Sensory reception is an attribute of both primary cilia and motile cilia

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Summary

A recent cluster of papers has shown that motile cilia in the respiratory and reproductive tracts of humans and other mammals can exhibit sensory functions, a function previously attributed primarily to non-motile primary cilia. This leads to a new paradigm that all cilia and flagella (both motile and primary) can mediate sensory functions. However, examination of the literature shows that evidence of sensory functions of motile cilia and flagella is widespread in studies of invertebrates, and extends as back as far as 1899. In this Opinion article, I review the recent and historical findings that motile cilia have a variety of sensory functions, and discuss how this concept has in fact been evolving for the past century.

This article is part of a Minifocus on cilia and flagella. For further reading, please see related articles: 'The primary cilium at a glance' by Peter Satir et al. (*J. Cell Sci.* **123**, 499-503), 'The perennial organelle: assembly and disassembly of the primary cilium' by E. Scott Seeley and Maxence V. Nachury (*J. Cell Sci.* **123**, 511-518), 'Flagellar and ciliary beating: the proven and the possible' by Charles B. Lindemann and Kathleen A. Lesich (*J. Cell Sci.* **123**, 519-528) and 'Molecular mechanisms of protein and lipid targeting to ciliary membranes' by Brian T. Emmer et al. (*J. Cell Sci.* **123**, 529-536).

Key words: Cilia, Flagella, Motile, Sensory, Signaling

Introduction

The field of ciliary and flagellar biology is a dynamic area of study with a rich history. Cilia were probably first observed and their motile function appreciated by Antoni van Leeuwenhoek in 1674-75 (Dobell, 1932), although the term for these organelles was probably first used by Otto Friedrich Müller in 1786 (Muller, 1786). Note that the terms 'cilia' and 'eukaryotic flagella' refer to essentially the same class of organelle; the term 'cilia' will be used henceforth to refer to both. Cilia were originally defined by their motility and, for a long time, this was assumed to be the only function of these organelles. However, in the second half of the nineteenth century, a class of non-motile, solitary cilia was observed (Kowalevsky, 1867; Langerhans, 1876; Zimmermann, 1898). Zimmermann was the first scientist to observe these organelles in mammalian cells, including those of humans, the first to name these organelles (which he termed 'centralgeissel', meaning central flagella) and the first to hypothesize a sensory function for them. However, both Zimmermann's name for these organelles and his proposed function for them were soon forgotten. Renamed 'primary cilia' in 1968 (Sorokin, 1968), this special class of non-motile cilia remained a curiosity and received little attention until recently.

A convergence of events at the beginning of the twenty-first century then led to an explosive interest in primary cilia because of their clearly demonstrated sensory function and their clinical significance (Bloodgood, 2009). For the first time, the breadth of interest in primary cilia eclipsed that of motile cilia. There emerged a duality in which the world of cilia was divided into organelles with motile functions and organelles with sensory functions, the latter being much more widespread among mammalian cells and tissues. Currently, however, a new synthetic idea in the field of cilia and flagella is emerging – that all cilia have sensory functions (Christensen et al., 2007). A recent Perspectives article in *Science*

(Kinnamon and Reynolds, 2009) claimed that a recent and exciting report (Shah et al., 2009) represents "the first report of sensory function in motile cilia". This is not strictly true, neither on the basis of a short-term (past 5 years) nor a long-term (100 years) examination of the literature. This is a prime example of how difficult it is to label a finding as a 'first' discovery when, in fact, scientific discovery tends to be a gradual, evolutionary process that involves multiple players.

In this Opinion article, I demonstrate that evidence supporting a sensory role for motile cilia has been accumulating in the literature for a very long time. I begin by briefly reviewing recent scientific reports indicating that motile cilia in the mammalian respiratory and female reproductive tracts possess the capacity for sensing mechanical and chemical information in their extracellular environment.

Evidence for a sensory function of motile cilia in mammalian cells

Motile cilia in the mammalian respiratory epithelium exhibit mechanoreceptive and chemoreceptive properties

Motile cilia of the mammalian respiratory epithelium have been reported to exhibit both mechanosensitivity and chemosensitivity. For mucociliary clearance in the airways to function optimally, a process of autoregulation has evolved. As mucus viscosity around the cilia (i.e. the load on the system) increases, ciliary mechanics are adjusted so as to maintain a ciliary beat frequency, albeit somewhat reduced, that is sufficient to maintain transport of mucus (containing trapped pathogens and particulates) to the larynx, where it is swallowed or expectorated (Johnson et al., 1991). Cytosolic Ca^{2+} levels play an important role in this process of autoregulation, and increases in cytosolic Ca^{2+} are associated with changes in ciliary beat frequency (Salathe, 2006). This ability to

compensate for increased load is overwhelmed in patients with cystic fibrosis, leading to persistent infections by bacterial pathogens such as *Pseudomonas aeruginosa*.

How is mechanosensitivity perceived by the epithelium? One obvious candidate for the site of mechanoreception is the motile cilium itself. Sanderson and Dirksen observed that mechanical stimulation of cilia of cultured rabbit tracheal cells with fluid movement, by direct stimulation with a microprobe or by dragging mucus over the cilia using the microprobe, resulted in a transient increase in ciliary beat frequency that was dependent on the presence of Ca^{2+} in the extracellular medium and was inhibited by a Ca^{2+}-channel blocker (Sanderson and Dirksen, 1986). Furthermore, Lorenzo and colleagues localized the TRPV4 cation channel (Box 1) to the cilia in respiratory epithelial cells and showed that it was lost from the respiratory cilia of TRPV4 knockout mice (Lorenzo et al., 2008). A TRPV4 agonist induced Ca^{2+} influx and an increase in ciliary beat frequency in the tracheal epithelial cells from $Trpv4^{+/+}$ mice but not $Trpv4^{-/-}$ mice. Although both wild-type and $Trpv4^{-/-}$ cells were able to autoregulate ciliary beat frequency in response to a viscous load, only the cells with TRPV4 showed the normal intracellular Ca^{2+} oscillations associated with mechanoreception.

Shah and colleagues recently reported a dramatic demonstration of chemoreception when they localized different members of the bitter taste receptor family to motile cilia of airway epithelial cells (Shah et al., 2009); indeed, different classes of receptors were found to localize to different positions on the ciliary membrane. One class (T2R receptors) activated a signaling pathway that includes the G protein α-gustducin (which also localized to the cilia), phospholipase Cβ2 and a rise in cytosolic Ca^{2+} (Meyerhof, 2005; Chandrashekar et al., 2006). Shah and colleagues showed that bitter compounds that are known to activate this pathway induce both a transient, dose-dependent rise in intracellular Ca^{2+} in ciliated cells as well as an increase in ciliary beat frequency. The response is thought to provide protection for the airway epithelium from noxious compounds by speeding up the process of mucociliary clearance.

Other work has provided hints of other signaling pathways that might be associated with motile cilia in respiratory epithelium. The product of a planar-cell polarity (PCP) gene, *Vangl2*, has been localized to the motile cilia of respiratory epithelium in mice (Ross et al., 2005), as has the fibroblast growth-factor receptor (FGFR-1) in a study of rhesus monkeys (Evans et al., 2002). There is even evidence that the binding of pathogens to respiratory cilia can activate signaling pathways: binding of *Mycoplasma hyopneumoniae* to the ciliary membrane was shown to activate a G-protein-coupled receptor, which in turn activates a phospholipase C pathway that results in a rise in intracellular Ca^{2+} (Park et al., 2002).

Motile cilia in the mammalian oviductal epithelium exhibit responses to sex hormones as well as mechanoreception

Estrous-cycle-dependent changes in progesterone and estradiol induce changes in the secretions of the oviductal epithelium as well as changes in ciliary beat frequency to maximize fertilization and the transport of gametes and fertilized embryos (Brenner, 1969). The membranes of motile cilia of the mammalian oviduct contain progesterone receptors [mouse and human (Teilmann et al., 2006; Nutu et al., 2009)], estrogen receptor-β [rat (Shao et al., 2007)] and interleukin-6 receptor (IL6Rα) [mouse and human (Shao et al., 2009)]. Furthermore, progesterone (Mahmood et al., 1998; Paltieli et al., 2000; Wessel et al., 2004) and interleukin-6 (Papathanasiou et al., 2008) regulate oviductal ciliary beat frequency. Estradiol downregulates the expression of IL6Rα (a negative regulator of ciliary beat frequency) in mouse oviductal cilia, resulting in an increased ciliary beat frequency that promotes oocyte transport towards the uterus (Shao et al., 2009).

The membranes of motile cilia of the mouse oviduct also contain TRP cation channels (Box 1) [including TRPP1 (also known as polycystin-1 and PKD1), TRPP2 (also known as polycystin-2 and PKD2) and TRPV4] (Teilmann et al., 2005). Similar to the situation in respiratory epithelia, the beat frequency of cilia in the mouse oviduct is adjusted in response to viscous loading (Andrade et al., 2005). Although the ciliary beat frequency decreases to a new stable level in response to a high viscous load, the total force production is thought to increase in order to maintain the transport properties of the oviduct epithelium. This autoregulation observed at high viscous loads (20% dextran) required the entry of extracellular Ca^{2+} into epithelial cells and resulted in an oscillatory behavior of intracellular free Ca^{2+} levels (Andrade et al., 2005). An agonist of the TRPV4 channel induced the same responses as increased viscous load, and the effects were abrogated by a TRPV4-blocking antibody. Coupled with the observation that TRPV4 channels are localized to a subset of motile cilia in the oviduct epithelium (Teilmann et al., 2005; Fernandes et al., 2008), these findings strongly suggest that sensory responses to increased viscous load in the oviduct are mediated directly through motile cilia.

Teilmann and Christensen showed that tyrosine kinase with immunoglobulin-like and EGF-like domains 1 and 2 (Tie-1 and Tie-2), which are receptors for angiopoietins, are localized to motile cilia in the mouse oviduct (Teilmann and Christensen, 2005). Angiotensin II has been shown to stimulate ciliary beat frequency in vitro (Saridogan et al., 1996).

Motile cilia in other mammalian tissues

There are emerging hints that a third major population of mammalian motile cilia – ependymal cilia that line the ventricles of the brain – can also respond to changes in viscosity in the extracellular medium (mechanoreception) (O'Callaghan et al., 2008).

Although some of the evidence is still preliminary, a burst of reports in recent years suggests that all major populations of motile cilia in the mammalian body are capable of sensory reception (both chemoreception and mechanoreception). One common feature of the ciliated epithelia of the respiratory tract, oviduct and ependymal

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Box 1. Transient receptor potential channels

The transient receptor potential (TRP) channels are a superfamily of ion channels that are permeable to cations, including calcium, magnesium and sodium. There are six or seven families and most TRP channels are composed of six membrane-spanning domains. They are widely expressed among both vertebrates and invertebrates. Although they are found in many locations in the cell, TRP channels (especially TRPV, TRPP and TRPN) have been widely implicated in the sensory functions of non-motile primary cilia (reviewed by Pazour and Bloodgood, 2008). As noted in this Opinion, TRP channels (especially TRPV4 and TRPP2) are also found to be associated with motile cilia and implicated in some of their sensory functions. It has generally been shown that Ca^{2+} is the relevant ion being transported across ciliary membranes by TRP channels in the context of sensory roles played by motile and non-motile cilia.

lining of the ventricles of the brain is the need to adjust ciliary beat frequency in response to changes in viscosity in the fluids bathing the apical surface of these epithelia; this sensory-motor response circuit appears to be mediated by the cilia themselves.

Evidence for mechanoreception by motile cilia in studies of protists and other invertebrates

Although the evidence for sensory reception by motile cilia in mammalian epithelia has accumulated only recently, there have been numerous reports, spanning more than 100 years, suggesting that motile cilia in lower eukaryotic organisms participate in sensory reception. Most of these reports focused on mechanoreception. In a paper published in 1899 (Jennings, 1899) and a book published in 1906 (Jennings, 1906), Herbert S. Jennings described what he referred to as the 'avoiding reaction' in *Paramecium* (Fig. 1). When a *Paramecium* strikes a solid object, it transiently reverses the direction of swimming, alters the angle of orientation slightly and then resumes forward motion. This sequence is repeated until the organism is able to avoid the obstacle. Jennings showed that a similar behavior is associated with negative chemotaxis (avoidance of noxious chemicals) in *Paramecium* (Jennings, 1906).

Although Jennings made the observation that changes in ciliary motility were the basis of the avoiding reaction, the underlying molecular mechanism was not uncovered until much later. It is now known that the initial contact of the anterior end of the *Paramecium* with a solid object elicits a Ca^{2+}-based depolarizing mechanoreceptor potential in the plasma membrane, which triggers the rapid opening of voltage-sensitive regenerative Ca^{2+} channels located only in ciliary membranes, allowing Ca^{2+} to enter the cilia. The temporary rise in intraciliary Ca^{2+} concentration initiates a transient reversal in the pattern of axonemal beating, resulting in a temporary reversal in swimming direction (Ogura and Takahashi, 1976; Dunlap, 1977; Machemer and Ogura, 1979; Ogura and Machemer, 1980). Gray reported on a sensory function for the anterior motile flagellum of the protozoan *Heteromastix* when he noted that "its movements resemble those of the proboscis of an elephant because it is constantly 'feeling' for obstructions, and when one is found the flagellum seizes hold of it" (Gray, 1928). In addition, Thurm directly demonstrated the mechanosensitivity of motile cilia by using a glass needle to bend quiescent abfrontal cilia on the gills of the mollusk *Mytilus edulis*, thereby inducing a cycle of ciliary bending (recovery and active stroke) (Thurm, 1968). 'Balancer cilia' in ctenophores (comb jellies) were observed to increase or decrease their beat frequency when they were deflected

in opposite directions by the movements of gravity-sensing organelles known as statoliths (Horridge, 1965; Tamm, 1982); this change in beat frequency was later shown to occur owing to an influx of Ca^{2+} into the balancer cilia (Lowe, 1997).

The flagella of the green alga *Chlamydomonas* are some of the most extensively studied of all motile cilia and flagella, and data have been accumulating for decades that demonstrate their sensory role (Solter and Gibor, 1977). The initial contact between *Chlamydomonas* plus and minus mating-type gametes occurs through their respective flagellar surfaces. This contact initiates a complex signaling pathway that involves protein kinases, protein phosphorylation, activation of adenylyl cyclase and a rise in intracellular cyclic AMP levels (reviewed by Snell and Goodenough, 2009). *Chlamydomonas* flagellar membranes contain the TRPP2 cation channel, and knockdown of the expression of this protein in the flagellum resulted in a mating defect (Huang et al., 2007). *Chlamydomonas* flagella also exhibit direct mechanoreception mediated by Ca^{2+} influx (Yoshimura, 1996; Wakabayashi et al., 2009).

As in the case of *Chlamydomonas*, the initial contact between gametes during mating (conjugation) in some ciliate protozoa, such as *Paramecium*, involves direct cilium-cilium adhesion through specific mating substances that are localized to the ciliary membrane; these cilium-cilium adhesion events activate as-yet poorly understood signaling pathways that lead to subsequent events in mating (Watanabe, 1990). In *Paramecium*, one of the immediate downstream effects of the interaction between the gametic cilia is a dramatic decrease in ciliary motility and hence in swimming velocity, which is thought to promote the conjugation process (Kitamura and Hiwatashi, 1984).

Conclusions

Although it has not been widely appreciated, data have been gradually accumulating that support the idea that motile cilia in both vertebrate and invertebrate systems perform a variety of sensory functions, most of which are mechanosensory or chemosensory in nature. In addition to the examples reviewed above, there is also an unusual indirect signaling role played by motile mammalian cilia and flagella whereby the motility is itself the sensory output that influences other cells. This can be illustrated with two examples. The first relates to the node of the developing mammalian embryo: one of the leading theories for how left-right asymmetry of the body plan is established is that the motility of cilia on a population of nodal cells creates a leftward-directed flow in the embryo that bends a separate population of non-motile primary cilia, initiating a Ca^{2+}-based signaling cascade in the cells with which those primary cilia are associated (reviewed by Basu and Brueckner, 2008). A competing theory is that the leftward-directed flow mediated by the motile nodal cilia sets up a gradient of morphogen that initiates Ca^{2+} signaling specifically on one side of the developing embryo. The second example is equally fascinating: Sawamoto and colleagues reported that the motility of cilia on ependymal cells lining the ventricle of the brain is essential in order to establish a gradient of signaling molecules in the cerebrospinal fluid that directs the migration of neuroblasts from the subventricular zone to the olfactory epithelium (Sawamoto et al., 2006). Neuroblasts in mice deficient for Tg737 (a ciliary protein also known as IFT88), and hence exhibiting defective ependymal ciliary function, failed to migrate to the olfactory bulb.

As is the case for many of the sensory functions mediated by non-motile primary cilia, sensory reception in motile cilia also
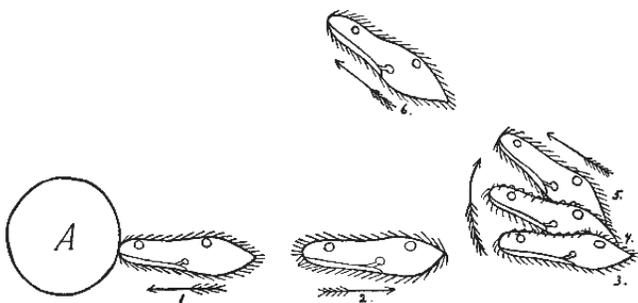

Fig. 1. The avoiding response. Mechanical stimulation of the anterior end of *Paramecium* results in a Ca^{2+} action potential in the ciliary membrane and entry of Ca^{2+} into the cilia, which alters axonemal waveform properties and results in transient backward swimming. Jennings called this the 'avoiding response'. Reproduced with permission from Jennings, 1899.

involves Ca^{2+} signaling. In addition, as in primary cilia (Kahn-Kirby and Bargmann, 2006; Pazour and Bloodgood, 2008), the TRP family of cation channels plays a major role in many (although not all) of the sensory functions exhibited by motile cilia. In keeping with the cellular function of motile cilia, it is not surprising that much of the sensory input to these organelles serves to regulate ciliary motility, which is obviously not the case for the sensory input to primary cilia, which are non-motile. However, the commonality of sensory function among virtually all eukaryotic cilia (both motile cilia and primary cilia) suggests that the original protocilium from which both types of organelles evolved was a sensory organelle. Cilia might have evolved from a simple 'sensory membrane patch' (Jekely and Arendt, 2006; Satir et al., 2008) that, over evolutionary time, extended, antenna-like, out from the cell surface and only later acquired motile function. Obviously, both sensory reception and motility provided selective advantages for the early eukaryotic cell.

It is hoped that the growing awareness that motile cilia share with primary cilia the capacity for sensory reception (and even share similar pathways for this sensory reception that involve TRP receptors and Ca^{2+} influxes) will lead to increased study of the membranes of motile cilia, as has already become the case for primary cilia.

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