Published in final edited form as:

Science. 2012 August 24; 337(6097): 924–925. doi:10.1126/science.1227091.

Walking on Solid Ground

Burton F. Dickey, MD

Department of Pulmonary Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

The mobile airway mucus gel glides over grafted glycoconjugates of greater density.

Mucosal surfaces throughout the body, including those of the respiratory, gastrointestinal, and genitourinary tracts, are wet epithelia that include some form of mucus gel among their defenses. The airway mucosa is notable for the propulsion of its mucus gel layer out of the lungs by ciliary beating (Figure A, B), allowing for the rapid removal of inhaled pathogens and toxicants (1). The conventional model has been that the mucus gel layer lies atop a periciliary fluid layer. Since the mucus gel is denser than water, it was hypothesized to be kept suspended by the beating of cilia. However, as reported by Button et al. in this issue of *Science* (2), this model turns out to be fundamentally wrong, with the periciliary layer now shown to contain a macromolecular structure with a mesh size smaller than that of the mobile gel layer and a correspondingly greater osmotic modulus.

The incorrect impression of a fluid periciliary layer seems to have derived from the lack of visible ultrastructure using older fixation techniques, together with the intuitive sense that motile cilia should move best in a fluid. More recent morphologic studies reveal a dense network of macromolecules in the periciliary layer, emanating from the surface of cilia, microvilli and apical cell membranes (2, 3). Structural and immunohistochemical characteristics of this network are consistent with it being composed primarily of particular mucins tethered to the cell surface by transmembrane domains, as well as tethered mucopolysaccharides closer to the cell surface (4). Mucins are large, heavily glycosylated proteins. Since the charged sugar moieties repel each other, membrane-tethered mucins are likely to adopt an extended configuration like bottle brushes protruding from the cell surface (Figure C, D). This leads to a model in which the periciliary layer can be conceived as a mucus gel grafted onto the cell surface.

This model has important implications across several domains. First, it offers an explanation for the formation of two distinct layers within the airway surface liquid since the dense packing of grafted mucins will tend to exclude unattached polymeric mucins that form the mobile gel layer. Second, it may help explain the coordination of beating cilia which are physically coupled by the spatial impingement of grafted mucins on neighboring cilia.

Third, Button et al. demonstrate that mucins and tethered mucopolysaccharides are grafted with increasing density from top to bottom of the periciliary layer (2). This would directionally propel exogenous particles out of the periciliary layer, minimizing their contact with the underlying epithelium, which would be particularly important for infectious microbes (5). Fourth, charged polymers are highly effective lubricants in an aqueous environment (6). This could allow for low friction ciliary beating despite the density of macromolecules in the periciliary layer, as well as low friction between the periciliary and mobile gel layers. Fifth and most importantly, this model offers a quantitative explanation of the movement of liquid between layers in health and disease as follows.

The higher density of glycoconjugates in the periciliary than in the gel layer and their grafting to the cell surface results in a nearly constant amount of liquid in the periciliary layer except under conditions of severe underhydration. Because they are grafted, periciliary glycoconjugates have little ability to absorb increased liquid and swell with increasing hydration. Instead, increased liquid causes swelling of the mobile gel layer, which is generally well tolerated (7). With decreasing hydration, the periciliary layer draws liquid from the gel layer because of its higher osmotic modulus, attenuating dehydration of the periciliary layer until the gel layer becomes sufficiently dehydrated to resist further liquid transfer. At this point, mucus clearance fails catastrophically due to compression of cilia preventing their propulsive action (2), and probably due to adhesion between the two layers as well (8). Underhydration may be caused by a primary defect in the volume of liquid within the airway lumen in cystic fibrosis or acquired defects in COPD and airway infections (1). Underhydration of the gel layer may occur indirectly when polymeric mucins are produced, stockpiled, and then suddenly released in asthma (9), or when polymeric mucins fail to fully expand after exocytosis due to defective bicarbonate secretion in cystic fibrosis, resulting in inadequate calcium ion sequestration and excessive mucin crosslinking (10–12).

One issue not addressed by Button et al. is the structure of the periciliary layer overlying mucin-secreting cells. Ciliated and secretory cells are present in similar numbers in the airways, forming a mosaic (1). The absence of cilia and their grafted mucins would seem to leave gaps in the periciliary macromolecular network (Figure B, C). Some gap may be important to allow the egress of mucin polymers from secretory granules so these can flow up to replenish the mobile gel layer (13), and the gap is partially filled by the outward bulging of secretory cells (Figure C). MUC16 is the largest protein in the mammalian genome and is tethered to the surface of secretory cells (3), so could form a glycoconjugate brush together with tethered mucopolysaccharides. In addition, the viscoelasticity of the gel layer and ciliary beating might resist extrusion into the gaps, and the entanglement and calcium-dependent crosslinking of individual mucin polymers might render them so tightly associated with the gel layer that they do not penetrate the gaps. Eventually these issues will need to be addressed to have a full accounting of the structure and function of the airway mucosal surface.

In summary, Button et al. have given us a new Gel-on-Brush model with the capacity to unify the pathogenesis of human airway diseases that have in common mucus stasis, inflammation, and infection. This model has immediate implications for understanding the

restriction of pathogens from contact with underlying epithelial cells and the allocation of airway surface liquid between the two layers. For the long term, they have given us a quantitative model to test how mucus clearance fails in conditions of pathophysiologic challenge, and together with genetic and pharmacologic approaches, how specific molecules such as individual mucins and ion transporters contribute to the physical properties of the airway surface bilayer. Eventually, this should yield novel therapeutic strategies for airway diseases.

Acknowledgments

Source of Support: This research was supported by the National Institutes of Health grant R01 HL097000.

References

1. Fahy JV, Dickey BF, Engl N. *J. Med* 363, 2233 (2010).
2. Button B. A periciliary brush promotes lung health *Science* [in press] (2012).
3. Kesimer M et al. Molecular organization of the mucins and glycocalyx underlying mucus transport of the airways *Mucosal Immunol.* [in press] (2012).
4. Hattrup CL, Gendler SJ, *Annu. Rev. Physiol* 70, 431 (2008). [PubMed: 17850209]
5. Lai SK, Wang YY, Wirtz D, Hanes J, *Adv. Drug Deliv. Rev* 61, 86 (2009). [PubMed: 19166889]
6. Raviv U et al., *Nature* 425, 163 (2003). [PubMed: 12968175]
7. Tarran R, Donaldson S, Boucher RC, *Semin. Respir. Crit Care Med.* 28, 295 (2007). [PubMed: 17562499]
8. Smart JD, *Adv. Drug Deliv. Rev* 57, 1556 (2005). [PubMed: 16198441]
9. Evans CM, Kim K, Tuvim MJ, Dickey BF, *Curr. Opin. Pulm. Med* 15, 4 (2009). [PubMed: 19077699]
10. Chen EY, Yang N, Quinton PM, Chin WC, *Am. J. Physiol Lung Cell Mol. Physiol* 299, L542 (2010). [PubMed: 20693315]
11. Gustafsson JK et al., *J. Exp. Med* 209, 1263 (2012). [PubMed: 22711878]
12. Raynal BD, Hardingham TE, Sheehan JK, Thornton DJ, *J. Biol. Chem* 278, 28703 (2003). [PubMed: 12756239]
13. Davis CW, Dickey BF, *Annu. Rev. Physiol* 70, 487 (2008). [PubMed: 17988208]

Airway mucus layers.

(A) A mobile mucus gel is continually swept out of the lungs and swallowed (blue). (B) The mucus layer moves over an immobile periciliary layer of greater glycoconjugate density. Secretory cells synthesize polymeric mucins that form the mobile gel, while ciliated cells propel the gel. (C) A dense array of membrane-tethered mucins and mucopolysaccharides coats airway epithelial surfaces, and secretory cells release mucin polymers that travel upwards to be incorporated into the mobile gel. (D) Densely packed sugar side-chains cause membrane-tethered mucins to assume a partially extended configuration, while mucin polymers in the gel layer are random entangled coils.