

## Editorial



# Mucus Plugs and Small Airway Dysfunction: An Important Concept in Airway Disease Pathophysiology

Youlim Kim , Kwang Ha Yoo

Division of Pulmonary and Allergy, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea

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### Correspondence to

**Kwang Ha Yoo, MD, PhD**

Division of Pulmonary and Allergy, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea.  
Tel: +82-2-2030-7014  
Fax: +82-2-2030-7018  
Email: 20010025@kuh.ac.kr

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### ORCID iDs

Youlim Kim   
<https://orcid.org/0000-0002-1051-0667>  
Kwang Ha Yoo   
<https://orcid.org/0000-0001-9969-2657>

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Airway hypersecretion is commonly observed in chronic lung diseases, such as asthma or chronic obstructive pulmonary disease (COPD), and is a major cause of airway obstruction in asthma and COPD.<sup>1</sup> Mucus is an extracellular gel mixed with water and glycoproteins, and an effective mucus clearance is an important defense mechanism against harmful environmental exposures (*e.g.*, cigarette smoking, noxious particles, or particulate matter).<sup>1</sup> In airway diseases, mucus plugging caused by excessive mucus or an impaired clearance results in not only respiratory symptoms, such as cough and sputum,<sup>1</sup> but also lower lung functions and subsequently more frequent exacerbations in asthma or COPD.<sup>2,3</sup> Therefore, there have been many studies to detect mucus plugging using high-resolution computed tomography (HRCT) and to assess the association between mucus plugging and airflow obstruction in asthma and COPD.

In this issue, Tamura *et al.*<sup>4</sup> investigated the prevalence of mucus plugs using HRCT in patients with asthma, COPD, and asthma-COPD overlap (ACO). In addition, authors assessed the relationship between mucus plugs and the parameters of conventional spirometry or small airway dysfunction (SAD) in patients with airway diseases mentioned above. They found that mucus plugs were detected in around 60% of patients with asthma or ACO, and less frequently in those with COPD. COPD patients with mucus plugs showed lower lung functions, compared to those without. SAD parameters, including forced vital capacity (FVC) and resonant frequency (Fres), were closely associated with the presence of mucus plugs in all patients, which suggests that mucus plugs may be associated with the pathophysiology of asthma, ACO, and COPD.

Regarding clinical features, asthmatic and ACO patients with mucus plugs showed positive correlations between mucus plugs and type 2 biomarkers, such as FeNO and total IgE; however, in COPD patients, the prevalence of mucus plugs was relatively lower, and associations between mucus plugs and lung function declines were stronger than those in asthmatic and ACO patients. All these observations implied that neutrophilic inflammation might be involved in mucus plug formation and that mucus plug has a significant effect on the pathophysiology of COPD. Future studies are needed to elucidate the mechanism of mucus plug formation in different airway diseases. Tamura *et al.*<sup>4</sup> also assessed SAD using FVC and Fres and reported that SAD rather than large airway dysfunction was associated

with mucus plugging in all the 3 obstructive airway diseases. Among several physiological measurements of SAD, FVC depends on patients' efforts and thus shows a lack of reproducibility.<sup>5</sup> Therefore, FVC values should be cautiously interpreted.

Based on the trend of personalized medicine, approaches to specific phenotypes in asthma and COPD are being extensively investigated. Mucus overproduction due to mucus gland hyperplasia, goblet cell metaplasia and airway inflammation is typical pathophysiological features of airway obstructive diseases.<sup>1,6</sup> In asthma, luminal plugging by goblet cell hyperplasia in large and small airway epitheliums was observed<sup>1</sup> and airway inflammation of small airway increased in acute fatal conditions or in the poorly controlled state of asthma; however, it remains uncertain whether small airway involvement exists in all asthmatic patients (or the presence of "SAD phenotype" in asthma).<sup>1,7,8</sup> In cases of COPD, mucus plugging was significantly associated with decreased lung function or poor health-related quality of life.<sup>1,3,6,9</sup> Even though small airway abnormalities are one of the prominent pathological features in COPD, the relationship between pathological changes in small airways and subsequent development of airflow limitation remains to be investigated.<sup>7</sup> In this study, although the association between mucus plugs and decreased lung function, type 2 inflammation, and SAD in obstructive lung diseases is has been well established, more efforts are needed to elucidate the clinical significance of the association between mucus plugs and SAD as well as mechanisms for the disease progression.

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