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Review

Primary cilia: Cell and molecular mechanosensors directing whole tissue function

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ABSTRACT

Primary cilia are immotile, microtubule-based organelles extending from the surface of nearly every mammalian cell. Mechanical stimulation causes deflection of the primary cilium, initiating downstream signaling cascades to the rest of the cell. The cilium forms a unique subcellular microdomain, and defects in ciliary protein composition or physical structure have been associated with a myriad of human pathologies. In this review, we discuss the importance of ciliary mechanotransduction at the cell and tissue level, and how furthering our molecular understanding of primary cilia mechanobiology may lead to therapeutic strategies to treat human diseases.

Contents

Abbreviations: PC1/2, *Pkd1/2*, polycystin 1/2; TRPV4, transient receptor potential vanilloid 4; AC6, adenylyl cyclase 6; cAMP, cyclic adenosine monophosphate; IFT88, intraflagellar transport 88; Kif3a, kinesin family member 3A; HDAC6, histone deacetylase 6; BBS, Bardet-Biedl syndrome; HH, hedgehog; FRET, fluorescence resonance energy transfer.

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1. Introduction

The primary cilium is a single immotile organelle protruding from the apical surface of nearly all mammalian cells [1]. Primary cilia share similar structural characteristics with motile cilia, both consisting of 9 microtubule doublets forming the ciliary axoneme. Motile cilia, however, also contain a central microtubule doublet, radial spokes, and a nexin ring, allowing for cellular functions, such as propulsion or clearing of mucus and debris, not experienced in primary cilia. While primary cilia were identified in mammalian cells over 100 years ago, they were long considered vestigial structures. Recently improved molecular and biochemical techniques have enabled keen insights into this once forgotten organelle. Today, primary cilia are understood to play a critical role in the transduction of chemical and mechanical cues. In addition, primary cilia have been implicated as a nexus for numerous signaling pathways critical to cell function, such as Wnt and Hedgehog [2].

Impairment of primary cilia function and ciliary associated proteins has been identified as the cause of numerous different conditions known as ciliopathies. Polycystic kidney disease can result from genetic mutations in *Pkd1* and *Pkd2*, coding for the PC1/2 mechanosensitive ion channel complex [3]. Bardet-Biedl Syndrome (BBS) is characterized by renal failure, polydactyly, and retinitis pigmentosis, and is caused by mutations in ciliary associated BBS proteins [4]. Retinal and skeletal conditions, such as Joubert and Meckel-Grouber Syndromes, are also attributed to cilia dysfunction [1,5]. Primary cilia have also been suggested to have a potential role in cystic and fibrotic liver disease, atherosclerosis, bone maintenance, and osteoarthritis, as described in the following section. The growing list of ciliopathies and cilia-associated conditions has stimulated further research into the vast array of roles of the primary cilium. A mouse model was also developed with a hypomorphic mutation to cause a partial loss of IFT88 function – an intraflagellar transport protein required for cilia formation [6]. The mice survive birth and develop to maturity, but with several noticeable traits, primarily a cystic renal phenotype, but also severe growth retardation, polydactyly, and diminished olfaction. Using a cell therapy strategy, it was demonstrated that adenoviral-mediated expression of IFT88 rescues both formation and sensory function of primary cilia [7]. This work suggests that rescuing cilia form and function may be a viable strategy to treat numerous ciliopathies.

While primary cilia do serve as chemosensors [8], this review focuses on their mechanosensory capabilities. Mechanical loading may result in a variety of physicochemical stimuli, such as changes in osmolarity, hydrostatic pressure, and pH, which may be sensed by the primary cilium [9,10]. The prevailing theory is that mechanical stimulation, such as fluid flow or tissue deformation, causes primary cilia deflection to initiate downstream mechanotransduction signaling cascades. In particular, this review concentrates on these cilia which project into the extracellular environment to sense fluid flow; but in specific cell types cilia may have distinct structure and mechanosensing mechanisms, such as chondrocyte cilia embedded within the extracellular matrix [11]. As will be discussed, the cilium forms a unique microdomain to which specific proteins localize to mediate the mechanotransduction response. Primary cilia play a critical role in mechanotransduction in a myriad of cell types, dictating tissue function. Furthering our understanding of the molecular and biophysical basis of primary cilia mechanobiology will allow development of therapeutic treatment strategies to manipulate primary cilia-mediated mechanosensing and direct whole tissue adaptation.

2. Primary cilia mediate cell mechanosensing and tissue function

The primary cilium is involved in mechanosensing in a wide range of cell and tissue types. These various tissues all require mechanical stimulation for proper function and homeostasis and rely on primary cilia-mediated mechanotransduction. Table 1 summarizes works describing various applied mechanical stimuli and the investigated response.

2.1. Embryonic node

Primary cilia play a critical role in embryonic development. In fact, global deletion of proteins required for formation of primary cilia, such as IFT88 or Kif3a, is embryonic lethal [6,12]. During development, motile cilia within the embryonic node actually begin to move and generate directional flow of extracellular fluid, which is sensed by non-motile primary cilia in the surrounding crown cells [12,13]. These cilia working in tandem results in proper left-right differentiation, and impairing either primary or motile ciliary function disrupts embryogenesis. Primary and motile cilia have distinct mechanical and functional characteristics; but play critical roles in directing cell and tissue function.

2.2. Kidney

Much of the early work describing primary cilia mechanotransduction was conducted in kidney cells [14,15]. Proper kidney function is dependent on regulated fluid flow through the nephrons and collecting ducts to control glomerular filtration rate, and this flow is sensed by kidney epithelial cell primary cilia [16,17]. Deflection of the primary cilium, by both fluid flow and micropipette manipulation, induces an increase in intracellular calcium, in a primary cilia-dependent manner [15,17,18]. This calcium influx is also mediated by the PC1/2 ion channel complex [17]. PC1 and PC2 both localize to the primary cilium, where PC1 is a mechanosensitive membrane protein regulating the opening of the PC2 channel [19]. In addition to calcium signaling, PC1 has been implicated in direct activation of STAT (signal transducer and activator of transcription) to regulate gene expression, demonstrating the potential for mechanotransduction pathways distinct from calcium [20–22]. In renal cells, functional defects of either portion of this ion channel complex, along with complete disruption of cilia formation, result in polycystic kidney disease [23].

2.3. Endothelia

Endothelial cells sense blood flow and regulate vessel diameter to maintain blood pressure [24]. The shear stress stimulates endothelial nitric oxide production, an important vasodilator, and endothelial primary cilia have been implicated as important mechanosensors that regulate nitric oxide production [25,26]. Furthermore, PC1/2 has been identified as a critical component for this