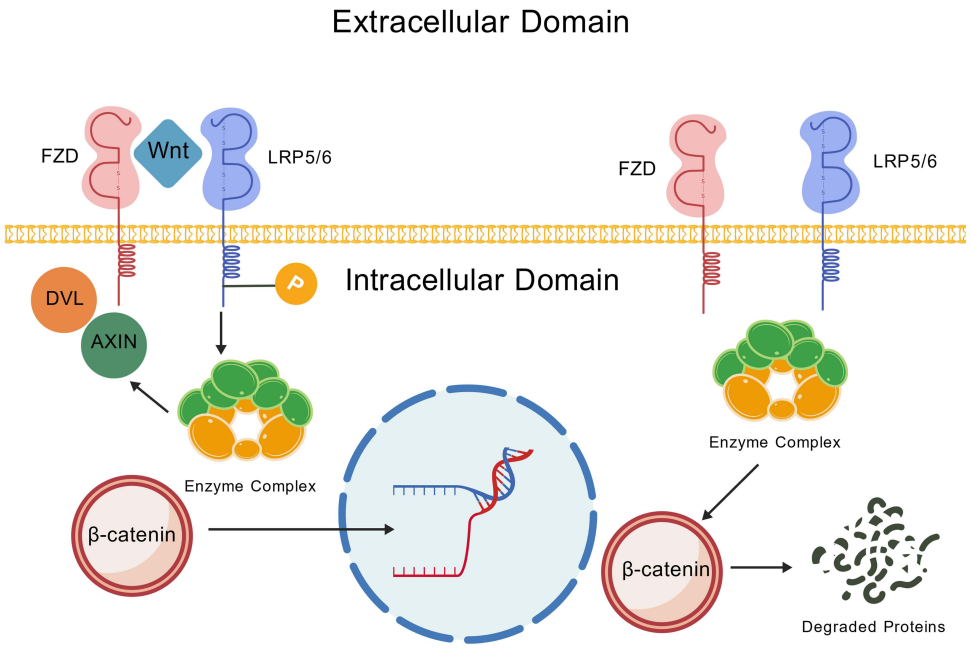

Figure 5 Schematic diagram of the Wnt/β-catenin signaling pathway.

A multitude of studies has demonstrated that mice possessing RYK gene mutations or abnormalities display goblet cell hyperplasia and increased mucus secretion, alongside elevated transcription of MUC5AC and MUC5B. RYK may function as a positive regulator of the Wnt pathway, independently influencing the airway epithelium.[22] The principal route regulating goblet cell development is the Wnt/β-catenin pathway (Figure 5), which primarily functions to prevent the transformation of basal cells into goblet cells. In the absence of extracellular Wnt ligands, β-catenin undergoes fast phosphorylation and degradation by a complex enzyme, inhibiting its accumulation and nuclear translocation, which consequently suppresses the transcription of target genes. Extracellular Wnt ligands bind to the cell surface receptors FZD and LRP5/6, resulting in the phosphorylation of LRP5/6 receptors and the recruitment of DVL and AXIN from the complex to the bound receptors. This impedes intricate processes, obstructs β-catenin degradation, and promotes β-catenin translocation into the cell nucleus, thereby activating target gene expression.[60]

The Wnt pathway, akin to the Notch pathway, is extensively prevalent throughout several systems and organs. Modifying its function can elicit numerous systemic responses. Consequently, the development of locally inhaled agents or extremely disease-specific therapeutics signifies a prospective avenue for investigation.[61]

Epigenetic Regulation: Regulatory Networks of miRNAs

miRNAs are a category of tiny non-coding RNA molecules that are essential in regulating target genes, affecting cellular processes. They function as regulators of specific genes within pertinent signaling pathways and engage in various biological processes. MiRNAs in the lungs are significant regulators of mucus secretion in airway epithelial cells.[23] Recent studies have identified 20 differentially expressed miRNAs in individuals with COPD, indicating a potential correlation with increased mucus secretion. Among these, miR-134-5p and miR-146a-5p are miRNAs with possible target genes associated with elevated mucus secretion. Their primary target genes comprise KRAS, EDN1, PRKAR2A, GSK3B, and POLR2H. These miRNAs can diminish TNF-α-induced hypermucus secretion by blocking the NF-κB and MAPK signaling pathways.[24] Recent studies indicate that miR-141 is significantly expressed in airway epithelial cells[62] and modulates IL-13-induced MUC5AC production in asthma, hence contributing to excessive mucus secretion in the airways. This pertains to the focused regulation of goblet cell-specific genes by miR-141. The study further demonstrated that the suppression of miR-141 diminishes airway hyperresponsiveness and mucus secretion. Additional research has revealed that miR-125a and miR-125b can directly target proteins produced by TNF-α, thereby suppressing goblet cell development.[63]

MiRNAs have garnered considerable attention in therapeutic target research owing to their ability to simultaneously regulate numerous biological processes. The principal problem presently involves the secure delivery of miRNA therapies to lung cells, with a central emphasis on advancements in delivery vehicles.

Stress Responses

Oxidative Stress

Oxidative stress is distinguished by an imbalance between the production and removal of reactive oxygen species (ROS) within the body, leading to an accumulation of ROS that exceeds the physiological limit. Cigarette smoke and atmospheric pollutants represent the principal external sources of oxidative stress, whereas the predominant endogenous source of ROS arises from mitochondria within cells. Oxidative stress directly assaults mitochondria, resulting in the release of damaged mitochondrial DNA (mtDNA) into the cytoplasm.[64] mtDNA in the cytoplasm can initiate the STING pathway in innate immunity,[65] resulting in the activation of MUC5AC transcription and enhanced expression of MUC5AC.[25] Oxidative stress is intricately linked to the inflammatory signaling system NF-κB, which amplifies the activation of inflammatory mediators, ultimately resulting in persistent airway inflammation and elevated mucin expression.

Presently accessible pharmaceuticals, such as N-acetylcysteine, vitamins C, E, and D, and sulforaphane, are predominantly used for their antioxidant attributes. Research indicates that augmenting the consumption of vegetables and fruits may diminish oxidative stress; however, their clinical efficacy remains constrained.[66] Consequently, the advancement of mitochondrial protectants and STING pathway inhibitors is emerging as a novel therapeutic strategy for addressing airway illnesses characterized by excessive mucus production associated with oxidative stress, including asthma and COPD.

Environmental Stress: Cold-Induced RNA-Binding Protein (CIRP)

CIRP is a stress-responsive protein activated by various environmental stresses, present in diverse cell types, and functions in RNA chaperoning by altering the stability of its target mRNAs.[67] The expression of CIRP in bronchial epithelial cells is inducible by many environmental stimuli, including cigarette smoke and cold air exposure. The increase of pro-inflammatory cytokines such as TNF-α, IL-8, and IL-6, together with MUC5AC, induces inflammation and excessive mucus production.[68]

Considering the function of CIRP in environmental stress, neutralizing antibodies against it or small-molecule inhibitors aimed at its receptor are emerging as innovative therapeutic strategies for airway inflammatory disorders. These approaches seek to interrupt the "stress-inflammation" axis; however, research in this domain is still nascent.

Alterations in Mucus Rheological Properties

Abnormal Hydration

Calcium-Activated Chloride Channel Modulator 1 (CLCA1) and Transmembrane Chloride Channel 16A (TMEM16A)

CLCA1 is a soluble secreted protein that modulates mucus production in goblet cells. It functions as a crucial mediator in hypersecretory lung diseases, including asthma, COPD, CF, and diseases marked by elevated mucus production.[69] CLCA1 enhances mucin expression, with the IL-13/STAT6 inflammatory pathway as its primary upstream mechanism. This pathway directly augments CLCA1 gene expression, while CLCA1 serves as a robust, specific inducer of MUC5AC gene expression. Consequently, this enhances MUC5AC gene expression and elevates mucin secretion.[70] Hans-Peter Hauber et al[26] discovered that in an ex vivo model of human upper airway mucosa, TNF-α activation enhances the expression of the CLCA1 and MUC5AC genes, resulting in elevated mucin levels. Shamus P Keeler et al[27] demonstrated via CLCA1 gene deletion in domestic pigs that the absence of MUC5AC mucus-secreting cells transpired throughout the pulmonary airway mucosa, although MUC5B mucus-secreting cells remained unaltered. This confirmed the function of CLCA1 in modulating MUC5AC gene expression. In addition to its impact on mucin, CLCA1 also improves mucus hydration. CLCA1 is not a Cl^- channel but functions as a regulator to enhance the activity and membrane stability of TMEM16A channels, facilitating the transfer of Cl^- and water molecules from cells (Figure 6). This subsequently promotes mucin hydration. Nonetheless, the influence of inflammatory factors may result in mucus accumulation in the airways, potentially leading to airway obstruction.[71] CLCA1 ostensibly enhances mucus hydration through the activation

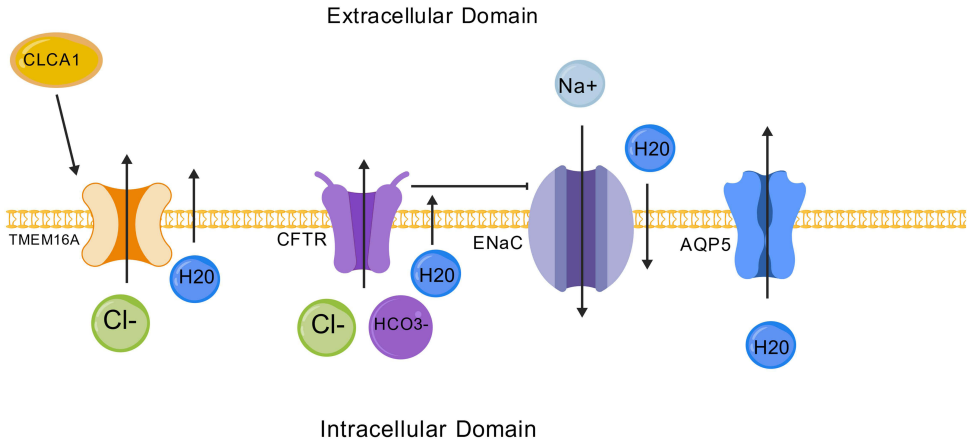

Figure 6 Schematic of mechanisms regulating airway mucus hydration.

of TMEM16A. In chronic inflammatory disorders, its persistent expression induces excessive mucus formation and hypersecretory activity, ultimately surpassing clearance systems. This may result in mucus retention and dehydration-induced concentration, becoming a significant cause of airway obstruction.

Currently, targeted therapies that inhibit IL-6 receptors in the upstream pathway of CLCA1 constitute the most efficacious treatment approach. Conversely, pharmaceuticals aimed at TMEM16A inside the downstream pathway of CLCA1 are still under investigation. Modulators of TMEM16A may potentially become significant pharmaceuticals for inhibiting airway mucus formation in the future.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

CFTR is a chloride channel that facilitates the secretion of chloride ions and water molecules into the airway lumen. Furthermore, it modulates the sodium channel (ENaC), impeding the reabsorption of sodium ions and water molecules[72] (Figure 6). The hydration of mucus is chiefly controlled by two ion channels, CFTR and ENaC, which facilitate the efflux of water molecules from the cell through mechanisms that modulate osmotic pressure via Cl^- secretion and Na^+ absorption,[73] thereby preserving the normal flow and clearance of airway mucus. CF is predominantly induced by mutations in the CFTR gene, resulting in the total cessation of CFTR protein synthesis, folding, transport, or functionality. When CFTR expression is inhibited, elevated levels of Cl^- and Na^+ within cells facilitate the movement of water across the respiratory epithelial surface via aquaporins and the cell membrane. This process dehydrates and concentrates mucus, hence augmenting its viscosity.[74] CFTR is also involved in HCO_3^- transfer (Figure 6). HCO_3^- regulates the normal pH (6.5–7.5) of airway surface fluid,[75] and acid-base equilibrium substantially impacts mucociliary clearance and respiratory defense mechanisms against inhaled microorganisms. Juliette Simonin et al[28] observed that diminished antimicrobial efficacy in the airways of CF patients is substantially correlated with aberrant acidity of airway surface fluid.

Besides congenital genetic anomalies, cigarette smoke,[29] smog, and cold climates[30] can also inhibit CFTR gene expression, resulting in acquired CFTR protein shortage. Drugs that enhance CFTR function in cellular membranes comprise elacatol, tezacatol, and ivacatol. These therapeutics enhance the opening of CFTR channels on cell membranes to allow ion transport,[76] consequently ameliorating symptoms, lung function, and quality of life in CF patients. These medications are exclusively applicable to cystic fibrosis patients with particular genetic mutations, may demonstrate reduced efficacy over time due to the emergence of drug resistance, and are not suitable for other types of airway mucus hypersecretion.

Aquaporin 5 (AQP5)

Aquaporins (AQPs) constitute a group of transport proteins that facilitate the selective transmembrane movement of water molecules across multiple organ systems, including the lungs, kidneys, central nervous system, heart, skin, and eyes. Acting as water-selective channels, they exclusively facilitate the rapid passage of water molecules across the cell

membrane along osmotic gradients, without transporting ions or other solutes[77] (Figure 6). AQP1, AQP2, AQP4, AQP5, and AQP8 are predominantly water-selective, but AQP3, AQP7, AQP9, and AQP10, known as "water-glycerol aquaporins", additionally facilitate the transport of glycerol and other minor solutes.[78] The aberrant expression or deficiency of aquaporins (AQPs) is significantly linked to various diseases, including malignant tumors, cerebral edema, glaucoma, epilepsy, obesity, neuroinflammation, excessive airway mucus secretion, and cardiovascular and cerebrovascular disorders.[79] AQP 1, 3, 4, and 5 are present in the lungs,[80] with AQP5 being intricately associated with airway mucus secretion and demonstrated to localize to the apical membrane of the expressing cells.

AQP5 performs a crucial function in fluid production in the airway's submucosal glands. Song Yi et al[81] discovered that the ablation of the AQP5 gene diminished fluid secretion by roughly 60% while leaving total protein and chloride levels unaffected, thereby compromising mucus hydration. The inflammatory milieu affects AQP5 expression. Lü Changming et al[31] found that increased levels of inflammatory mediators, including TNF-α and IL-13, dramatically diminish AQP5 expression. The downregulation of AQP5 significantly hinders water transport, resulting in heightened viscosity of airway mucus.[32]

The expression of AQP5 is modulated by various processes, encompassing transcriptional and translational control, post-translational modifications, and transport to the plasma membrane.[82] Phosphorylation modification serves as a crucial regulatory mechanism. Proteins such as protein kinase A (PKA) can phosphorylate AQP5 through the cAMP route, modifying its shape and function to enhance its water transport efficiency.[33]

This indicates that AQP5 is essential for mucus dilution, positioning it as a potential therapeutic target for AQP5 agonist development.[83] Despite aquaporins being recognized as validated drug targets, there are currently no clinically licensed treatments that specifically target any aquaporin channel.

Polymer Surplus

Deoxyribonucleic Acid (DNA) and Filamentous Actin (F-Actin)

Patients with CF demonstrate excessive mucus secretion in their airways, rendering them more vulnerable to inflammation and infection. DNA predominantly derives from neutrophil extracellular traps (NETs), with additional contributions from necrotic and inflammatory cells. F-actin is mostly generated via actin polymerization in necrotic cells. The concentration of these two polymers considerably modifies the rheological properties of mucus, hence increasing its viscosity.[84] Recombinant human DNase efficiently decreases sputum viscosity by hydrolyzing phosphodiester linkages, therefore cleaving lengthy strands of DNA. This drug has been applied in clinical treatment. A study including severely ill COVID-19 patients[85] revealed that nebulized inhalation of 5 mg recombinant human DNase twice daily markedly alleviated dyspnea symptoms in 19 patients. All 19 patients ceased oxygen therapy within 4–15 days. Proteomic research demonstrated a significant decrease in the proportion of NET cells and extracellular DNA in sputum, alongside a drop in plasma inflammatory proteins. Nonetheless, evidence substantiating the effectiveness of these medicines in alternative airway disorders is inadequate.

Previous studies have established that cryoprotein is an endogenous protein that cleaves F-actin and can swiftly diminish the viscosity of CF sputum samples in vitro.[86] It facilitates the dissociation of the actin-DNase complex, resulting in the stimulation of DNase activity.[87] In contrast to DNase1, DNase1L2 demonstrates enhanced resistance to actin inhibition,[34] presenting a unique therapeutic strategy for CF as an alternative to DNase1.

Fibrin

In chronic airway inflammation, the aberrant activation of the coagulation system results in fibrin aggregation, which further elevates the viscosity of airway mucus and intensifies airway blockage.[88] In acute respiratory distress syndrome (ARDS), inflammation induces damage to the endothelium and epithelium, resulting in heightened vascular permeability.[89] Endothelial damage facilitates the secretion of tissue factor (TF) into the circulation. TF associates with coagulation factor VII, creating a TF-factor VIIa complex that activates factor X. Thereafter, factor Xa and factor Va form the prothrombin complex on the surface of activated platelets, which are supplied with calcium and phospholipids. This complex activates the conversion of prothrombin to thrombin, and the synthesis of thrombin ultimately results in the formation and deposition of fibrin.[90] Tetsuji Takabayashi et al[35] discovered that nattokinase, a powerful fibrinolytic

enzyme, can diminish the viscosity of nasal secretions and sputum in individuals with asthma and chronic sinusitis. Fibrinolytic strategies, such as nebulized tissue plasminogen activator (tPA) or nattokinase, aim to dissolve mucus plugs by degrading fibrin, presenting a novel method for addressing refractory mucus obstruction unresponsive to traditional mucolytic treatments. The use of these treatment strategies in airway illnesses is still in the preliminary exploratory phase and necessitates validation through rigorously designed clinical trials.

Dysfunction of the Ciliary Clearance System

Primary Ciliary Dyskinesia (PCD)

PCD is an autosomal recessive disorder marked by axonemal structural abnormalities that impair the motility of cilia. The clinical spectrum of PCD includes chronic otitis media, hearing loss frequently accompanied by speech delay, persistent nasal congestion and sinusitis, recurrent lower respiratory tract infections resulting in bronchiectasis, male infertility, organ laterality anomalies (present in 50% of patients), and respiratory distress in neonates.[91] A conclusive diagnosis of PCD requires the integrated application of high-speed video microscopy analysis and transmission electron microscopy inspection. Electron microscopy demonstrates that specific ciliary structural abnormalities are associated with the clinical manifestations of PCD. The predominant flaws consist of outer dynein arm defects (ODA), faults affecting both outer and inner dynein arms (ODA+IDA), and inner dynein arm defects associated with microtubule (or axoneme) disorganization (IDA+MTD).[92]

More than 50 genes have been identified as causative factors for PCD. Ciliated cells possessing mutations in the DNAH5 gene exhibit an absence of DNAH5 protein in their cilia, leading to compromised ODA functionality.[93] The protein encoded by the DNAI1 gene is involved in the assembly of IDA. Studies on PCD pigs with altered DNAI1 genes indicated that their airway cilia lack ODA and demonstrate compromised motility.[36] The CCDC39 and CCDC40 genes are essential for the assembly and functionality of IDA in human respiratory cilia; mutations in these genes lead to impaired microtubule organization and IDA abnormalities.[94]

The formation of cilia and flagella is fundamentally reliant on intraflagellar transport (IFT), a mechanism characterized by the bidirectional transfer of protein complexes along the axoneme.[95] This system provides crucial structural elements, including tubulin, to the developing flagellar tip for axoneme assembly. The LRRC56 gene engages with the IFT88 protein, which is implicated in intraflagellar transport. Research using Trypanosoma brucei revealed that the recruitment of LRRC56 to the developing axoneme requires functional IFT. Harmful mutations in LRRC56 result in abnormalities in the distal section of the axoneme's dynein arms.[37] Mutations or deletions in LRRC56 may also affect human ciliary motility. PCD presently lacks a cure. The standard treatment essentially consists of the routine clearing of airway secretions using hypertonic saline nebulization. Prolonged antibiotic regimens are frequently prescribed during acute exacerbations. Patients are recommended to arrange follow-up consultations with both respiratory medicine and otolaryngology experts every 3–4 months.[96] Gene therapy signifies the prospective trajectory for PCD. As gene editing technology advances, it may ultimately result in a cure for PCD.

Secondary Ciliary Diseases

Secondary ciliary disorders are diseases characterized by abnormalities in ciliary structure or function resulting from various acquired factors. They are strongly linked to smoking, environmental pollution, illnesses, and substance misuse and are partially reversible.[97] Secondary ciliary disorders may induce ciliary motility failure, thereby hindering the cilia's mucus-clearing capability. Respiratory syncytial virus (RSV) infection of the respiratory epithelium generates oxidative stress.[98] This stress induces excessive ROS production, resulting in ultrastructural abnormalities in ciliocytes, including ciliary loss and heightened mitochondrial damage,[99] thereby compromising energy supply and ciliary motility. Consequently, antioxidants may be employed to manage RSV-induced secondary ciliary disease.[38] In vitro studies have demonstrated that the green pigment and 1-hydroxyphenothiazine produced by Pseudomonas aeruginosa can impede the motility of human respiratory cilia; however, the precise mechanism underlying their ciliary toxicity is still to be elucidated.[100] Exposure to toxic chemicals or smoking may also lead to secondary ciliary disorders. Studies indicate that the cilia length of smokers is significantly reduced compared to that of non-smokers under electron microscopy.[39]

In secondary ciliary dyskinesia, cilia typically demonstrate functional deficiencies under electron microscopy, with modified beating frequency but generally intact structure. Treatment primarily aims to eradicate causative factors, such as smoking or infection. In certain instances, ciliary function may restore following the elimination of the trigger. Nonetheless, drugs designed to improve ciliary motility remain in the preliminary phases of research.

Discussion

This research methodically examines the fundamental pathogenic causes of excessive airway mucus secretion, creating a thorough framework that encompasses molecular signaling to pathophysiological manifestations. The method principally includes four essential components: Aberrant activation of inflammatory signaling pathways (NF-κB, IL-13/STAT6, EGFR, and associated epigenetic regulatory networks) triggers mucus secretion; Dysregulated mucin gene expression, primarily influenced by transcription networks, including SPDEF, Notch, and Wnt, induces goblet cell metaplasia and excessive mucin production; Modified mucus rheological properties, resulting from hydration deficiencies in CLCA1, CFTR, and AQP5 and the accumulation of polymers such as DNA and F-actin, exacerbate the physical characteristics of mucus; concurrently, dysfunction of the mucociliary clearance system, encompassing both primary and secondary damage, signifies the ultimate failure of clearance mechanisms. The four elements are interconnected, creating a detrimental loop that cumulatively results in mucus retention and airway obstruction.

Nonetheless, current therapy alternatives possess considerable constraints. Corticosteroids, as first-line medications, exhibit significant efficacy in managing airway inflammation; nevertheless, prolonged usage poses hazards of immunosuppression. Therefore, inhaled corticosteroids are primarily employed to mitigate systemic side effects. Macrolide antibiotics exhibit anti-inflammatory properties but include the potential for bacterial resistance. IL-13 antagonists are exclusively suitable for specific patients with Th2-mediated asthma. EGFR inhibitors are predominantly designated for targeted cancer therapy owing to systemic toxicity; CFTR modulators are effective solely for CF patients with particular genetic mutations; mucolytic agents, including N-acetylcysteine, have demonstrated contentious efficacy in certain clinical studies; the mechanisms of mucoregulators such as carbocisteine remain inadequately elucidated; and Recombinant human DNase is mostly utilized for CF patients, with inadequate evidence endorsing its effectiveness for other conditions characterized by high airway mucus secretion. More critically, most existing treatments remain symptomatic rather than targeting the underlying cause. Consequently, greater focus should be allocated to the formulation of innovative therapeutic approaches aimed at these pathways.

Conclusion

This study offers a comprehensive examination of the multi-tiered regulatory systems governing airway mucus hypersecretion and clarifies the intricate interactions among inflammatory signaling pathways, mucin gene expression, and changes in mucus characteristics. These mechanistic insights provide a robust theoretical foundation for the formulation of precision-targeted treatment options, especially those aimed at critical inflammatory pathways such as IL-13 and EGFR. Future research should aim to effect a fundamental transformation in therapeutic tactics, transitioning from broad-spectrum symptomatic approaches to precision treatments that address the underlying causes: ①Employ multi-omics technologies to investigate novel core biomarkers and signaling pathways associated with excessive mucus secretion in various diseases, thereby identifying new targets for targeted medication development; ②Formulate pharmaceuticals that obstruct mucin secretion via the IL-13-mediated non-classical GABAAR pathway; ③Create inhaled, locally administered formulations aimed at pan-expressed pathways (eg, EGFR, Notch, Wnt) to circumvent systemic reactions; ④Develop agents that target channel proteins or regulators of water transport to preserve normal hydration; ⑤PCD treatment should emphasize gene therapy directed at core gene mutations, although existing technology is still significantly inadequate for this purpose. For secondary ciliary diseases, actively develop pharmacological agents that enhance ciliary motility and facilitate functional recovery. Ultimately, enhance theoretical underpinnings for clinical application, devise innovative targeted therapy procedures, and transition from symptom management to the reversal of pathogenic processes.

This study systematically integrates multi-level mechanisms to establish a robust theoretical framework and a clear translational perspective for developing precision-targeted therapies that aim to reduce acute exacerbation frequency and hospitalization rates, while enhancing quality of life and long-term outcomes in patients with chronic airway diseases.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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