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DEVELOPMENT

Going with the flow

> PCP controls the positioning and beating of cilia

Planar cell polarity (PCP), the coordinate polarization of cells across the plane of a tissue, is required for many cellular processes in vertebrates, including convergent extension during gastrulation, oriented cell division and polarity establishment in epithelial tissues. Motile cilia cover several organs and their dysfunction can result in severe diseases. It has been proposed that PCP regulates cilium formation, but its exact role in ciliogenesis was unclear. Two studies now show that PCP does not affect ciliogenesis *per se*, but instead controls cilium positioning and the orientation of their beating.

Borovina *et al.* analysed the phenotype of zebrafish embryos lacking vang-like 2 (Vangl2) — a core and specific component of the PCP signal transduction pathway. Zebrafish Kupffer's vesicle is a ciliated fluid-filled organ that initiates left–right development by creating a directional fluid flow that triggers asymmetric gene expression. Embryos lacking Vangl2 displayed left–right patterning defects, suggesting a defect in Kupffer's vesicle flow. Indeed, by following the movement of fluorescent beads injected in the Kupffer's vesicle lumen, the authors found that Kupffer's vesicle flow was disordered; however, the Kupffer's vesicle cilia looked normal. Following the movement of green fluorescent protein-labelled cilia in live embryos lacking Vangl2 showed that cilia were not uniformly oriented and were unable to tilt in the posterior direction, which is essential to establish directional flow. Furthermore, the localization of cilia at the apical membrane of neuroepithelial cells was disrupted in Vangl2-deficient embryos — cilia were located centrally rather than posteriorly. These findings indicate that PCP has an essential role in the positioning and tilting of motile cilia in different cell types.

Guirao *et al.* studied the orientation of ciliary beating in ependymal cells during mouse brain development. Ependymal cells are multiciliated epithelial cells that line the cerebrospinal fluid (CSF)-filled ventricles in the brain and the central canal of the spinal cord. Cilia grow from basal bodies docked at the apical membrane of these cells; they initially occupy random positions but gradually reorient to become aligned to the direction of CSF flow. By visualizing the beating of cilia in cultured cells that differentiate into ependymal cells, the authors found that single cells can gradually align their cilia and that cell clusters spontaneously coordinate their ciliary beating to propel fluid in one direction. Importantly, by applying a controlled shear flow over the cell cultures, they showed that hydrodynamic forces applied on cilia during cell maturation drive their reorientation towards the direction of flow. Cell cultures expressing a non-functional form of VANGL2 showed normal ciliogenesis but failed to align cilia in response to CSF flow, indicating the importance of VANGL2 in ciliary alignment mediated by hydrodynamic forces. This was confirmed *in vivo*, as overexpression of the non-functional VANGL2 in brain ventricles disrupted the localization of endogenous VANGL2 and the orientation of beating cilia.

Together, these studies show that PCP controls the positioning and beating of cilia, and that coupling between hydrodynamic forces and PCP orients cilia in a uniform direction.

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ORIGINAL RESEARCH PAPERS Borovina, A. *et al.* Vangl2 directs the posterior tilting and asymmetric localization of motile primary cilia. *Nature Cell Biol.* **12**, 407–412 (2010) | Guirao, B. *et al.* Coupling between hydrodynamic forces and planar cell polarity orients mammalian motile cilia. *Nature Cell Biol.* **12**, 341–350 (2010)

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