Introduction

During normal breathing, the airways transport large quantities of environmental air into the lungs. This air is frequently contaminated with a variety of pollutants, particles and bacteria that are deposited in the airways. The nose, paranasal sinuses, trachea, and lower airways are lined with a superficial epithelium consisting primarily of two types of cells: mucus-producing goblet cells (20%) and ciliated cells (80%). This epithelial layer comprises the mucociliary escalator, the primary mode of defense for the entire respiratory system. Mucus produced by goblet cells traps inhaled particulate and infectious debris, while the propulsive force generated by the ciliated cells transports this mucus blanket to the gastrointestinal tract for elimination [1]. Unlike the lower airways or nasal cavity, in which debris-laden mucus can be cleared with a cough or sneeze reflex respectively, the paranasal sinuses are solely dependent on ciliary activity to clear mucus [2].

Mucociliary clearance (MCC) is dynamically regulated by both the inhaled environmental stimuli as well as host factors such as neurotransmitters and cytokines. Although multiple etiologies contribute to the development of chronic rhinosinusitis (CRS), a common pathophysiologic sequela is ineffective sinonasal MCC, leading to stasis of sinonasal secretions, with subsequent infection and/or persistent inflammation. The predominant goal of medical and surgical intervention in the management of CRS is restoration of MCC. Thus, in this chapter we will review respiratory ciliary cell biology and physiology, and the ciliary pathophysiology associated with respiratory diseases.

Ciliary Structure and Function

Respiratory cilia clear mucus and debris from both the upper and lower respiratory passages by beating in a coordinated and rhythmic manner. There are approximately 50–200 cilia per epithelial cell; each measures 5–7 µm in length and has a diameter of about 0.2–0.3 µm [3, 4]. Cilia are organelles located in the apical surface of epithelial cells that are anchored to the basal bodies derived from the centrioles. Each cilium comprises a bundle of interconnected microtubules termed the axoneme and an overlying membrane that is part of the cell plasma mem-
brane. Microtubules comprise protofilaments, which are assembled from α- and β-tubulin dimers. The major β-tubulin in the cilia is the type IV isotype [5], which is much more abundant in the cilia than in the cell and makes for an ideal marker for respiratory cilia in the research setting (Fig. 6.1). The axonemes of motile cilia, which are found in the respiratory system, oviduct, and ventricular ependymal cells, contain two central singlet microtubules surrounded by nine doublet microtubules (Fig. 6.2). The doublet consists of an A-tubule, a complete circle of 13 protofilaments, and a B-tubule, an incomplete circle of 10 protofilaments. The two central microtubules are attached by paired bridges, while the peripheral doublets attach to the central pair via radial spoke heads. Each outer doublet interacts with the adjacent outer doublet via inner dynein arms (IDA), outer dynein arms (ODA), and nexin, each of which have distinct roles in the dynamic motion of cilia bending [6]. Activation of the dynein arms generates a sliding motion of one microtubule doublet against the adjacent doublet. While phosphorylation of the ODA regulates cilia beat frequency, phosphorylation of the IDA regulate the wave form pattern of beating [7, 8]. Although the function of the radial spoke heads is not entirely understood, it seems that they are involved in regionally limiting the sliding between the microtubules during the ciliary stroke, thus converting the sliding motion generated by the dynein arms into the bending motion of the axoneme [9].

Each cilium has a forward effective stroke followed by a recovery stroke. During the effective stroke the cilia is fully extended, and at the apogee of the arc, the distal tip makes contact with the viscous outer mucus layer (see the section “Mucus and Periciliary Fluid”), thereby transmitting directional force to the overlying mucus blanket. During the recovery stroke, the cilia bends 90° and sweeps back to the starting point within the thin periciliary fluid layer. As mentioned above, the mechanism of ciliary motion depends on a series of molecular motors built into the axoneme, which act to produce a vectorial force that causes the outer doublet microtubules to slide relative to one another. The central pair divides the axoneme into opposite halves. As proposed by the "switch point" hypothesis, the dynein motors on one side of the axoneme are predominantly active during the effective stroke, while the motors on the other side are mainly active during the recovery stroke [10]. If the microtubules are numbered in a clockwise fashion from 1 to 9, the effective stroke would involve the ODA on the 9-1-2-3-4 microtubules, and the recovery stroke would involve activity of the dynein in the 5-6-7-8 microtubules [11]. The power generated by the cilium is directly proportional to the number of the dynein–microtubule interactions [12], while under normal circumstances, there is a reserve to increase the power of the stroke [13]. The orientation of the stroke is dictated by the orientation of the basal body of the axoneme [14, 15].

Although it is well established that cilia beat in a coordinated fashion, referred to as a metachronous wave, the mechanism of coordination is not entirely understood. A possible way of explaining the presence of this wave might be the close relationship between the cilia in the cell and the hydrodynamic forces between the cilia, since they beat submerged in a partly liquid environment [16]. Additionally, gap junctions, predominately connexin-43, may generate directional propagation of intracellular calcium waves to adjacent cells driving the metachronous wave [17].

![Fig. 6.1a,b Type IV beta-tubulin specifically stains respiratory cilia. a Intact and b dissociated human paranasal sinus mucosa stained with a monoclonal antibody against type IV beta-tubulin demonstrate intense specific staining of the respiratory cilia.](image)