The Primary Cilium as the Cell's Antenna: Signaling at a Sensory Organelle

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Almost every vertebrate cell has a specialized cell surface projection called a primary cilium. Although these structures were first described more than a century ago, the full scope of their functions remains poorly understood. Here, we review emerging evidence that in addition to their well-established roles in sight, smell, and mechanosensation, primary cilia are key participants in intercellular signaling. This new appreciation of primary cilia as cellular antennae that sense a wide variety of signals could help explain why ciliary defects underlie such a wide range of human disorders, including retinal degeneration, polycystic kidney disease, Bardet-Biedl syndrome, and neural tube defects.

Eukaryotic cilia and flagella are cell surface projections familiar to schoolchildren everywhere for the elegant swath they cut as they propel protozoa through pond water. Although assigned different names to reflect their different beating motions, cilia and flagella are structurally similar (the two names are used interchangeably here) and they show remarkable conservation from protozoa to humans.

Cilia can be viewed as specialized cellular compartments or organelles. All cilia are generated during interphase from a plasma membrane–associated foundation called the basal body (Fig. 1A). At the heart of the basal body is a centriole (Fig. 1B), an important component of the mitotic spindle apparatus in dividing cells. During interphase, however, the centriole moves to the plasma membrane and templates the nucleation of the axoneme, the structural core of the cilium. Construction of the axoneme requires intraflagellar transport (IFT), a bidirectional transport system discovered in the green alga *Chlamydomonas* [reviewed in (*1*)] (Fig. 1C). Because no protein synthesis occurs within cilia, IFT needed to move the organelle's structural components from the cell body to the ciliary tip (the anterograde direction) where axoneme synthesis occurs. This anterograde movement of the IFT complex is driven by the heterotrimeric motor Kinesin-2 (*2*) and, at least in the nematode *Caenorhabditis elegans*, by the kinesin OSM-3 (*3*). IFT returns proteins from the cilium to the cell body by means of a retrograde movement driven by a dynein motor (*4*). IFT also brings signaling proteins to the cilium. For example, adhesion of the flagella of two *Chlamydomonas* gametes activates an IFT-dependent signaling pathway, resulting in cell fusion (*5*).

Structural elements contribute to the specialization of the ciliary environment. Among these elements are the terminal plate at the distal end of the basal body and the transitional fibers at the base of the cilium, which may physically restrict entrance of proteins into the cilium (*6*) (Fig. 1B). The most prominent structural element is the axoneme, consisting of nine doublet microtubules that originate at the triplet microtubules of the basal body centriole and extend the length of the cilium. Most motile cilia have an additional central microtubule pair (the 9+2 microtubule arrangement). Primary cilia are usually immotile, and they lack this central pair (the 9+0 arrangement). The motile primary cilia present on the node, a specialized signaling structure in the early mammalian embryo, are an exception (Fig. 1D). The twirling of these primary cilia creates a leftward flow of the surrounding fluid and this flow is essential for the development of the left-right axis (*7*).

The developmental and physiological roles of motile cilia have been reviewed elsewhere (*8*, *9*). Here, we discuss the established and emerging functions of the single, immotile primary cilia that are present on almost all vertebrate cell types (*10*) (Fig. 1, D to L).

Cilia Are Sensory Organelles: Smell and Sight

The role of cilia in sensing the extracellular environment is best understood in the context of olfaction and photoreception. In the first step of olfaction, an odorant interacts with a G protein–coupled receptor (GPCR) (*11*) on the ciliary membrane of an olfactory sensory neuron (*12*), producing the second messenger cyclic adenosine monophosphate (cAMP) within the cilium (*13*). Elevated levels of cAMP then depolarize the cell by opening a cyclic nucleotide-gated channel also located in the ciliary membrane (*14*). Other important regulators of olfactory signaling such as GPCR kinase 3 (GRK3), β-arrestin–2, Phosphodiesterase 1C, and Ca^{2+}/calmodulin-dependent kinase II are all present in cilia (*15*), suggesting that these organelles are sites of both odorant reception and signal amplification. Indeed, olfactory neurons lacking either cilia or odorant receptors on their cilia cannot respond to odorants (*16*, *17*).

Photoreception occurs through a cilium-based signaling pathway broadly similar to that of olfaction. The rod and cone cells of the vertebrate retina possess a primary cilium equipped with an expanded tip called the outer segment, which is specialized for the reception and transduction of light. At the outer segment, opsin GPCRs respond to photons of light by increasing hydrolysis of a different cyclic nucleotide, cyclic guanosine monophosphate (cGMP), thereby closing cGMP-gated channels. Signal initiation and termination components such as the heterotrimeric G protein transducin and GRK1 (Rhodopsin Kinase) also localize to the outer segment (*18*, *19*).

Maintenance of the photoreceptor signaling machinery requires continuous IFT-mediated transport of prodigious quantities of both lipids and proteins into the cilium. The retinal protein Opsin, for example, moves through the cilium at a rate of about 2000 molecules per minute (*20*). Mutations affecting IFT components or the anterograde Kinesin-2 motor cause the accumulation of Opsin and membranes outside of the cilium, which ultimately leads to cell death (*21*). Inherited defects in this transport system are one cause of human retinal degeneration. For example, mutations in Rhodopsin that disrupt its transport to the cilium cause retinitis pigmentosa, a common form of retinal degeneration (*22*).

The link between cilia function and the senses of sight and smell is underscored by Bardet-Biedl syndrome, a polygenic disorder associated with basal body and ciliary defects. Patients with Bardet-Biedl syndrome display retinal degeneration and cannot smell (*23*). Other characteristics of this multifaceted disorder include polydactyly, diabetes, obesity, hearing loss, and polycystic kidney disease, suggesting that primary cilia may play additional roles in human physiology (*24*, *25*).

Cilia Link Mechanoreception and Polycystic Kidney Disease

In addition to sensing odorants and light, cilia can sense movement. These functions have been well characterized in model organisms. Cilia are the sites at which the vanilloid family of transient receptor potential (TRP) ion channels function as mechanosensors in the fruit fly *Drosophila* and the nematode *C. elegans*. In *Drosophila*, two TRP channels on the cilia of auditory sensory neurons mediate reception of sound vibrations at the antenna (*26*). Similarly, two *C. elegans* TRP channels localize to sen-

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sory neuron cilia, where they respond to nose touch and high osmolarity (*27*). Other cilia-associated TRP channels in sensory neurons play a different role in *C. elegans*: the mating behavior of males requires PKD-2, a member of the polycystin family of TRP channels, and its binding partner LOV-1 (*28*).

The vertebrate homologs of LOV-1 and PKD-2 are polycystin-1 (PC1) and polycystin-2 (PC2). Mutations in either of the polycystin genes cause PKD in humans (*29*). In PKD, loss of PC1 or PC2 function results in clonal expansion of kidney epithelial cells. These cells then form cysts that crowd out normal nephrons, causing kidney failure. PC1 and PC2 localize to primary cilia of kidney epithelial cells (*30*), suggesting that the functional link between these proteins and cilia is conserved from nematodes to mammals.

Insight into how these proteins participate in cyst formation has come from studies showing that PC1 and PC2 comprise a mechanosensory complex that translates deflection of the primary cilium of kidney epithelial cells into signals associated with the control of growth and differentiation. Also present in this complex are the transcription factor STAT6 and its coactivator P100, which are retained in the cilium by binding to the cytoplasmic tail of PC1 (*31*) (Fig. 2A). During normal kidney function, urine flows over kidney epithelial cells, bending their primary cilia. This bending results in a PC1- and PC2-dependent increase in intracellular Ca^{2+} concentration and the inhibition of the regulated intramembrane proteolysis (RIP) of PC1 (*32*–*34*) (Fig. 2A). Insults to the kidney that disrupt urine production or flow allow the cilium to straighten, blocking Ca^{2+} flux and activating the RIP of PC1. RIP releases a portion of the PC1 cytoplasmic tail, which translocates to the nucleus together with STAT6 and P100 where they activate transcription (Fig. 2B). These observations suggest that in PKD, defects in ciliary mechanosensation result in the cell activating this "no flow" response even in the presence of normal urine production, leading to unregulated cell proliferation and cyst formation. Consistent with this model, complete loss of primary cilia in the mouse kidney also produces cysts (*35*).

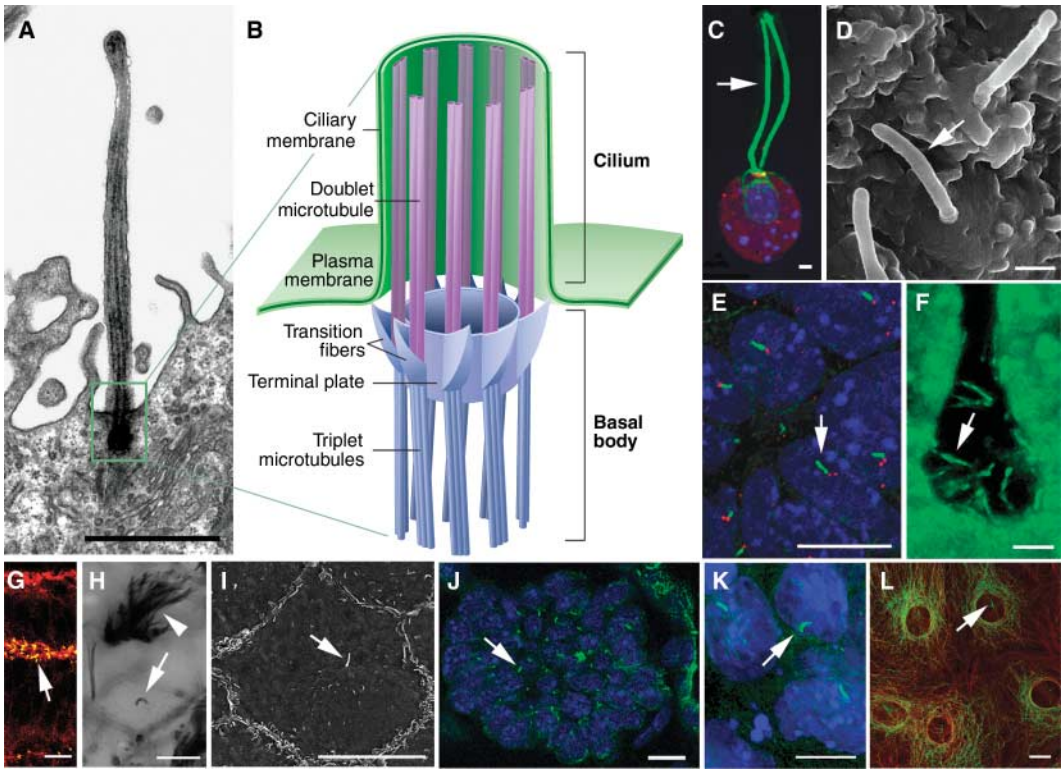

Fig. 1. Primary cilia are highly structured and are found in many organisms and on many cell types. (**A**) Electron micrograph of the primary cilium of a canary brain radial glia (*69*). (**B**) Schematic showing structure of the basal body and primary cilium [modified from (*6*, *70*)]. (**C**) The green alga *Chlamydomonas* showing flagella (green, arrow) and basal body (red). Nuclei are blue. [(D) to (L)] Scanning electron and immunohistological images of primary cilia (arrows) of (**D**) the mouse node, (**E**) the mouse neural tube, emanating from basal bodies (red), (**F**) the *Xenopus* neural tube, (**G**) the zebrafish neural tube, (**H**) a mouse neurogenic astrocyte, (**I**) a mouse embryonic epidermal cell, (**J**) a mouse somite, (**K**) mouse embryonic stem cells, and (**L**) mouse astrocytes expressing glial fibrillary acidic protein (red). Also shown in (H) are motile ependymal cell cilia (arrowhead). Scale bars, 1 μm [(A), (C), and (D)] and 10 μm [(E) to (L)].

Primary Cilia Coordinate the Mammalian Hedgehog Signal-Transduction Machinery

A clue that vertebrate cilia may be involved not only in sensing environmental inputs but also in transducing intercellular signals came from the surprising finding that mutations in genes encoding IFT components cause defects in mammalian Hedgehog (Hh) signal transduction (*36*). Hh family members are secreted lipoproteins that regulate tissue patterning, cell proliferation, and many other biological processes [reviewed in (*37*)]. Defects in Hh signaling can cause human birth defects and cancer [reviewed in (*38*)].

Hh signaling culminates in the conversion of Gli transcription factors from repressors to activators. Central to this conversion are two transmembrane proteins, Smoothened (Smo) and the Hh receptor Patched (Ptc). In the absence of Hh signals, Ptc maintains Smo in an inactive state, and Gli transcription factors are processed to their repressor forms. Upon binding Hh, Ptc loses the ability to repress Smo, leading to the generation of Gli transcriptional activators that execute the Hh transcriptional program.

How do IFT proteins participate in mammalian Hh signal transduction? An answer is suggested by recent studies demonstrating that several Hh pathway components, including Smo and Gli proteins, are present at the primary cilium (*39*, *40*) (Fig. 3A). Smo moves to the cilium in response to Hh signaling (Fig. 3B). Disrupting the transport of Smo to the cilium blocks Hh signal transduction, suggesting that Smo activates the downstream pathway at the primary cilium. Analysis of limb bud patterning in mouse IFT mutants indicates that IFT proteins are not only essential for Gli activator function but also for Gli repressor function (*41*), implying that both the "on" and "off" states of the mammalian Hh pathway depend on the presence of a primary cilium. Together, these data begin to suggest a dynamic model describing how primary cilia coordinate the mammalian Hh signaling machinery. Without Hh stimulation, Smo is present on intracellular vesicles and Gli proteins are processed to their repressor form at the ciliary tip (Fig. 3A). Hh signals alter Ptc regulation of Smo, allowing Smo to move to the cilium (Fig. 3B), where it interacts with the Gli processing machinery to promote Gli activator formation. Gli activators then move down the cilium, enter the nucleus, and turn on Hh-dependent genes.

Interestingly, the primary cilium is not critical to Hh signaling in all metazoans. Although Hh signal transduction in both mice and frogs is disrupted by loss of cilia, mutations in the *Drosophila* homologs of IFT genes do not

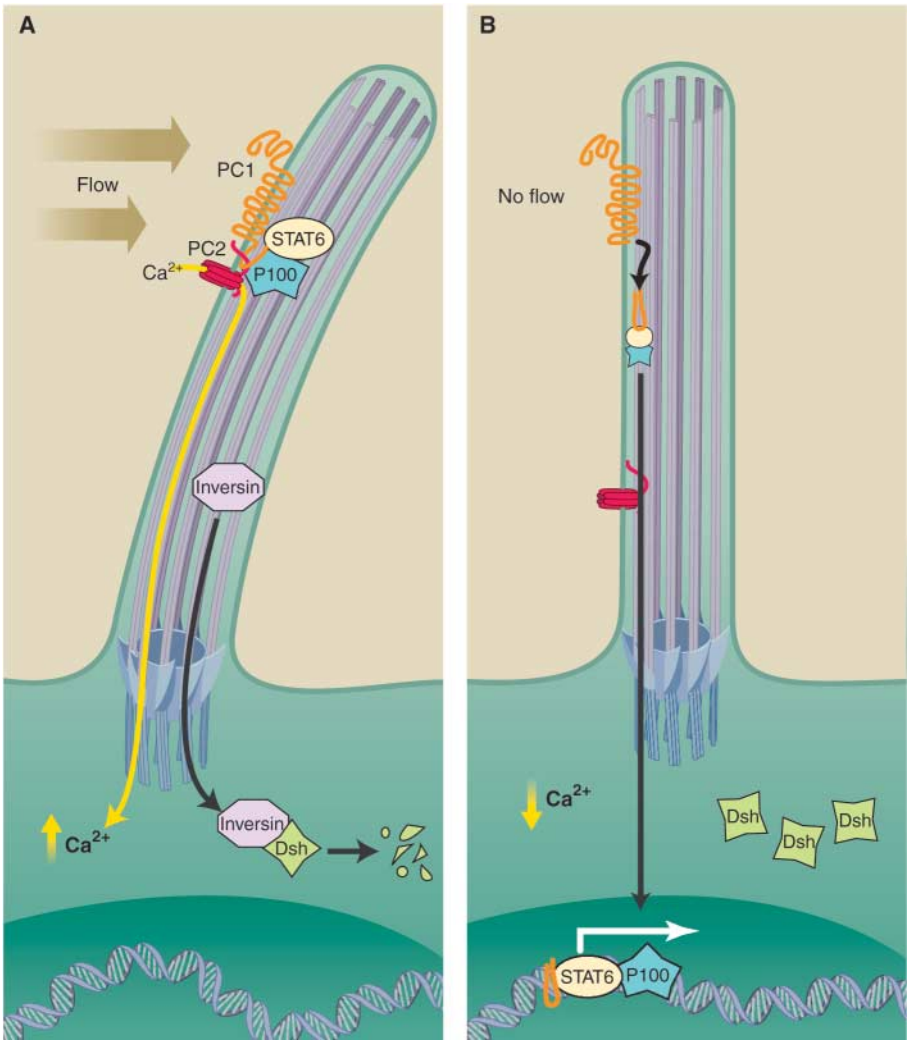

Fig. 2. Primary cilia of kidney epithelial cells sense urine flow and control cell proliferation. (**A**) Deflection of the primary cilium caused by flow within the nephron tubule is detected by PC1 (orange) and PC2 (red), two transmembrane proteins. Flow induces Ca^{2+} influx through PC2 and maintains STAT6 (yellow) and P100 (turquoise) in a complex bound to the tail of PC1. Flow also leads to up-regulation of Inversin (purple), which targets cytoplasmic Dsh (green) for degradation by the proteasome. (**B**) In the absence of flow, Ca^{2+} influx is reduced and the tail of PC1 is cleaved, allowing P100 and STAT6 to translocate to the nucleus and activate transcription. Lack of flow also reduces Inversin levels, stabilizing Dsh levels and permitting β-catenin to initiate transcription of canonical Wnt pathway target genes. The same pathways may be activated in the absence of PC1, PC2, or the cilium itself, leading to unregulated cell proliferation and formation of cysts.

disturb embryonic development (*42*, *43*). The involvement of the microtubule binding protein Cos2 specifically in *Drosophila* Hh transduction suggests that the Hh signal transduction machinery may be coordinated by other microtubular structures.

Primary Cilia, Wnt Signaling, and Planar Cell Polarity

Like Hh, Wnt family members are secreted lipoproteins that regulate both cell proliferation and differentiation [reviewed in (*44*)]. However, unlike Hh, Wnt proteins activate several distinct signaling pathways, classified as either β-catenin dependent (the so-called canonical pathway) or β-catenin independent (the noncanonical pathways). The protein Dishevelled (Dsh) acts as a switch between the canonical and noncanonical pathways. Plasma membrane–localized Dsh is essential for noncanonical signaling, whereas a cytoplasmic pool of Dsh functions in canonical signaling (*45*).

Similar to loss of the cilium, constitutive activation of the canonical Wnt pathway in the mouse kidney causes cyst formation (*46*), raising the possibility that overactivity of this pathway contributes to human PKD. Recent investigations into the function of the primary cilium–associated protein Inversin support this hypothesis. Mutations in the gene encoding Inversin both disrupt mouse left-right axis formation and cause one form of human PKD, two processes linked to cilia function (*47*, *48*). Reduction of Inversin in embryos of the frog *Xenopus laevis* causes a third defect—disruption of convergent extension movements (*49*) (Fig. 4A). These coordinated cellular movements are essential for both vertebrate gastrulation and neural tube closure, and they are regulated by the planar cell polarity (PCP) pathway, one form of noncanonical Wnt signaling. PCP is the orientation of cells along an axis orthogonal to the apical-basal axis and is manifested in ways that, in addition to convergent extension, include *Drosophila* bristle orientation and stereocilia orientation in the vertebrate inner ear [reviewed in (*50*)]. Mice lacking Inversin develop misoriented hair pattern, a defect similar to that seen in mice lacking the PCP regulator Frizzled-6 and superficially similar to the wing bristle misorientation displayed by *Drosophila* PCP mutants (*49*, *51*).

Biochemical analyses have shown that Inversin participates in the Dsh-mediated switch between the canonical and noncanonical Wnt pathways. Specifically, Inversin targets the cytoplasmic pool of Dsh for degradation, inhibiting the canonical pathway (*49*). Inversin does not degrade the plasma membrane–localized pool of Dsh and thus does not inhibit noncanonical signaling. Indeed, Inversin appears to actively promote PCP signaling during *Xenopus* convergent extension. Inversin displays some homology to the *Drosophila* PCP protein Diego, which protects Dsh from the PCP antagonist Prickle (*52*). Perhaps Inversin acts similarly, given that both Diego and Inversin can interact with Prickle, as well as another conserved PCP protein, Van Gogh (*49*, *53*).

Studies of other known regulators of PCP and cilia further support a functional connection between the two. In addition to their roles in ciliary function, the products of two Bardet-Biedl genes, *Bbs4* and *Bbs6*, function in vertebrate PCP (*24*). Similarly, proteins with conserved roles in PCP can also be required for ciliogenesis; homologs of Fuzzy and Inturned, two proteins that participate in *Drosophila* PCP, are essential for *Xenopus* ciliogenesis (*54*).

This involvement of several proteins in both cilia and PCP raises the question of how the two are mechanistically connected. One possibility is that these proteins act in a single process fundamental to both PCP and ciliogenesis, such as the orientation of microtubule growth, as suggested by Park *et al*. (*54*). Oriented microtubules form the heart of the cilium and are essential for the asymmetric localization of PCP determinants (*55*). In support of this possibility, Bbs4 participates in the ordering of microtubules outside of the cilium (*23*, *56*). Alternatively, the primary cilium could be directly involved in the execution of the PCP program. Interestingly, a mammalian Van Gogh protein localizes to the cilium and basal body, suggesting that some components of the PCP pathway may function at the primary cilium (*24*). This model predicts that any fundamental disruption

of cilia structure will disrupt PCP by interfering with the functions of ciliary proteins such as Van Gogh and Inversin. Consistent with a link between cilia and PCP is the observation that Meckel syndrome, a human disorder associated with neural tube defects, is caused by mutations in genes implicated in ciliary function (*57*, *58*).

PCP defects may also contribute to the pathogenesis of PKD. Notably, during kidney tubule elongation, the mitotic apparatus of cells is precisely oriented to direct cell division parallel to the axis of the tubule (Fig. 4B). Decreased expression of the ciliary protein Pkhd1 results in both PKD and disoriented kidney cell mitosis (*59*) (Fig. 4C). Given that the noncanonical Wnt pathway performs similar roles in the orientation of mitosis in *Drosophila*, *C. elegans*, and zebrafish (*60*–*62*), it will be interesting to assess whether Pkhd1 participates in the known PCP pathway or orients the mitotic spindle through a different mechanism.

Together with the finding that fluid flow modestly up-regulates Inversin and represses canonical Wnt pathway activity in ciliated kidney cells (*49*), these results suggest an attractive model of kidney cyst pathogenesis. Normally, flow sensation by the primary cilium acts through Inversin to repress the canonical Wnt pathway, preventing inappropriate cell proliferation. Either ciliary defects or loss of Inversin disinhibits the canonical pathway which, together with the PC1- and PC2-dependent defects in Ca^{2+} signaling and STAT6 activity, leads to unregulated cell proliferation. Ciliary defects or loss of Inversin may also disrupt PCP, resulting in the misorientation of mitoses. Thus, ciliary defects may have two consequences—inappropriate cell proliferation and disorganization of tissue growth—which act in concert to generate cysts.

An Evolutionarily Conserved Role for Cilia in Signaling?

Although all metazoans appear to have primary cilia, two of the most widely studied model organisms, *Drosophila* and *C. elegans*, have cilia in only a small set of cells. Does this indicate that our last common ancestor used the cilium in a similarly limited fashion?

As noted above, many protozoa use flagella for propulsion, including the closest known

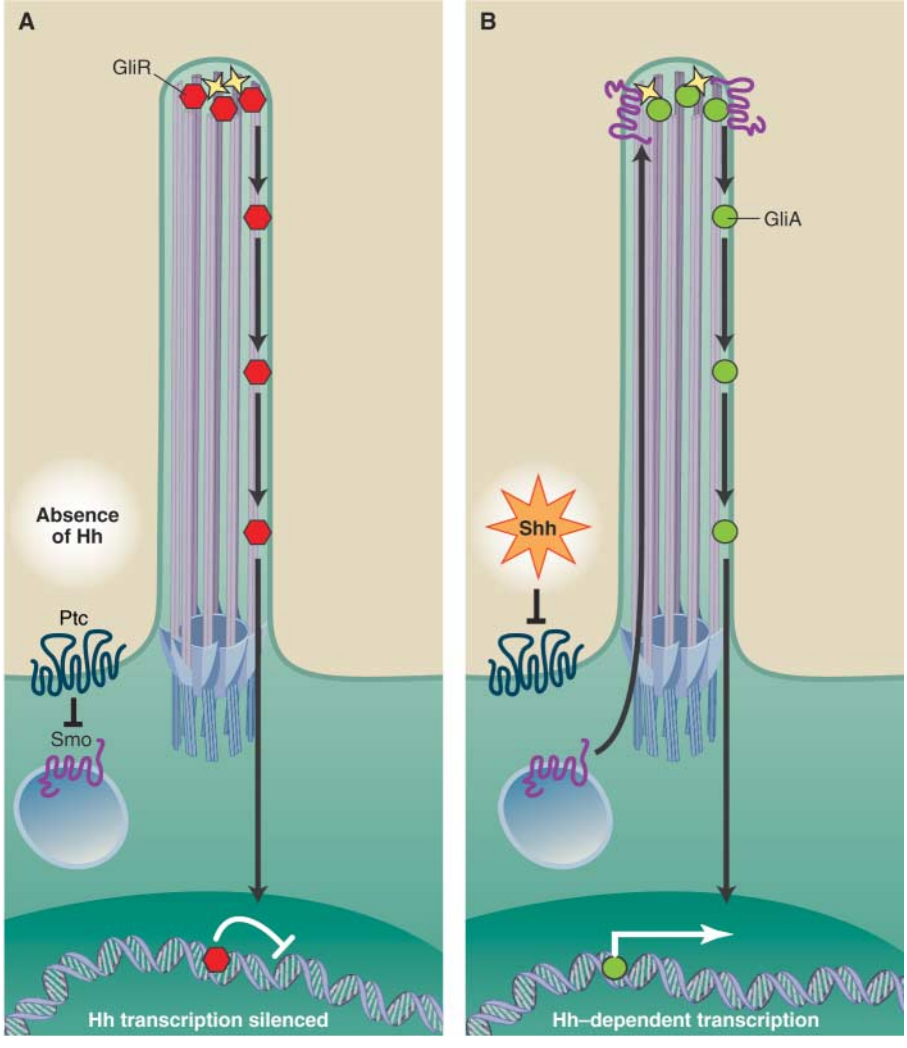

Fig. 3. A model of vertebrate Hh signal transduction. (**A**) In the absence of Hh, Ptc (blue) represses the function of Smo (purple), which is predominantly on intracellular vesicles. Gli proteins are processed at the cilium into their transcriptional repressor forms (red). These repressors move down the cilium to the nucleus and bind regulatory elements to maintain the silence of the Hh transcriptional program. (**B**) In the presence of Hh proteins such as Shh (orange), the inhibition of Smo by Ptc is blocked and Smo moves to the cilium. There, it presumably interacts with the Gli processing machinery (yellow) to promote formation of transcriptional activator forms (green). Gli activators then enter the nucleus where they activate Hh-dependent transcription.

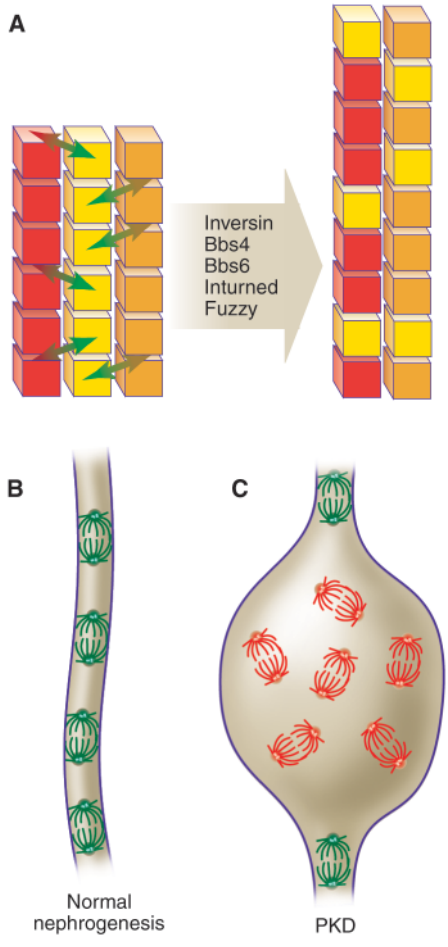

Fig. 4. Noncanonical Wnt signaling in vertebrates may be modulated by ciliary function. (**A**) One form of noncanonical Wnt signaling regulates convergent extension, the coordinated intercalation of cells (green arrows) that narrows and lengthens a tissue. Inversin, Bbs4, Bbs6, Inturned, and Fuzzy all participate in both cilia function and convergent extension, suggesting that the two are mechanistically related. (**B**) During normal kidney tubule growth, the mitotic spindle (green) is aligned with the axis of the nephron. In other systems, noncanonical Wnt signaling can control the orientation of mitosis. (**C**) In some forms of PKD, misorientation of the mitotic spindle (red) may act in concert with deregulated cell proliferation to trigger cyst formation.

relatives of animals, the choanoflagellates [reviewed in (*63*)]. Some protozoa also use cilia for signaling. For example, when *Paramecium tetraurelia* swims into an object, the force bends its motile cilia, opening mechanosensitive Ca^{2+} channels (*64*). The subsequent increase in intraciliary Ca^{2+} concentration reverses ciliary beat direction and, consequently, swimming direction. This is reminiscent of kidney epithelial cells in which mechanical deformation of primary cilia opens mechanosensitive Ca^{2+} channels.

Other unicellular eukaryotes may use the cilium to sense their environment in additional ways. Proteins involved in *Chlamydomonas* light reception and interpretation are present on flagella (*65*, *66*). Similar to *Chlamydomonas*, dinoflagellates also use flagella and an eyespot for phototaxis (*67*). Interestingly, several dinoflagellate species do not absorb light at the eyespot. Instead, the eyespot is adapted to focus and reflect light onto a flagellum, the presumptive photoreceptor location (*68*). This mechanism is similar to light reception by the human eye; a lens focuses light on cilia called rods and cones where the light is absorbed, translated into biochemical signals, and communicated to the cell body. This "ciliocentric" view suggests that the ancestral organelle for the detection and reception of light was a cilium and that cilia may have ancient and widespread roles in sensing information from the extracellular environment, whether that information takes the form of light, movement, or signals from other cells.

Conclusions

The primary cilium has several characteristics that make it an ideal cellular location for sensing and transducing signals. It extends into the extracellular space, affording access to environmental signals. Its elongated geometry provides a high surface-to-volume ratio that may promote interaction of transmembrane receptors with downstream signaling machinery. Finally, the regulated entry of proteins into the cilium confers the advantages of specialization and compartmentalization. Evolution appears to have made use of these characteristics to adapt the cilium for the interpretation of information both from the environment and from other cells.

We have discussed established and emerging mechanisms by which cilia participate in several types of signal reception and transduction. Ciliary defects can cause diverse human diseases (Table 1), which may well reflect the involvement of cilia in diverse sensory modalities and signaling pathways. The unexplained phenotypic manifestations of these diseases raise the possibility that cilia have additional, unexplored roles in skeletal development, brain function, diabetes, and obesity.

Table 1. Defects in ciliary functions cause several human diseases.

Ciliary function	Disease phenotype
Nodal flow	Heterotaxia (*7*, *9*)
Photoreception	Retinal degeneration (*22*, *71*)
Odorant reception	Anosmia (*23*)
Mechanosensation	Polycystic kidney disease (*28*–*35*)
Gli repressor formation	Polydactyly, neural patterning defects (*41*)
Gli activator formation	Neural patterning defects (*36*, *39*, *41*)
Convergent extension	Neural tube closure defects (*24*, *49*, *54*, *57*, *58*)

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