

Molecular and cellular differences between tissue polarity and translational polarity in mammalian cochlear epithelium

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In ciliated mammalian cells, the precise migration of the primary cilium at the apical surface of the cells, also referred to as translational polarity, defines planar cell polarity (PCP) in very early stages of development. Recent research has revealed a co-dependence between planar polarization of some cell types and cilium positioning at the surface of cells. This important role of the primary cilium in mammalian cells is in contrast with its absence from *Drosophila* PCP establishment.

Our recent work uncovers the role of two proteins complexes in controlling the specific migration of the primary cilium at the surface of hair cells in the classical mammalian PCP model, the cochlea. Specifically, we show that deletion of GTP-binding protein alpha-i subunit 3 (Gnai3) and mammalian Partner of inscuteable (mPins) disrupts the migration of the kinocilium at the surface of cochlear hair cells and affects hair bundle orientation and shape. Pharmacological Inhibition of G-protein function in vitro leads to kinocilium migration defects, PCP phenotype and abnormal hair bundle morphology. Remarkably, these phenotypes are qualitatively similar to the phenotypes reported in the absence of cilium in a conditional *Ift88/Polaris* mutant. Reciprocally, a ciliary-dependant mutation (Mkks or BBS6) leads to a more extended Gai3 domain of expression, suggesting a relationship between BB (basal body)/PCM (pericentriolar material) function and Gai3 distribution. We also show that Gai3/mPins are expressed in an apical and distal asymmetrical domain, which is opposite and complementary to an aPKC/Par-3/6b expression domain, and non-overlapping with the core PCP protein Vangl2. Our data are consistent with a model where Gai3/mPins on one side and aPKC/Par-3/Par-6b on the other side could exert pulling forces on the microtubule aster emanating from the BB/PCM area, similar to a mechanism described for positioning and orienting the centrosome during *C. elegans* oocyte division.

In conclusion, our findings support a model in which two PCP signalling pathways cooperate to control the planar orientation of the cochlear ciliated epithelium at a cellular and a tissue level. The G-protein-dependent signalling controls the migration of the cilium cell autonomously, whereas core PCP signalling controls long-range tissue PCP.