What it takes for a cough to expel mucus from the airway

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Cough is one of the most common symptoms for seeking medical care (1, 2). If cough is going to cause that much trouble, it better be worth it, and the clinical evidence is that indeed it is. Patients with impaired cough due to neuromuscular disease or postoperative sedation suffer high rates of atelectasis and pneumonia due to the failure to clear secretions from the airways, and there is evidence that a heightened cough reflex improves health (3, 4). Chief among airway secretions is mucus, and, in PNAS, Button et al. (5) analyze the biophysical requirements for a cough to separate adherent mucus from an airway wall. Before diving into the details, it is worth reviewing what is known about the biochemistry of mucus and the forces generated by a cough.

Mucus is an important defense against perturbations from the outside world at wet epithelial surfaces throughout the body, including the eyes, airways, gastrointestinal tract, and genitourinary tract. Its importance is revealed when the mucus barrier malfunctions in disorders such as dry eyes or inflammatory bowel disease. Mucus is a remarkable and protean substance, with properties on the border between a viscous fluid and a soft elastic solid. Its properties primarily reflect the interactions of mucin glycoproteins (~0.5% of mass) with water (~98%) and salts (~1%). Globular proteins are also present in normal mucus (~0.5% of mass) but do not have a major impact on the physical properties of mucus unless they and DNA are present in abnormal amounts during pathologic processes (3). Mucins are very large highly glycosylated molecules, accounting for their avid interactions with water. Secreted mucins polymerize into chains and networks that confer on mucus its semisolid consistency. However, the physical properties of mucus are highly dependent on mucin concentration, with dilute mucus acting like a fluid, and concentrated mucus like a solid (6). Furthermore, dilute mucus is an excellent lubricant, whereas concentrated mucus is adhesive (7–10).

In the lungs, a layer of mucus is continuously propelled from peripheral to central airways by the beating of cilia on epithelial cells that are interspersed among secretory cells in a mosaic pattern (Fig. 1, Lower Right). Inhaled particles and pathogens land on the mucus layer and are moved by cilia up the trachea, through the vocal cords, and then swallowed and cleared by the gastrointestinal tract (Fig. 1, Upper Right). Topologically, the lung is a blind sac, so without the clearance of particles and pathogens by a mobile mucus layer, these materials would accumulate. In contrast, the gastrointestinal tract is an open tube through which particles and pathogens pass readily. The mucus layer is generated by the secretion of mucins from surface epithelial cells (Fig. 1, Lower Right) and submucosal glands (not illustrated). Ciliary beating is the primary mechanism for clearance of mucus, with cough being a backup mechanism when mucus accumulates in the airways or adheres to airway walls (3, 11).

Cough has been studied extensively, so its mechanism and the forces it generates are well known (12). A cough begins with a rapid inspiration to fill the lungs with air, followed by closure of the glottis, contraction of the expiratory muscles of the chest and abdomen to generate a high intrathoracic pressure, and the sudden opening of the glottis to forcefully expel air from the mouth. During coughing, intrathoracic pressure can reach 200 cmH2O, which both provides the motive force for airflow (up to 8 L/s) and narrows the central airways by compression (Fig. 1, Middle Right) to maximize velocity (up to 28,000 cm/s or 626 mi/h). This expels secretions from the airways and into the throat (pharynx) (Fig. 1, Left), where they can be either swallowed or expectorated. What has been almost entirely unknown until now is how the shear force generated by cough interacts with adherent mucus in the airways.

To address this issue, Button et al. (5) first developed a conceptual model whereby adherent mucus could be separated from the airway wall either by cohesive or adhesive failure. Cohesive failure involves fracture of the adherent mucus by physically breaking mucins and other polymers within the mucus, whereas

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adhesive failure involves separating the adherent mucus from the glycocalyx of the underlying cell surfaces (see figure 1 of ref. 5). Next, they set up a peel-testing device to measure the force required to peel an adherent mucus layer off a layer of airway epithelial cells to test their model. This system was also used to assess the roles of mucin concentration and pH in determining the strength of mucus cohesion and adhesion, finding that the effects of mucin concentration dominated over pH within physiologic ranges of these two parameters. Last, they assessed the effects of therapeutic modalities such as mucus hydration with saline solution, mucin polymer lysis with a reducing agent to break disulfide bonds, and decreasing cohesion and adhesion with a surfactant. Each of these modalities provided benefit when used alone, and the combination of hydration and mucin lysis was particularly effective.

The mobile mucus layer is an essential defense of mammalian lungs, as shown by the death of mice from infection, inflammation, and obstruction when the major secreted airway mucin, Muc5b, is deleted (13). The importance of this defense to human health is highlighted by the fact that an overexpressing allele of MUC5B has been so strongly selected that it is present in 20% of whites (14), similar to the allele frequency of sickle hemoglobin in areas of hyperendemic malaria. Also similar to sickle hemoglobin, protection comes at a price because the MUC5B-overexpressing allele is the major risk factor for idiopathic pulmonary fibrosis late in life, probably as a result of epithelial progenitor depletion caused by the proteostasis stress of producing high levels of this large and complex molecule (14, 15).

Far more common than the problems that MUC5B hyper-expression causes in pulmonary fibrosis are the central roles that mucus dysfunction plays in obstructive diseases of the airways such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). In asthma, mucus dysfunction is mostly due to hyperproduction of the other secreted airway mucin, MUC5AC, together with the abnormal presence of plasma proteins, both resulting from inflammation as part of aberrant pathogen defenses (16). In CF, mucus dysfunction is due to insufficient chloride and bicarbonate transport into the airway lumen to allow adequate mucin hydration and expansion (17). In COPD, mucus dysfunction is due to a combination of the mechanisms operating in asthma and CF, as well as to ciliary dysfunction, all induced by cigarette smoke (3). In these disorders, mucus both accumulates in large central airways and plugs small peripheral airways. Accumulated mucus in central airways is cleared relatively effectively by cough because, at that level, airflow is high and mucus is not as concentrated as in peripheral airway plugs.
However, in small airways, airflow during coughing tapers off peripherally, and concentrated mucus becomes impacted. A radiographic imaging study in subjects with asthma has shown that peripheral airway mucus plugs persist for years (18). Airways of intermediate size and distance from the trachea are where work like that of Button et al. (5) is likely to have the biggest impact. The careful definition of forces involved in clearing mucus adherent to airway walls by cough, combined with analysis of the interactions of new mucus therapies with these forces, will allow us to derive the benefits of the complex biological defense mechanism that is mucus clearance, while minimizing the adverse effects of mucus dysfunction (19).

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