Cilia Dysfunction

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KEYWORDS

• Mucus • Mucociliary clearance • Ciliary beat frequency
• Chronic rhinosinusitis • Primary ciliary dyskinesia

Cilia are a ubiquitous organelle found on diverse cell types including sperm cells of vertebrates and some invertebrates, unicellular protozoa, and several vertebrate epithelial cell types. In mammals, for example, motile cilia found on cells lining the brain ventricles circulate cerebrospinal fluid; cilia in the respiratory tract sweep debris from the upper airway and the lungs; and oviduct cilia move the fertilized egg to the uterus. In addition, epithelial cilia present early in development are involved in left-right axis determination. Some epithelial cells, such as retinal photoreceptor cells and certain renal epithelial cells, possess immotile cilia that are now known to play important sensory roles in cell function. Individuals with motility-impaired cilia or defects in ciliary assembly may have any number of serious disorders, including respiratory disorders, hydrocephaly, retinal degeneration, polycystic kidney disease, liver disease, and infertility.

SINONASAL EPITHELIUM

The unique structure of the sinonasal epithelium facilitates normal cilia function and mucociliary clearance, thereby protecting the airway from debris, pathogens, and inhaled toxins. The anterior margin of the nasal vestibule is protected by a stratified squamous epithelium whose protective barrier includes sebaceous glands, sweat glands, and vibrissae. Near the nasal valves there is a histologic transition to pseudostratified columnar ciliated epithelium. Most of the nasal cavity epithelium consists of pseudostratified columnar ciliated cells, whereas the paranasal sinus epithelium is predominantly simple columnar ciliated cells.[1] In addition to the cilia projecting from their apical surface, the epithelial cells are lined with hundreds of immotile microvilli, hairlike projections of actin filaments, 1 to 2 μm in length, that lie beneath the cell membrane. By increasing the total mucosal surface area, the microvilli aid in sinonasal mucus production, sensation, secretion, and warming and humidifying inspired air.[2,3]

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Ciliated columnar epithelial cells comprise approximately 80% of sinonasal mucosa, goblet cells that produce mucus approximately 20%, and progenitor basal cells less than 5%.

MUCUS

Mucus production and structure are integrally associated with normal cilia function. Just as abnormal mucus production can impair normal cilia function, abnormal cilia function can result in stagnant mucus containing abundant pathogens and debris and result in chronic inflammation. The mucus layer functions to trap inspired pathogens, particulate matter, and cellular debris, and through the process of mucociliary clearance this layer is continuously cleared and reproduced. The superficial layer of mucus is a viscous gel phase that rides along the tips of fully extended cilia. The deep layer is the sol phase that surrounds and bathes the shafts of cilia. The sol phase is a solution of water and electrolytes (Na1, K1, Ca^{2+}, Cl^{-}) of lower viscosity than the gel phase. Mucus is a complex immunologically active substance made of carbohydrates, enzymes, proteins, immunoglobulins, and other active molecules.

The composition of mucus is essential to normal mucociliary clearance, and disorders of mucus production can be debilitating by causing severe secondary ciliary dysfunction. Cystic fibrosis, an autosomal recessive disease resulting from a mutation in a single gene, involves several organ systems and is characterized by defective electrolyte transport resulting in abnormal mucus production.[4] The genetic defect is found in the cystic fibrosis transmembrane conductance regulator gene product, a cyclic adenosine monophosphate–mediated membrane glycoprotein that forms a chloride channel and regulates the open probability of the sodium channel, ENaC.[5] The defective sodium chloride transport yields abnormally viscous mucus. The goblet cells in such patients are subsequently engorged and distended. These patients have severely impaired mucociliary clearance and frequently develop severe recurrent sinopulmonary infections.[6]

CILIA STRUCTURE AND FUNCTION

Sinonasal cilia beat in a coordinated manner to clear the paranasal sinus cavities and upper airway of the mucus blanket containing pathogens and debris. Normal cilia are cylindrical projections from the apical surface of epithelial cells, anchored by intracellular basal bodies. Each epithelial cell is lined with approximately 50 to 200 cilia, measuring 5 to 7 μm in length and 0.2 to 0.3 μm in diameter.[7,8] The cilium is composed of interconnected microtubules bundled into axonemes, and its overlying membrane is continuous with the cell's plasma membrane. The microtubules are made of protofilaments, which in turn are composed of α- and β-tubulin dimers.

The axonemes of motile cilia contain 2 central singlet microtubules surrounded by 9 doublet microtubules. Each doublet consists of 1 α-tubule, a complete circle of 13 protofilaments, and 1 β-tubule, an incomplete circle of 10 protofilaments. This structure is consistent among the motile cilia of the respiratory epithelium, oviduct, and cerebral ventricular ependymal cells. The 2 central microtubules are attached by paired bridges whereas the peripheral doublets attach to the central pair via radial spoke heads. Each outer doublet interacts with the adjacent outer doublets via inner dynein arms (IDAs), outer dynein arms (ODAs), and nexin, each having a distinct role in the dynamic motion of cilia bending.[9] Activation of the dynein arms generates a sliding motion of 1 microtubule doublet against the adjacent doublet. It is thought that phosphorylation of the ODAs regulates cilia beat frequency while phosphorylation of the IDAs regulates the waveform pattern of beating.[10,11] Although the function of the radial