Moving Mucus:
The Primary Defensive Strategy of the Airways

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The lung and airways bud off from embryonic foregut at a point directly below the naso-oropharynx and the paranasal sinuses, and this renders them susceptible to inhaled potentially noxious agents and also to aspiration of oropharyngeal microflora and mucus draining from the paranasal sinuses. An efficient firstline defence mechanism for the lower airways is therefore essential to health. This function is carried out principally by the mucociliary clearance apparatus which lines the airway epithelium of the paranasal sinuses, nose, Eustachian tube and bronchial tree. It is composed of cilia beating within thin periciliary fluid which propel thick mucus, situated above the cilia within the airway lumen, in a cephalad direction so that it is expelled from the larynx and swallowed imperceptibly.

Cilia are small cell appendices, about 200 of which are anchored into the luminal aspect of each ciliated epithelial cell by basal foot processes. The latter are aligned in the direction of the effective beat of the cilia which move with a metachronal wave form. Each cillum is composed of 9 peripheral pairs of microtubules which are connected by radial spokes to a central pair of microtubules aligned perpendicular to the plane of ciliary beating. At the tip of each cillum are protuberances which hook into the thick overlying mucus so as to propel it along the airway. Material which has been breathed in or aspirated sticks to this mucus and is thus cleared from the respiratory tract. Periciliary fluid is composed of the products of alveolar and airway epithelium and moves centrally, undergoing modification in ion content and volume. It is not clear whether, in the normal situation, this fluid forms a continuum with the thicker overlying mucus or whether the latter forms a distinct "belt" above the periciliary fluid propelled by the cilia.

The importance of mucociliary clearance as a first-line defence is illustrated by the fact that genetic abnormalities of cilia are associated with development of bronchiectasis, sinusitis and otitis as inflammatory sequelae to the persistence of material within the airway lumen due to defective clearance in the upper and lower airways. In chronic sinusitis, chronic bronchitis, bronchiectasis and cystic fibrosis it can be demonstrated (eg. by measuring clearance of technetium-labelled microspheres) that

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Mucociliary clearance is slow. A compelling argument can be made that most of the causes of bronchiectasis act via a pathogenetic pathway which involves impairment in airway mucus transport. Similarly, in an experimental model in which mucus transport is surgically impaired in a single lobe of rat lung, persistence of viable microorganisms in the airway serving this lobe leads to progressive inflammatory bronchiectatic damage. Nevertheless, there are other mechanisms for clearance of mucus from airways if ciliary clearance fails, including two-phase flow and cough/sneeze expulsive reflexes.

Mucociliary transport can be measured by a variety of techniques in vivo—some more invasive (therefore possibly falsely increasing clearance by stimulation) than others which probably provide a more realistic transport rate. There appears to be a gradient of ciliary beat rate up the airways, with those situated centrally beating faster than those peripherally—and this is thought to enable smooth clearance of mucus without its accumulation at sites where many thousands of small peripheral airways empty into an ever diminishing number of airways as the trachea is approached.

Mechanisms by which mucociliary clearance may be impaired are primary and secondary. Primary ciliary dyskinesia (PCD) may be due to genetic defects in the energy generating system of the cilium, in the ultrastructure of the apparatus required to move cilium, or in the orientation of cilia. Secondary ciliary dyskinesia may be caused by exotoxin molecules synthesized and released by microorganisms which have been allowed to persist in airways by some primary event or by underlying genetic disease reducing mucus clearance. Some of these toxins interfere with the energy pathways of beating cilia and also cause cytotoxic damage to epithelial cells. Such toxic effects may lead to selective colonisation of the airways by microorganisms producing such molecules.

Reduction in airway mucus transport from any cause is likely to lead to stasis of mucus and of its burden of bacteria—and it transpires that mucus is the main site of bacteria in chronic infection of the airways. This implies that antimicrobial agents should penetrate mucus to reach and kill bacteria, and that methods of improving mucus transport would remove the bacterial source of toxin-mediated damage. Persistence of microorganisms in the airway mucus stimulates a host response principally of migrating neutrophils which are though to cause further damage to the airways through release of damaging molecules, eg. proteinases.

Mucus itself is a difficult substance to study for it has both solid and liquid properties. It is salutary that despite our considerable and increasing knowledge of the genetics of cystic fibrosis the mechanism by which the mutated gene product renders mucus less transportable and allows airway infection is still obscure. There is obvious need for truly mucokinetic agents but those rendering the thick mucus, plugging the airways, thinner and more readily cleared by coughing or gravity-assisted drainage are only a temporary answer. They will not bring closer the real therapeutic requirement—to render mucus clearable by the normal ciliary mechanism. This remains perhaps the greatest challenge for researchers in the field of mucociliary clearance.