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Review

# The mechanics of the primary cilium: An intricate structure with complex function

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ABSTRACT

The primary cilium is a non-motile singular cellular structure that extends from the surface of nearly every cell in the body. The cilium has been shown to play numerous roles in maintaining tissue homeostasis, through regulating signaling pathways and sensing both biophysical and biochemical changes in the extracellular environment. The structural performance of the cilium is paramount to its function as defective cilia have been linked to numerous pathologies. In particular, the cilium has demonstrated a mechanosensory role in tissues such as the kidney, liver, endothelium and bone, where cilium deflection under mechanical loading triggers a cellular response. Understanding of how cilium structure and subsequent mechanical behavior contributes to the roles that cilium plays in regulating cellular behavior is a compelling question, yet is a relatively untouched research area. Recent advances in biophysical measurements have demonstrated the cilium to be a structurally intricate organelle containing an array of load bearing proteins. Furthermore advances in modeling of this organelle have revealed the importance of these proteins at regulating the cilium's mechanosensitivity. Remarkably, the cilium is capable of adapting its mechanical state, altering its length and possibly it's bending resistance, to regulate its mechanosensitivity demonstrating the importance of cilium mechanics in cellular responses. In this review, we introduce the cilium as a mechanosensor; discuss the advances in the mechanical modeling of cilia; explore the structural features of the cilium, which contribute to its mechanics and finish with possible mechanisms in which alteration in structure may affect ciliary mechanics, consequently affecting ciliary based mechanosensing.



**Contents**



## 1. Introduction

Primary cilia are non-motile, solitary extensions that protrude from the apical surface of nearly every cell in the human body. These organelles were originally discovered over a century ago and, until recently, their function was a mystery. Indeed, they were believed by some to be vestigial (Davenport and Yoder, 2005). In the past several decades a plethora of studies have revealed the primary cilium to be a multifunctional antenna, sensing both mechanical (fluid flow, pressure, touch, vibration) and chemical (light, odor, PDGF) changes in the extracellular environment (Singla and Reiter, 2006). More recently the primary cilium has also been implicated as a complex signaling center for

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the cell, regulating key signaling pathways during development such as Hedgehog and Wingless (Berbari et al., 2009). The structural integrity of this versatile extracellular sensor is paramount to its function as defects in the primary cilium have been linked to numerous pathologies (ciliopathies) such as arthritis, osteoporosis, polycystic kidney disease, heart failure, obesity and cancer (Badano et al., 2006; Adams et al., 2008; Veland et al., 2009; Hildebrandt et al., 2011).

The basic structure of the primary cilium is very similar to that of the better understood motile cilium and flagellum. They all consist of a membrane bound axoneme containing nine circumferentially arranged doublet microtubules, which extend upwards from the mother centriole/basal body out into the extracellular space. Despite the similarities, there are distinct structural differences, which dramatically affect the mechanics of each. Both motile cilia and flagella have two additional central microtubules, which are attached to each of the surrounding doublets by connections called radial spokes. Therefore motile cilia are commonly referred to as 9+2 cilia in contrast to the primary cilium's 9+0 arrangement. In addition, the doublets of the 9+2 cilium are connected via nexin links, which in combination with the radial spokes, reinforce the axoneme resulting in an order of magnitude increase in the resistance to bending (flexural rigidity) in comparison to the primary cilium (Rikmenspoel and Sleigh, 1970; Schwartz et al., 1997). This increase in flexural rigidity demonstrates that even a small change in molecular arrangement at these scales can yield a dramatic difference in organelle level mechanical behavior.

Changes in the structural mechanics of primary cilia greatly affect the molecular mechanisms of mechanosensing. For example recent studies have demonstrated that upon mechanical perturbation the primary cilium decreases in length coinciding with a reduction in amiloride-sensitive sodium current (Resnick and Hopfer, 2007; Besschetnova et al., 2010; Gardner et al., 2011). Therefore alterations in primary cilium length, and possibly other mechanical properties and features, may be a central mechanism for regulating cellular mechanosensitivity. It may also alter responsiveness to biochemical stimuli and be a fundamental synergistic mechanism whereby cells sense, integrate and coordinate responses to combined physical and chemical signals. In this review, we introduce the cilium as a cellular mechanosensor (Section 2); discuss the recent advances in the mechanical modeling of the primary cilium (Section 3); explore the structural features of the cilium, which contribute to its mechanics (Section 4) and finish with possible mechanisms in which alteration in cilium structure may affect ciliary mechanics and as a consequence, affect ciliary based cellular mechanosensing (Section 5).

## 2. The mechanosensing primary cilium

The primary cilium first emerged as a mechanosensor in the kidney after defects in cilia structure and function were found to correlate with cyst formation. Further study revealed that fluid flow within the kidney resulting in the deflection of the primary cilium causes an extracellular calcium dependent increase in intracellular calcium, a response that was lost with removal of the primary cilium (Praetorius and Spring, 2001, 2003). Nauli et al. first demonstrated that this calcium response is mediated by a mechanosensory complex located at the base of the cilium. This complex consists of two membrane bound proteins, Polycystin 1 and a stretch activated cationic channel known as Polycystin 2 (Nauli et al., 2003). In addition to this complex regulating calcium influx, unloading of the cilium has been shown to result in an intra-membrane proteolysis of PC1, which acts as a transcription factor in association with STAT6 and P100 (Low et al., 2006). This mechanosensing mechanism has also been reported in liver cholangiocytes, where bending of the cilium not only results in an influx of calcium but also suppresses a forskolin stimulated increase in the second messenger cyclic adenosine monophosphate (cAMP) (Masyuk et al., 2006). The primary cilium has also emerged as a mechanosensor in bone where deflection of the primary cilium under fluid flow resulted in an increase in the osteogenic gene Cox-2. Furthermore, an inactivating mutation in the Pkd1 gene, which encodes the ciliary protein PC1, in a mouse model results in an osteopenic phenotype (Xiao and Quarles, 2010). Interestingly primary cilia in bone cells do not mediate flow-induced intracellular calcium assayed by Fura-2, indicating that the mechanotransduction pathway in bone differs relative to that in kidney and liver (Malone et al., 2007). Additional studies in bone have revealed that upon deflection of the primary cilium a rapid and transient decrease in cAMP occurs and that this decrease is dependent on adenylyl cyclase 6 (AC6) which is also localized to the cilium (Kwon et al., 2010).

In addition to sensing fluid flow, primary cilia have been shown to sense other mechanical signals such as pressure, touch and vibration. For example, the stretch activated ion channel TRPV4 localizes to the primary cilia of cholangiocytes and chondrocytes and has been shown to be involved in sensing osmotic pressure (Gradilone et al., 2007; Phan et al., 2009). In Drosophila, neurons extend a cilium that attaches into a cavity created by support cells known as scolopale (Ernstrom and Chalfie, 2002). Vibrations are then detected by the stretching of the cilium resulting in a rapid electrical response mediated by ion channels in the membrane. Furthermore in *C. elegans*, cilia are located along the dendrites of neurons, which are known to be mechanoresponsive. Although the exact mechanism of mechanotransduction in these cells is not known, the primary cilia are surrounded by extracellular matrix (ECM) and disruption of this ECM results in impaired mechanosensation (Ernstrom and Chalfie, 2002). It has been postulated that the cilium acts to transfer loads from the ECM to the underlying cytoskeleton regulating the activity of sodium channels mec-4 and mec-10 (ENaC superfamily) and converts the stimuli into a rapid electrical response.

In the past two decades the primary cilium has been demonstrated to play an important mechanosensory role in numerous tissues across many species and organisms. The cilium's ability to do so depends on its mechanical properties. For example, an interesting feature of the primary cilium is its ability to dynamically modulate its length, fine tuning its sensitivity to the extracellular environment. Besschetnova et al. (2010) recently demonstrated that by blocking calcium ion, $Ca^{++}$ entry (using gadolinium) and increasing intracellular cAMP (using forskolin) the length of the primary cilium in mammalian epithelial and mesenchymal cells increased 2-fold in 3 h. After the application of fluid shear, which is known to increase intracellular $Ca^{++}$ and decrease intracellular cAMP the average cilia length decreased by 20–35%. Furthermore it has been demonstrated that overloading of chondrocytes results in a decrease in cilia length and conversely stress deprivation in tendon cells results in an immediate and significant increase in length (McGlashan et al., 2010; Gardner et al., 2011). Therefore understanding the mechanics of the primary cilium and how ciliary mechanics may change in a diseased state may yield insight into the cause of the numerous debilitating ciliopathies (Fig. 1).

## 3. Modeling primary cilia mechanics

The primary cilium is emerging as a central nexus for sensing a number of biochemical and biophysical extracellular signals. As a