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Mini Review

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Airway mucins: "aircraft carriers" in the apical surface fluid

Abstract

Airway mucins, the major component of airway mucus or apical surface fluid that covers the entire surface of the airways, have been shown to possess multi-factorial functions that are necessary for first line defense, the major function of airway mucus. In this mini-review, I will provide some evidence, both theoretical and experimental, that the multi-factorial functions of airway mucins are most likely due to various bioactive proteins that are tightly associated with mucins. Thus, the first line defense of airway mucus requires both the mucociliary clearance and the activity of various bioactive proteins tightly associated with mucins, which depend on the quality and quantity of airway mucins.

Keywords: airway mucins, physicochemical, mucociliary, viscoelasticity, pharmacology

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Structure of mucins

Mucus in the airway, also called the apical surface liquid, forms the first line defensive layer against particles or chemicals entering the lung. Airway mucus is produced by goblet cells of the underlying epithelium and mucous cells of the sub mucosal gland. Its defensive role is thought to be attributable to both its physical location and the physicochemical property through mucociliary clearance. The latter, more specifically referred to as the viscoelastic property of mucus, is controlled mainly by mucins which are present in mucus. Mucins are heavily glycosylated (>60% of molecular weight) and also negatively charged due to sialyation and sulfation of the oligosaccharides. Thus, the polydispersity of mucins in size and charge depends on the structure of their oligosaccharides and makes these molecules unique in both physiology and pathology. Studies with cultured airway goblet cells indicated that excessive production and secretion of mucins are induced by inflammatory mediators[1] suggesting that mucus hypersecretion in patients is due to airway inflammation.

Twenty two mucin genes have been cloned in human of which 17 have been identified in the lung.[2] Among these 17 mucin genes, 5 mucins showed relatively high expression in the lung, which are MUC1, MUC4, MUC5AC, MUC5B and MUC16.[3] While MUC5AC and MUC5B are secreted mucins or also called gel-forming mucins, MUC1, MUC4 and MUC16 are cell surface mucins or also called membrane-tethered mucins. The membrane-tethered mucins can be shed by proteases[4] and therefore, mucins in the apical surface liquid consist of mainly these two types of mucins, i.e. full length MUC5AC and MUC5B and MUC1, MUC4 and MUC16 with only extracellular domains.[3]

Mucins are tightly associated with various kinds of molecules

In an attempt to understand the biochemistry of mucins, a great deal of effort was made to purify mucins from patient's mucus. However, its extreme viscoelasticity, often heavily contaminated with various inflammatory products, made it difficult to separate mucins from contaminants until the early 1980's.However, in the late 1980's, use of the 4M guanidinium hydrochloride density gradient method, which was successfully used to separate individual proteoglycans from cartilage,[5,6] made it possible to separate mucins from various contaminants in the patients' pathologic mucus,[7] which opened a new era of airway mucin biology. The first in vitro mucins were characterized from cultured primary tracheal epithelial cells as high molecular glycoproteins (>10^6 MW) free of proteoglycans.[8–10] Being free from extreme contamination and degradation due to inflammation as seen in patients' mucus, the availability of "clean" primary airway epithelial cell cultures and the mucin separation technique opened a door to study the biochemistry of "pure" mucins[11] as well as the pharmacology of airway mucin secretion.[12]

One of the major findings from studies of in vitro airway mucins was their hydrophobicity. High molecular weight "mucins" free of proteoglycans are tightly associated with various lipids and proteins under a physiological condition.[10,11,13] Such interaction was dissociated in the presence of 0.1% SDS but not 4M guanidinium hydrochloride.[10,13] Interestingly, the composition of the lipids associated with secreted mucins was comparable to that with cellular mucins[14] suggesting that the association with lipids may take place inside the mucinsecretory granules prior to granule exocytosis. This also suggests that the lipid association with mucins may play a crucial role in packaging the highly thermodynamically active mucin molecules[15] into "small" secretory granules.[16,17] It has been documented that a mucus gel has a property of rapid swelling to more than 500 times in volume during exocytosis[15] likening active eruptions of volcanos during mucin granule exocytosis. How such thermodynamically active molecules can be packaged into "small" secretory granules inside mucous cells is still not fully understood.

Mucins are "aircraft carriers" in the airway surface fluid

Kesimer et al.[18] identified 134 proteins from apical secretions of primary airway epithelial cells, with 84 proteins (62.7%) being common with the proteins identified *in vivo* human tracheobronchial sputum. Later, Ali et al.[19] identified 56 proteins in a "mucin" fraction isolated under physiological conditions from primary human tracheobronchial

epithelial cells grown in air/liquid interface, supporting the previous report [11]that airway mucins are tightly associated with various molecules. Proteomic analysis of the 56 proteins included not only mucins but also many functionally active proteins, including anti-microbial, anti-proteolytic, anti-oxidative, and anti-inflammatory proteins.[19] This finding is highly significant because it had been thought that the complex structure of "mucins" itself was responsible for their multifaceted properties that are necessary for host defense against inhaled harmful substances, including anti-microbial, anti-proteolytic, and anti-oxidative activities.[20] Judging from both the hydrophobicity of airway mucins and their ability to tightly associate with many bioactive proteins under physiological conditions, the multi-faceted activities of "mucins" seem most likely due to the bioactive proteins that are tightly associated with mucins under physiological conditions, but not the mucins themselves. Thus, mucins resemble a large "aircraft carrier" bearing a variety of "weapons" to be used against invading pathogens.[2] It might be possible that mucins are already associated with bioactive proteins inside the secretory granule in a highly condensed complex and released upon a proper stimulus (e.g., invading bacteria) through granule exocytosis likening the eruption of volcanos quickly covering the large airway surface with fully equipped "aircraft carriers."If it is true, the efficiency of the first line defense by mucus should depend on the polydispersity of mucin molecules. How and when such associations take place inside the mucous cell and how the associated molecules are packaged into mucous granules, remains to be discovered.

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Conflicts of interest

The authors have declared that no competing interests exist.

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