Mucus hypersecretion in chronic obstructive pulmonary disease: From molecular mechanisms to treatment

Ruonan Yang[1], Xiaojie Wu[2], Abdelilah Soussi Gounni[3], Jungang Xie[1]

[1]Department of Respiratory and Critical Care Medicine, National Clinical Research Center of Respiratory Disease, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China;
[2]Department of Respiratory and Critical Care Medicine, Wuhan NO. 1 Hospital, Wuhan Hospital of traditional Chinese and Western Medicine, Wuhan 430022, Hubei Province, China;
[3]Department of Immunology, Faculty of Medicine, University of Manitoba, Manitoba R3E 0W3, Canada

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the leading causes of mortality and morbidity worldwide, which has caused tremendous burden on society.[1,2] Mucus hypersecretion is recognized as one of the main pathophysiological changes and is associated with lung function decline, exacerbations, hospitalization and mortality in patients with COPD.[3] Exposure to cigarette smoke or other irritants promote submucosal gland hypertrophy and goblet cell metaplasia to overproduce mucus through the activation of a variety of signaling pathways. In turn, mucus accumulated in airways worsens the symptoms of airway obstruction and hypoxemia.[4] With the function of blocking specific signaling pathway, it has been identified that drugs targeting mucus hypersecretion can not only alleviate clinical symptoms but also reduce the respiratory inflammatory response in COPD.[5]

Thus, research for a better understanding about molecular mechanisms of mucus hypersecretion has become a hotspot for the treatment of COPD.

RISK FACTORS OF AIRWAY MUCUS HYPERSECRETION

The most common exogenous factor that stimulates mucus hypersecretion is cigarette smoke.[6] Previous studies have shown that cigarette smoke extract (CSE) can increase the expression of mucin-5 subtype AC(MUC5AC) in a concentration-dependent manner.[7] Another common risk factor is particulate matter 2.5 (PM2.5), which can be deposited in the small airways and induce MUC5AC expression caused by oxidative stress.[8,9]

Most of endogenous factors that induce mucus hypersecretion are inflammatory mediators, including neutrophil elastase (NE),[10] interleukin-13 (IL-13),[11] interleukin-1β (IL-1β),[12]interleukin-4 (IL-4),[13] lipopolysaccharide(LPS),[14] matrix metalloproteinase-9 (MMP-9),[15] *etc.* To date, NE is the most potent secretagogue.[16] NE can cleave pro-transforming growth factor (TGF)-α to release mature TGF-α, which can activate epidermal growth factor receptor (EGFR) signaling in a ligand-dependent manner. In addition, NE is locally released to induce goblet cell degranulation when neutrophils and goblet cells are in close contact.[17]

MOLECULAR MECHANISMS OF AIRWAY MUCUS HYPERSECRETION

Signaling pathways leading to mucus overproduction

EGFR signaling pathway: EGFR is activated by exogenous reactive oxygen species (ROS) induced by cigarette smoke and endogenous ROS generated by neutrophils. The downstream of EGFR can activate the nuclear transcription factors like nuclear factor kB (NF-kB) to trigger the transcription of MUC gene.[18] Moreover,

Address for Correspondence:
Prof. Jungang Xie, Department of Respiratory and Critical Care Medicine, National Clinical Research Center of Respiratory Disease, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China.
Email: xiejjgg@hotmail.com

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2023-0094

EGFR can phosphorylate signal transducer and activator of transcription 6 (STAT6), resulting in the down-regulation of forkhead box A2 (FOXA2) expression, thereby promoting the proliferation of goblet cells and the secretion of mucus.[19]

NF-kB signaling pathway: Both *in vitro* and *in vivo*, tumor necrosis factor (TNF)-α-mediated mucin production is dependent on IKB kinase (IKK) and NF-kB. NF-kB can regulate a variety of genes, including the MUC gene. Sequence analysis of the MUC2 and MUC5AC promoter clones revealed the presence of NF-kB response elements.[20] A study in mouse models of COPD has demonstrated that NF-kB is essential for mucus production.[21]

p38 mitogen-activated protein kinase (MAPK) signaling pathway: p38 kinase, a member of the MAPK family, is a highly conserved protein kinase that can be activated by many inflammatory signals. Hemophilus influenzae is a common pathogen of COPD, and studies have found that Hemophilus influenzae can upregulate MUC gene transcription through the activation of TLR2-MyD88-dependent p38 MAPK pathway.[22]

Signaling pathways leading to mucus secretion and clearance dysfunction

Myristoylated alanine-rich C kinase substrate (MARCKS) protein signaling pathway: MARCKS is a key regulatory molecule that mediates the release of mucin granules from human bronchial epithelial (HBE) cells.[23] Phosphorylation of MARCKS by protein kinase C(PKC) leads to its translocation to the cytoplasm, followed by dephosphorylation of MARCKS by protein kinase G (PKG). Dephosphorylated MARCKS can bind to the membrane of mucin granules, then MARCKS promotes the transport of mucin granules to the membrane for release.[24]

Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein signaling pathway: SNARE proteins can initiate vesicle fusion, regulate intracellular membrane fusion events, and participate in the fusion of mucin particles and cell membranes. Through interacting with Ca^{2+} sensor and other factors, SNARE proteins mediate Ca^{2+}-triggered mucin exocytosis.[25] Studies have shown that the most abundant SNARE protein in the airway epithelium is mainly vesicle-associated membrane protein 8 (VAMP8).[26]

Epithelial sodium channel (ENaC) signaling pathway: Airway surface hydration is mainly controlled by ENaC and cystic fibrosis transmembrane regulator (CFTR) pathways. Studies have shown that cigarette smoke-induced ROS can disrupt the function and activity of ENaC, thereby disrupting mucin hydration and reducing mucus expulsion.[27]

Ciliophagy signaling pathway: Normal ciliary structure and function help to transport the mucus from the airway to the larynx. A study has demonstrated that histone deacetylase 6 (HDAC6) and other regulators of the autophagic pathway can lead to cilia shortening and abnormal function, resulting in impaired mucociliary clearance during CS exposure.[28]

TREATMENT OF AIRWAY MUCUS HYPERSECRETION

For the above-mentioned risk factors and signaling pathways of airway mucus hypersecretion, the current treatment principles include eliminating exogenous risk factors, inhibiting mucus synthesis and secretion, promoting mucus clearance and other physical expectoration therapy.[29] It has also been summarized in the Table 1.

Elimination of exogenous risk factors

As described above, smoking and air pollution are important risk factors for COPD. Therefore, smoking cessation and improvement of air quality should be the primary measures to prevent and treat mucus hypersecretion in chronic airway inflammatory diseases.[30]

Drugs that inhibit mucus synthesis

EGFR tyrosine kinase inhibitors: Cigarette smoke, PM2.5 and oxidative stress can all stimulate EGFR activation, resulting in increased mucin secretion. It can be seen that the EGFR signaling pathway plays a central regulatory role in mucus hypersecretion. Studies have shown that pretreatment with the selective EGFR tyrosine kinase inhibitor BIBX1522 can effectively prevent the secretion of MUC5AC in asthma models and in a rat model of TNF-α-induced mucus hypersecretion.[31]

Macrolide antibiotics: Studies have shown that macrolide antibiotics can significantly reduce LPS-induced expression of MUC5AC in rat bronchi and reduce neutrophil counts as well as mucin levels in bronchoalveolar lavage fluid, which may be caused by the inactivation of NF-kB.[32] Another study has shown that macrolide antibiotics can quickly accumulate in neutrophils and macrophages, thus inhibiting the secretion of NE and mucus secretion.[33]

NE inhibitors: Studies have shown that the NE inhibitor ONO-5046 can reverse ozone-induced mucus hypersecretion and neutrophil aggregation in guinea pig models.[34] The selective NE inhibitor ICI2000355 has also been shown to reverse mucus hypersecretion induced by ovalbumin sensitization in guinea pig models.[35]

p38 MAPK inhibitors: Administration of the p38 MAPK

Table 1. Targets and relative inhibitors for the treatment of mucus hypersecretion in COPD

Target	Inhibitor(s)
Smoking, PM2.5	Smoking cessation, improvement of air quality
Mucus synthesis	
NE	NE inhibitors, batimastat, suramin
EGFR	EGFR tyrosine kinase inhibitors: AG1478, BIBX1522, ZD1839
	p38 MAPK inhibitors: SB-202190
p38 MAPK	Macrolide antibiotics: erythromycin, flurythromycin
NF-kB	
Mucus secretion	
MARCKS	MARCKS inhibitors: MARCKS-specific antisense oligonucleotides
SNARE	SNARE protein inhibitors: EGF-LHN-C
Mucus clearance	
Cholinergic pathway	Expectorants: Guaifenesin, hypertonic saline
Mucus viscosity	
P2Y2	Mucolytics: N-Acetyl Cysteine
	P2Y2 receptor agonists

COPE: Chronic obstructive pulmonary disease; NE: neutrophil elastase; EGFR: epidermal growth factor receptor; MAPK: mitogen-activated protein kinase; MARCKS: myristoylated alanine-rich C kinase substrate; SNARE: soluble N-ethylmaleimide-sensitive factor attachment protein receptor; NF-kB: nuclear factor kappa B.

inhibitor (SB-202190) significantly improved IL-13-induced goblet cell hyperplasia *in vitro*.[36]

Drugs that inhibit mucus secretion

MARCKS inhibitors: As previously mentioned, MARCKS mediates the intracellular movement and exocytosis of mucin particles.[24] Studies have shown that MARCKS-specific antisense oligonucleotides can downregulate MARCKS levels in HBE cells and significantly attenuate PKC/PKG activation-induced mucin secretion.[37]

SNARE protein inhibitors: SNARE protein inhibitor (EGF-LHN-C) inhibits mucin secretion by inhibiting the fusion of mucin granules with the cell membrane.[38]

Drugs that promote mucus clearance

Expectorants: Expectorants can stimulate the cholinergic pathway and increase the secretion of serous fluid from the bronchial submucosal glands to reduce mucus viscosity, resulting in promotion of mucus clearance.[39]

Mucolytics: With the characteristics of reducing mucus viscosity, mucolytics are the most widely used drugs for the treatment of mucus hypersecretion. For example, N-Acetyl Cysteine (NAC) can break disulphide bonds linking mucin polymers to reduce the viscosity of mucus.[40]

Purinergic receptor P2Y, G-protein coupled, 2 (P2Y2) receptor agonists: Studies have shown that the efficiency of P2Y2 receptor agonists to increase airway mucus clearance is significantly greater than that of hypertonic saline solution, which may be related to the increase of water secretion and ciliary beating frequency by P2Y2 receptor agonists.[41]

In addition to the above drug treatment, the symptoms of patients can be alleviated to a certain extent through autogenic drainage,[42] high-frequency chest wall oscillation (HFCWO)[43] and bronchoscopic treatment.[44]

SUMMARY

So far, some progress has been made in the molecular mechanisms and drug treatment of mucus hypersecretion in COPD. A variety of drugs have been found to have certain therapeutic effects on mucus hypersecretion. However, most of the above drugs are still in the experimental research stage and there is still a long way to go before they can be used in clinical treatment. Further investigation is urgently needed to develop understanding and therapies for airway mucus hypersecretion in COPD.

Source of Funding

This study was supported by the National Natural Science Foundation of China (No., 82170049, 81973986), Health Research Fund of Wuhan (No. WX21Q07) and Leading talents of public health in Hubei Province (2022SCZ047).

Conflicts of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691–706.
2. Labaki WW, Rosenberg SR. Chronic Obstructive Pulmonary Disease. *Ann Intern Med* 2020;173:ITC17–32.
3. Martin C, Frija-Masson J, Burgel P-R. Targeting mucus hypersecretion: new therapeutic opportunities for COPD? *Drugs* 2014;74:1073–89.
4. Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, *et al*. Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med* 2021;203:957–68.
5. Vestbo J, Hogg JC. Convergence of the epidemiology and pathology of COPD. *Thorax* 2006;61:86–8.
6. Yang D, Xu D, Wang T, Yuan Z, Liu L, Shen Y, *et al*. Mitoquinone ameliorates cigarette smoke-induced airway inflammation and mucus hypersecretion in mice. *Int Immunopharmacol* 2021;90:107149.
7. Chen R, Liang Y, Ip MSM, Zhang KY, Mak JCW. Amelioration of Cigarette Smoke-Induced Mucus Hypersecretion and Viscosity by Polysaccharides

In Vitro and In Vivo. *Oxid Med Cell Longev* 2020;2020:8217642.
8. Val S, Belade E, George I, Boczkowski J, Baeza-Squiban A. Fine PM induce airway MUC5AC expression through the autocrine effect of amphiregulin. *Arch Toxicol* 2012;86:1851–9.
9. He X, Zhang L, Xiong A, Ran Q, Wang J, Wu D, *et al*. PM2.5 aggravates NQO1-induced mucus hyper-secretion through release of neutrophil extracellular traps in an asthma model. *Ecotoxicol Environ Saf* 2021;218:112272.
10. Gehrig S, Duerr J, Weitnauer M, Wagner CJ, Graeber SY, Schatterny J, *et al*. Lack of neutrophil elastase reduces inflammation, mucus hypersecretion, and emphysema, but not mucus obstruction, in mice with cystic fibrosis-like lung disease. *Am J Respir Crit Care Med* 2014;189:1082–92.
11. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, *et al*. Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight* 2021;6:139019.
12. Faiz A, Weckmann M, Tasena H, Vermeulen CJ, Van den Berge M, Ten Hacken NHT, *et al*. Profiling of healthy and asthmatic airway smooth muscle cells following interleukin-1β treatment: a novel role for CCL20 in chronic mucus hypersecretion. *Eur Respir J* 2018;52:1800310.
13. Hammad H, Lambrecht BN. The basic immunology of asthma. *Cell* 2021;184:1469–85.
14. Wang J. Casticin alleviates lipopolysaccharide-induced inflammatory responses and expression of mucus and extracellular matrix in human airway epithelial cells through Nrf2/Keap1 and NF-κB pathways. *Phytother Res: PTR* 2018;32:1346–53.
15. Deshmukh HS, Case LM, Wesselkamper SC, Borchers MT, Martin LD, Shertzer HG, *et al*. Metalloproteinases mediate mucin 5AC expression by epidermal growth factor receptor activation. *Am J Respir Crit Care Med* 2005;171:305–14.
16. Sommerhoff CP, Nadel JA, Basbaum CB, Caughey GH. Neutrophil elastase and cathepsin G stimulate secretion from cultured bovine airway gland serous cells. *J Clin Invest* 1990;85:682–9.
17. Kim S, Nadel JA. Role of neutrophils in mucus hypersecretion in COPD and implications for therapy. *Treat Respir Med* 2004;3:147–59.
18. Rubin BK, Priftis KN, Schmidt HJ, Henke MO. Secretory hyperresponsiveness and pulmonary mucus hypersecretion. *Chest* 2014;146:496–507.
19. Oh S-Y, Kim Y-H, Kang M-K, Lee E-J, Kim D-Y, Oh H, *et al*. Aesculetin Inhibits Airway Thickening and Mucus Overproduction Induced by Urban Particulate Matter through Blocking Inflammation and Oxidative Stress Involving TLR4 and EGFR. *Antioxidants* (Basel) 2021;10:494.
20. Lai H, Rogers DF. New pharmacotherapy for airway mucus hypersecretion in asthma and COPD: targeting intracellular signaling pathways. *J Aerosol Med Pulm Drug Deliv* 2010;23:219–31.
21. Xu H, Sun Q, Lu L, Luo F, Zhou L, Liu J, *et al*. MicroRNA-218 acts by repressing TNFR1-mediated activation of NF-κB, which is involved in MUC5AC hyper-production and inflammation in smoking-induced bronchiolitis of COPD. *Toxicol Lett* 2017;280:171–80.
22. Gaffey K, Reynolds S, Plumb J, Kaur M, Singh D. Increased phosphorylated p38 mitogen-activated protein kinase in COPD lungs. *Eur Respir J* 2013;42:28–41.
23. Fang S, Crews AL, Chen W, Park J, Yin Q, Ren X-R, *et al*. MARCKS and HSP70 interactions regulate mucin secretion by human airway epithelial cells in vitro. *Am J Physiol Lung Cell Mol Physiol* 2013;304:L511–L8.
24. Li Y, Martin LD, Spizz G, Adler KB. MARCKS protein is a key molecule regulating mucin secretion by human airway epithelial cells in vitro. *J Biol Chem* 2001;276:40982–90.
25. Lai Y, Fois G, Flores JR, Tuvim MJ, Zhou Q, Yang K, *et al*. Inhibition of calcium-triggered secretion by hydrocarbon-stapled peptides. *Nature* 2022;603:949–56.
26. Jones LC, Moussa L, Fulcher ML, Zhu Y, Hudson EJ, O'Neal WK, *et al*. VAMP8 is a vesicle SNARE that regulates mucin secretion in airway goblet cells. *J Physiol* 2012;590:545–62.
27. Åstrand ABM, Hemmerling M, Root J, Wingren C, Pesic J, Johansson E, *et al*. Linking increased airway hydration, ciliary beating, and mucociliary clearance through ENaC inhibition. *Am J Physiol Lung Cell Mol Physiol* 2015;308:L22–L32.
28. Cloonan SM, Lam HC, Ryter SW, Choi AM. "Ciliophagy": The consumption of cilia components by autophagy. *Autophagy* 2014;10:532–4.
29. Li X, Jin F, Lee HJ, Lee CJ. Recent Advances in the Development of Novel Drug Candidates for Regulating the Secretion of Pulmonary Mucus. *Biomol Ther (Seoul)* 2020;28:293–301.
30. Willemse BWM, ten Hacken NHT, Rutgers B, Lesman-Leegte IGAT, Timens W, Postma DS. Smoking cessation improves both direct and indirect airway hyperresponsiveness in COPD. *Eur Respir J* 2004;24:391–6.
31. Takeyama K, Dabbagh K, Lee HM, Agustí C, Lausier JA, Ueki IF, *et al*. Epidermal growth factor system regulates mucin production in airways. *Proc Natl Acad Sci U S A* 1999;96:3081–6.
32. Ou X-M, Feng Y-L, Wen F-Q, Wang K, Yang J, Deng Z-P, *et al*. Macrolides attenuate mucus hypersecretion in rat airways through inactivation of NF-kappaB. *Respirology* 2008;13:63–72.
33. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J* 2013;42:239–51.
34. Nogami H, Aizawa H, Matsumoto K, Nakano H, Koto H, Miyazaki H, *et al*. Neutrophil elastase inhibitor, ONO-5046 suppresses ozone-induced airway mucus hypersecretion in guinea pigs. *Eur J Pharmacol* 2000;390:197–202.
35. Voynow JA, Young LR, Wang Y, Horger T, Rose MC, Fischer BM. Neutrophil elastase increases MUC5AC mRNA and protein expression in respiratory epithelial cells. *Am J Physiol* 1999;276:L835–L43.
36. Atherton HC, Jones G, Danahay H. IL-13-induced changes in the goblet cell density of human bronchial epithelial cell cultures: MAP kinase and phosphatidylinositol 3-kinase regulation. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L730–L9.
37. Poole PJ, Black PN. Preventing exacerbations of chronic bronchitis and COPD: therapeutic potential of mucolytic agents. *Am J Respir Med* 2003;2:367–70.
38. Rogers DF, Barnes PJ. Treatment of airway mucus hypersecretion. *Ann Med* 2006;38:116–25.
39. Ohar JA, Donohue JF, Spangenthal S. The Role of Guaifenesin in the Management of Chronic Mucus Hypersecretion Associated with Stable Chronic Bronchitis: A Comprehensive Review. *Chronic Obstr Pulm Dis* 2019;6:341–349..
40. Lin VY, Kaza N, Birket SE, Kim H, Edwards LJ, LaFontaine J, *et al*. Excess mucus viscosity and airway dehydration impact COPD airway clearance. *Eur Respir J* 2020;55:1900419.
41. Kellerman DJ. P2Y(2) receptor agonists: a new class of medication targeted at improved mucociliary clearance. Chest 2002;121:201S–5S.
42. McCormack P, Burnham P, Southern KW. Autogenic drainage for airway clearance in cystic fibrosis. *Cochrane Database Syst Rev* 2017;10:CD009595.
43. Osman LP, Roughton M, Hodson ME, Pryor JA. Short-term comparative study of high frequency chest wall oscillation and European airway clearance techniques in patients with cystic fibrosis. *Thorax* 2010;65:196–200.
44. Mineshita M, Inoue T, Miyazawa T. [Bronchoscopic treatments for COPD]. *Nihon Rinsho* 2016;74:807–12.

How to cite this article: Yang RN, Wu XJ, Gounni AS, Xie JG. Mucus hypersecretion in chronic obstructive pulmonary disease: from molecular mechanisms to treatment. J Transl Int Med 2023; 11: 312-315.