Chair's Summary: Secreted Mucins in Lung Diseases

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The 33rd Transatlantic Airway Conference was held January 17–19, 2018, in Lucerne, Switzerland. The topic of this year's conference was the protective and pathologic roles of secreted airway mucins. Clinically, mucus dysfunction is increasingly recognized as being critically important to the pathogenesis of multiple common lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and idiopathic pulmonary fibrosis. Considerable progress has been made recently in understanding of the molecular basis for the physical properties of mucus and how these interact with cellular and organ biology. This understanding has led to new insights into disease mechanisms and to the development of mechanism-based diagnostic tests and therapeutic interventions.

To appreciate the roles of airway mucus in health and disease, a basic understanding of mucus biology is helpful. Put simply, mucus is a dilute aqueous solution of mucins and salts that forms a gel-like substance on the border between a viscous liquid and a soft elastic solid. Secreted mucins are large, highly glycosylated proteins that polymerize into chains and networks. They are synthesized and stored dehydrated in airway epithelial secretory cells, and after their secretion, they interact with several hundred-fold their mass of water to form mucus. There are two principal secreted mucins in the airway: mucin 5AC (MUC5AC) and MUC5B. Recent work has shown distinct properties of these two mucins in mucociliary clearance, pathogen defense, and disease pathogenesis. Their expression is regulated by different signaling

pathways, and their secretion is regulated by yet other pathways. The normal mucin life cycle may be illustrated as follows:

synthesis → secretion → hydration → clearance

Mucus dysfunction may occur at any stage of this life cycle. Insufficient synthesis can lead to impaired clearance of particles and pathogens, whereas upregulated synthesis can promote airway occlusion if coupled with rapid secretion. Prolonged upregulated synthesis of MUC5B appears to cause epithelial injury in idiopathic pulmonary fibrosis. Rapid stimulated secretion of stored mucins can help trap pathogens, but it can also pathologically cause airway occlusion or the failure of detachment of mucus strands from submucosal glands. Insufficient hydration leads to excessively concentrated mucus that is particularly prominent in cystic fibrosis but also contributes to airway dysfunction in asthma and COPD. Clearance of mucus from the airways by ciliary beating or cough is essential to remove inhaled particles and pathogens and to prevent mucus occlusion. Several review articles provide further information on well-established mucus biology (1–4). Recent developments in the field were presented at the Transatlantic Airway Conference and are summarized in the four sections below.

Mucin Expression, Intracellular Processing, and Secretion

Secreted mucins are expressed in club cell secretory protein–positive (CCSP⁺) airway secretory cells, both constitutively and in response to inflammatory stimuli. Jeffrey

Whitsett reviewed airway secretory cell development in health and disease (pp. S143–S148) (5). Max Siebold described changes in human airway epithelial cell gene expression in response to interleukin 13, as recently summarized in *Annals of the American Thoracic Society* (6). David Thornton reviewed mucin glycoprotein synthesis in the endoplasmic reticulum, processing in the Golgi apparatus, and packaging into secretory granules (pp. S154–S158) (7). Gunnar Hansson described the intracellular assembly of mucins into polymers and their release as bundles (pp. S159–S163) (8). Jean-Luc Desseyn described a green fluorescent protein–labeled Muc5b knock-in mouse that his laboratory generated, which facilitates studies of Muc5b expression and protein trafficking (pp. S149–S153) (9). Burton Dickey reviewed the molecular mechanism and pathophysiologic significance of airway mucin secretion (pp. S164–S170) (10).

Physical Properties of Mucus in Health and Disease

Mehmet Kesimer reviewed data on the correlation between the elevated mucin concentrations of the mucus of patients with airway diseases and the 10-fold preponderance of MUC5B compared with MUC5AC in healthy mucus with the MUC5AC fraction increasing in multiple airway diseases. Michael Rubinstein noted the need for an optimal mucin concentration in healthy mucus, with dilute mucus being insufficiently adhesive to

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effectively trap inhaled particles and concentrated mucus being too viscoelastic and adhesive to be efficiently cleared by ciliary beating. Brian Button reported new data indicating that mucin polymers possess distinct biophysical properties that promote ciliary clearance in comparison to nonmucin synthetic polymers. David Erle reviewed studies of the adhesivity and poor transportability of MUC5AC done at his laboratory and others, and he described new data on the identification of a candidate MUC5AC enhancer. The talks of Kesimer, Rubinstein, Button, and Erle are not summarized in articles in this issue, either because primary research articles were recently published and accompanied by commentaries (11, 12) or because the primary data have not yet been peer reviewed and published. David Stoltz described studies of newborn pigs with cystic fibrosis showing defects in mucociliary transport owing to the formation of mucus strands that fail to detach after cholinergic stimulation of submucosal gland secretion (pp. S171-S176) (13).

Mucus in Defense against Pathogens and Particles

Christopher Evans reviewed the importance of mucociliary clearance for protection against inhaled particles and microbial pathogens (pp. S210-S215) (14). Richard Grenis described how MUC5AC

upregulation in response to type 2 inflammation promotes the clearance of parasitic worms from the gut and their trapping within airways, as recently summarized elsewhere (15). David Corry reviewed recent studies revealing mechanisms for the induction of mucoobstructive lung disease by fungi (pp. S198-S204) (16). Stokes Peebles reported new insights into host and viral determinants of chronic mucin overproduction after RSV infection (pp. S205-S209) (17). Duncan Rogers pointed out the role of viral infections in altering the airway bacterial microbiome, increasing mucin production, and inducing exacerbations in COPD, as recently reviewed (18). Katharina Ribbeck described the selective permeability of mucus to microbial pathogens and that mucus can surprisingly prevent biofilm formation under some circumstances, as recently summarized elsewhere (19).

Emerging Diagnostics and Therapeutics for Mucus Dysfunction

The importance of optimal mucus concentration for lung health was mentioned above under the PHYSICAL PROPERTIES OF MUCUS IN HEALTH AND DISEASE heading. The possibility of measuring mucin concentrations as an index of airway disease is now being tested in clinical studies (11). John Fahy gave a historical overview of the

increasing recognition of the importance of mucus plugs in airway obstruction from pathologic studies, and Eleanor Dunican described recent work identifying airway mucus plugs during life using computed tomography. They summarized their talks in a combined article in this issue (pp. S184-S191) (20). Steven Rowe described recent developments in imaging the functional microanatomy of the airway surface, particularly the use of microoptical coherence tomography (pp. S177-S183) (21). David Schwartz reviewed the role of a common polymorphism that causes MUC5B overexpression in the pathogenesis and clinical presentation of idiopathic pulmonary fibrosis (pp. S192-S197) (22). Henry Danahay gave an overview of therapeutic strategies to reduce mucin production and secretion, or to increase hydration, to improve mucociliary clearance. Richard Boucher described the ineffectiveness of cough in clearing mucus plaques from small airways, as well as recent work toward developing a safe and effective mucolytic drug. Marcus Mall reviewed the importance of mucus plaques in promoting epithelial apoptosis and lung inflammation, as well as the utility of mucus clearance therapies. Danahay, Boucher, and Mall summarized their talks in a combined article in this issue (pp. S216-S226) (23). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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