A Slippery Cause of a Slimy Problem: Mucin Induction by an Esterified Lipid

Secreted gel-forming mucins (1) are key components of mucociliary transport, a vital airway innate defense mechanism (2). Mucin and mucus alterations are present in asthma (3), cystic fibrosis (4), and chronic bronchitis (5), and mucin gene polymorphisms are also implicated in the pathogenesis of idiopathic pulmonary fibrosis (6). Increased numbers of mucin-producing goblet cells at locations where they are normally present (hyperplasia) or absent (metaplasia) are pathognomonic responses of the airways to diverse environmental stimuli. Although they are clearly important and protective at homeostatic levels, mucin and mucus are likely harmful when produced in excess, as most vividly and tragically illustrated in fatal asthma (Figure 1). Importantly, specific therapies targeting mucin hypersecretion in asthma and other lung pathologies are not currently available.

Many signaling pathways increase mucin gene expression and glycoprotein secretion. Most relevant to the lung and asthma, the mucin MUC5AC is induced by the T-helper cell type 2 (Th2) mediator IL-13 in human airway epithelial cells (7). In this issue of the *Journal*, Zhao and colleagues (pp. 692–701) (8) extend previous studies showing that elevated 15-lipoxygenase-1 (15LO1) expression, activity, and responsiveness to IL-13 occur in airway epithelial cells from asthmatics versus healthy controls, that 15LO1 expression correlates with asthma severity, and that IL-13–induced 15LO1 expression stimulates production of the lipid mediator 15-hydroxyeicosatetraenoic acid (15-HETE) esterified to phosphatidylethanolamine (15-HETE-PE) (9, 10).

In the current study, Zhao and colleagues used long-term, established airway epithelial cell cultures from both asthmatics and healthy donors to address whether 15-HETE-PE directly induces mucin gene expression and glycoprotein production, and to elucidate the relevant signaling mechanisms involved. Interestingly, differences in 15LO1 expression and response to IL-13 between asthmatic and nonasthmatic subjects did not persist after extended culture. In this study, the basal media was supplemented with equimolar amounts of linoleic acid and arachidonic acid to ensure that substrate availability was not rate limiting. In the presence of the linoleic acid/arachidonic acid supplement, 15LO1 preferentially generated 15-HETE-PE and not 13-hydroxyoctadecadienoic acid (13-HODE) or esterified 13-HODE-PE, supporting the importance of the specific conjugated metabolite. An extended half-life of the 15-HETE-PE–generating 15LO1 protein, even after IL-13 removal, was reported, suggesting the possibility of sustained effects. Elegant 15LO1 small interfering RNA studies in primary airway epithelial cell air–liquid interface cultures and the use of a selective 15LO1 inhibitor (BLX2477) showed decreased IL-13–induced FOXA3 expression, enhanced FOXA2 expression, and reduced expression of MUC5AC and periostin. Direct addition of 15-HETE-PE to the cells, without added IL-13, recapitulated many of the key effects on airway epithelial cells, suggesting the importance of this specific lipid mediator in Th2-type mucin hyperproduction.

Like all good work, the current study raises several important questions and suggests future directions for research in the field. Does the 15LO1/15-HETE-PE pathway induce FOXA3 and MUC5AC *in vivo* in animals or humans, and is 15-HETE-PE elevated in the asthmatic airway? Can it serve as a biomarker of severe asthma? Is 15-HETE-PE a key mediator of mucin hyperproduction by non–Th2-type stimuli, and does it play a role in other mucin hypersecretory pathologies? Are there functional polymorphisms in the gene encoding 15LO1, and are these variants associated with altered MUC5AC expression/mucus hypersecretion and/or increased asthma risk? What is the effect of exogenous 15-HETE-PE on airway epithelial cell morphology? Does it increase MUC5AC mRNA and protein from the same number of goblet cells, or does it increase goblet cell numbers? Finally, can specific 15LO1 inhibitors (11) or 15-HETE-PE–selective antagonists be developed, and will they be effective therapies for asthma and other lung diseases characterized by excessive mucus secretion?

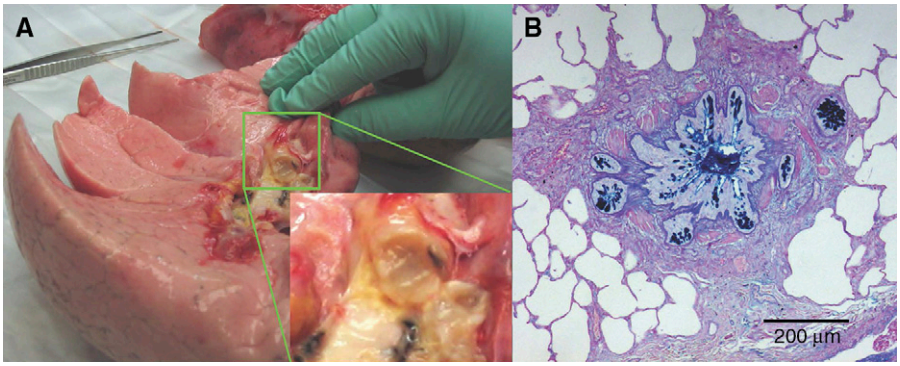

Figure 1. Mucin hypersecretion in a case of fatal asthma. (*A*) The gross lung specimen will not deflate. The inset illustrates obstruction of bronchial lumens with copious mucoid secretions. (*B*) Alcian blue/periodic acid Schiff staining shows nearly complete blockage of an extremely constricted small airway. *Scale bar*: 200 μm.

It is becoming clear that too much slime (mucin/mucus) in the airway (mucin hypersecretion) is a defining feature of many lung diseases, including asthma. Slippery (lipid) mediators are especially important, as illustrated by their role in aspirin-exacerbated airway disease (12, 13) and the success of lipid mediator–directed therapies for asthma and other lung pathologies (14). The study by Zhao and colleagues (8) points us toward novel approaches to understand this important and almost omnipresent airway response, and may lead to the development of new therapies for chronic lung conditions characterized by harmful mucus hypersecretion. ■

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