Basal bodies, kinocilia and planar cell polarity

Jeffrey D Axelrod

Primary cilia and planar cell polarity (PCP) proteins both contribute to cell polarization, but their relationship is unclear. A new study shows that, in the organ of Corti, primary cilia are required for morphological polarization of sensory hair cells and function downstream of the PCP signaling proteins.

The organization of the single kinocilium and multiple stereocilia atop each sensory hair cell in the organ of Corti, within the inner ear, confers a precise polarity within the plane of the epithelium. It has long been hypothesized that directed migration of the kinocilium toward one side of the cell determines the polarity of individual hair cells[1]. More recent evidence indicates that the Frizzled/Van Gogh (Fz/Vang)-dependent planar cell polarity (PCP) signaling system provides directional information governing hair cell polarity[2]. In an interesting convergence, primary cilia, of which the kinocilium is a specialized example, have been implicated in many, and possibly all, vertebrate planar polarization events[3], but the relationship between primary cilia and the PCP signaling system is not understood. On page 69 of this issue, a collaborative group led by Ping Chen reports disruption of ciliogenesis in the inner ear[4]. Their work demonstrates that basal bodies direct planar polarization of sensory hair cells, and that an intact kinocilium is indeed necessary for hair cells to respond correctly to the PCP signaling system.

PCP and primary cilia

Precise organization of the four rows of sensory hair cells in the organ of Corti is essential for auditory function. During development of the differentiating hair cell, the microtubule-based kinocilium emerges from the center of the apical surface and then undergoes a directed migration toward its final destination, where actin-rich stereocilia organize around it to form a chevron with the vertex, occupied by the kinocilium, pointing abneurally[1] (**Fig. 1a,b**). Because the direction of kinocilium migration predicts the orientation of the mature stereociliary bundle, and the kinocilium regresses postnatally, the kinocilium has been proposed to have a developmental role in directing the polarization of these cells[1,5].

Jeffrey D. Axelrod is in the Department of Pathology, Stanford University School of Medicine, Stanford, California 94305, USA. e-mail: jaxelrod@stanford.edu

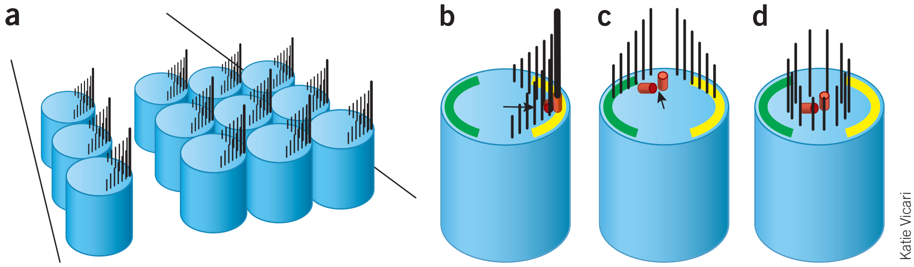

Figure 1 PCP and kinocilia in the organ of Corti. (**a**,**b**) Sensory hair cells in the organ of Corti each have a single kinocilium (thick black vertical line) located on the abneural side of the cell and an associated stereociliary bundle (thin black vertical lines), forming a chevron pattern that points abneurally (right). (**c**) When the axoneme, which normally arises from the maternal centriole (also known as the basal body; red cylinders), fails to form, the basal body is positioned randomly, and the stereociliary bundle becomes oriented toward the randomly positioned basal body. (**d**) Alternatively, when the basal body remains centrally located, the stereociliary bundle forms a circular structure. PCP proteins (green and yellow crescents) remain normally oriented in the ciliary mutants, suggesting that normal basal body migration (arrow) and orientation of the stereociliary bundle require an intact axoneme to respond to directional information provided by the PCP proteins.

In animals as diverse as fruit flies and mice, the polarization of cells within the plane of an epithelium requires a conserved PCP signaling pathway, first discovered in *Drosophila*[6]. PCP signaling proteins, including Fz and Vang, accumulate on opposite sides of the cell, providing a molecular signature for polarization. In the organ of Corti, Vangl2, Fz3 and Fz6 accumulate asymmetrically at the borders of sensory hair cells, and mice mutant for these proteins have disrupted hair cell polarity, indicating that the proteins have key roles in inner ear PCP[7–9]. An understanding of how these proteins function to polarize cells is beginning to emerge[6].

Although the kinocilium is likely to be important for establishing PCP of hair cells, several observations indicate that primary cilia have a more ubiquitous role in PCP. Disruption of the Bardet-Biedl syndrome ciliary proteins causes PCP phenotypes in mice[3], and the PCP proteins Vangl2 and Inturned localize to cilia and/or ciliary basal bodies in some cells[3,10]. But just how primary cilia function in PCP signaling, and their relationship to the asymmetrically segregated PCP proteins Fz and Vang, remains unclear. Although the primary cilium, or kinocilium, in sensory hair cells migrates to one side of the cell during establishment of PCP, it is not obvious that this is a general phenomenon in planar-polarized tissues. In addition, primary cilia have recently gained attention as putative 'antennae' responding to extracellular signals, including Hedgehog, PDGF and Wnt ligands[11–13]. Although Wnts are required for vertebrate PCP signaling[14], no signaling role for primary cilia in PCP has been shown.

Kinocilia determine polarity

To ask what function kinocilia fulfill during development of the mouse inner ear sensory epithelium, Chen and colleagues used conditional knockout of the Ift88/Polaris and Kif3a intraflagellar transport proteins to disrupt construction and maintenance of kinocilia in the developing organ of Corti[4]. Expression was interrupted as early as embryonic day 10.5, and by embryonic day 14.5, before kinocilia migration, axonemes, the extracellular structural elements of kinocilia, were lost. Notably, loss of Ift88 or Kif3a resulted in misrotated sensory hair cells, indicating that kinocilia (or at least ciliary transport proteins) are required for hair cell PCP.

Although many misoriented cells retained a chevron-shaped stereociliary bundle (**Fig. 1c**), others arranged their stereocilia in more or less symmetric, circular patterns (**Fig. 1d**). By observing the position of the basal bodies relative to the stereociliary bundles, the authors found that bundle orientation was strongly correlated with the direction of basal body migration (**Fig. 1c**). Furthermore, the presence of centrally located basal bodies correlated with the appearance of round, symmetric stereociliary bundles (**Fig. 1d**). Therefore, it seems that basal body positioning determines stereociliary bundle orientation and morphology. This idea is reminiscent of the finding that basal body positioning orients the polarity of migrating cells.

Notably, despite the marked disruption of morphological polarization of hair cells in the mutant animals, Fz3 and Vangl2 maintained their normal, asymmetric subcellular localization patterns (**Fig. 1c,d**). This finding clearly indicates that an intact kinocilium is required for basal body migration and for hair cell polarization to respond to directional cues provided by the asymmetrically arrayed PCP proteins. One can therefore conclude that the kinocilium functions downstream of the PCP proteins in hair cell polarization.

The authors also conclude that the asymmetric subcellular localization of PCP proteins does not require kinocilia or potential signals transduced through kinocilia. Certainly, the persistence of kinocilia is not necessary for maintenance of PCP protein localization. However, because localization was not examined at the time of kinocilium disruption, these results do not rule out the possibility that a signal from the kinocilium might be required to establish their asymmetric localization, after which that localization might be inherited through feedback control[15].

The work by Chen and colleagues[4] shows that, in the inner ear, kinocilia function downstream of the core PCP proteins, where they are required to direct basal body migration and morphological polarization. However, a potential additional upstream function has not been ruled out. Because the subcellular localization of primary cilia may be a specialized readout of PCP that is present in sensory hair cells but not other planar-polarized cell types, it is tempting to speculate that primary cilia might transduce a signal, such as a Wnt signal, that is required for planar polarization, including polarization of the PCP proteins. In inner ear sensory hair cells, the kinociliary axoneme would then function again at a later step to link PCP protein localization to basal body migration and stereociliary bundle orientation. Additional work in the ear, and other planar-polarized tissues, will be required to address these possibilities.

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