Sensorium: The Original *Raison D’être* of the Motile Cilium?

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The role of non-motile (primary) cilia as sensory antennae critical for metazoan development and physiology has surfaced over the last decade, long after the function of motile cilia in propelling cells or moving fluids across tissues was well established. A new study of motile cilia from respiratory airways raises the possibility that transducing sensory cues from the environment is a universal characteristic of cilia and may have been the original *raison d’être* of the ancestral cilium.

Cilia are tail-like cellular projections found on the surfaces of most eukaryotic cells (Pedersen and Rosenbaum, 2008). The quintessential motile cilium, also termed flagella, are used to propel cells through an aqueous medium or move fluid over cell surfaces. For example, they provide motility to gametes and protists such as *Chlamydomonas* or *Paramecium*, which are engaged in moving through their environment in response to various stimuli, such as light, chemicals or touch. In vertebrates, motile cilia bestow tissues—such as brain ventricles, fallopian tubes or respiratory tract—with the ability to create circulation or flow. The molecular machinery responsible for driving the coordinated whip-like beat of the organelle, which includes ciliary dyneins, is evolutionarily conserved among a wide range of eukaryotic species, and thus represents a primordial trait of the ancestral ciliated organism.

Although most animal cells lack motile cilia, almost all possess a single immotile variant known as the primary cilium. Some metazoan cells have acquired highly specialized sensory roles during evolution through the modification of this primary cilium. For example, vertebrates possess rod- or cone-shaped ciliary photoreceptors that transduce light signals, and olfactory epithelial cells harbour singularly long cilia involved in smell. Nematodes such as *Caenorhabditis elegans* represent the only known animal species to possess only non-motile sensory cilia; these have evolved remarkably diverse shapes and sensory functions, while their sperm are restricted to an amoeboid-type movement.

When the machinery responsible for ciliary motility is defective, cilia no longer beat effectively, leading to several ailments, including recurrent respiratory infections such as bronchitis and pneumonia. This relationship between loss of motile cilium function and disease has been known for over 100 years, but it is only in the past ~10 years that we have gained an appreciation for disease states that arise from defects affecting the primary cilium. By studying diseases such as polycystic kidney disease and the multi-systemic Bardet–Biedl syndrome, we have learned that the unassuming primary cilium, previously thought to be vestigial, plays important roles in capturing and processing environmental cues critical for development and physiology (Pedersen and Rosenbaum, 2008). In considering the seemingly disparate functions of motile and non-motile cilia, the question of which came first arises—did the use of cilia as sensory antennae emerge before, or after, the acquisition of motile functions?

Attempts to understand the evolutionary history of motile and non-motile cilia have recently been made, with the promise that they will help illuminate the functions of the organelles at the molecular and cellular levels. The most central, parsimonious finding is that the ur-eukaryote possessed a single motile cilium (Richards and Cavalier-Smith, 2005). Biogenesis of its microtubule-based axoneme utilized an intraflagellar transport machinery derived at least in part from pre-existing coated vesicle-trafficking components and specifically adapted for mobilizing ciliary cargo within the organelle (Jékely and Arendt, 2006). Peering further back in time, it can be argued that the progenitor of the ancestral cilium may have been a sensory patch on a polarized cell that eventually elongated into an antenna-like structure capable of more effectively concentrating receptors and signalling components; the more complex multi-protein apparatus necessary for motility likely emerged later, or perhaps simultaneously with the development of a proto-cilium (Jékely and Arendt, 2006). Figure 1 illustrates this possibility.

The comparatively recent inception of the metazoan lineage, wherein organisinal motility could be conferred by specialized muscle or motile cilia-containing cell types, then permitted the evolutionary elaboration of a non-motile, strictly sensory primary cilium (Figure 1). It will be a fascinating exercise for evolutionary biologists to devise more detailed hypotheses regarding the molecular sequence of events needed to explain the emergence of cilia in general, and their two disparate functions (motility and sensory). In the meantime, there is one key question that is starting to be addressed. While it is evident that primary
cilia have lost the constituents required for generating ciliary bends, have motile cilia similarly become more specialized and lost their ability to sense and transduce environmental signals?

Unfazed by the widely reported unifunctional role of metazoan motile cilia, Shah et al. (2009) hypothesized that for ciliated human airway epithelia to most effectively clear offensive particulate or chemical matter, its motile cilia could directly participate in the sensing of noxious stimuli. As a first step in testing this hypothesis, the authors scanned for the expression of sensory-associated genes in a microarray transcriptome analysis of this tissue. The presence of several bitter taste receptor (T2R) genes was noted, and their expression confirmed by RT–PCR. Using a panel of antibodies against four of the T2R proteins, namely T2R4, T2R38, T2R43 and T2R46, it was observed that the receptors were present only in ciliated cells of the airway epithelia. Even more revealing was the finding that they localized specifically within the motile cilia. Given that the T2R signalling pathway is known to make use of the G protein α-gustducin (Chandrashekar et al., 2000), the authors tested for its presence in cilia by immunostaining. Similar to the T2R proteins, α-gustducin localized only in ciliated cells and subcellularly, within motile cilia. Thus, the sensory toolset to detect bitter compounds appears to be present in motile cilia. Another known component of the pathway, phospholipase C-β2, is also restricted to these ciliated cells. Consistent with a chemosensory function for the differentiated airway epithelial cells, application of various bitter compounds increased the intracellular concentration of the T2R-linked second messenger Ca\(^{2+}\). The functional consequence of exposing the cells to a bitter compound was also confirmed; similar to other ciliated cells, elevation of the Ca\(^{2+}\) concentration caused a statistically significant increase in ciliary beat frequency.

Altogether, these results suggest the presence of a cell-autonomous, cilium-dependent sensing mechanism for increasing the clearance of noxious compounds within the respiratory tract. Such a physiological response is in some ways not surprising. The same chemosensory T2R and α-gustducin signal transduction components are present within the nasal epithelium and respond to bitter chemical insults by neurally activating the sneezing reflex and increasing respiratory rate (Finger et al., 2003)—providing a second level of protection for the respiratory airway. But is this a special case of motile cilia acquiring a sensory function, or does it reflect as we hypothesize in Figure 1 that the ancestral motile cilium was also a sensorium?

It is well established that ciliated protists, both free-living and parasitic, exhibit cilia-mediated motile behaviours, such as chemotaxis. However, we have few examples demonstrating the specific localization of sensory machinery to cilia. Ostensibly the clearest example derives from studying Chlamydomonas, the unicellular alga that has contributed substantially to our understanding of cilia in general, and specifically motile cilia. During mating, gametes express receptor proteins known as agglutinins on the flagellar surface; the ligand is the agglutinin of the opposite mating type, and when the two proteins interact, they trigger signal transduction in both cells (Quarmby, 1994). This signal elicits a number of cellular responses, including shedding of the cell wall.

Among protists, there is some evidence for cilia-localized sensory receptors, including the insulin receptor-like and EGF receptor-like proteins of Tetrahymena (Christensen et al., 2003; Csaba et al., 2004), but their direct participation in sensory behaviour remains unclear. Proteomic studies of isolated flagella have identified many signalling molecules, including kinases, phosphatases and ion channels, but whether these flagellar signalling proteins are regulating motility or sensing the environment remains to be
established. The response of *Chlamydomonas* to light may provide examples of both situations. During phototaxis, flagellar signal transduction proteins regulate the differential waveform and beat frequency of the two flagella, but the original sensory input occurs at the eyespot within the cell body (Hegemann, 1997). In the case of gametogenesis, reception of an essential blue light signal may occur in the flagella and be transmitted to the nucleus (Huang et al., 2004).

For the ancestral eukaryote and descendant unicellular lineages, the cilium unquestionably served a critical role in locomotion, much as the evolutionarily distinct prokaryotic flagellum enables highly effective motility. Unlike the prokaryotic flagellum, however, which strictly serves as a cellular propeller, the eukaryotic cilium is encased in membrane and therefore can act as a sensorium. Arguably, the combined motility and sensory functions of the cilium likely provided substantial selective advantages to emergent eukaryotes and ensured the near-universal use of cilia in uni- and multicellular organisms (Figure 1). Although metazoans have evolved specialized cell types containing either motile or non-motile cilia, evidence now suggests that both are endowed with sensory modalities. Thus, one of the greatest challenges facing research on primary cilia—namely determining their varied cell-specific roles in signal transduction—also applies to researchers studying motile cilia.

**References**


