

Bad hair days for mouse PCP mutants

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Mammalian hairs have characteristic patterns of orientation, with a predominantly rostral to caudal direction, occasional swirls and a high level of local correlation between hairs. A detailed new study demonstrates that the polarity of hairs derives from an underlying planar polarity of the basal epidermal cells from which hair follicles arise.

Mammalian body hairs begin as placodes in the basal epidermis. The placodes, separated from one another by basal epidermal cells, invaginate into the dermis to form hair germs and ultimately hair follicles from which the hairs emerge. Early in their development, the hair germs tilt, causing the hairs to grow at an angle. Projection of the hairs onto the plane of the epithelium defines vectors representing their polarities, and they are far from random. On a given region of skin, these vectors all point in the same direction, producing an ordered, polarized array. On page 1257 of this issue, Devenport and Fuchs report progress in understanding how this coordinated polarization arises¹.

Many epithelial cells are individually polarized orthogonal to their apical–basal axes, a phenomenon called planar cell polarity (PCP). The most detailed studies of PCP have looked at the epidermis of *Drosophila melanogaster*, where individual cells produce trichomes, which emerge from the distal side of the cell and point distally (Fig. 1a)². PCP in *Drosophila* is characterized by the asymmetric accumulation of specific PCP proteins on proximal or distal sides of each cell. Among these, the serpentine receptor Frizzled (Fz)³, accumulates on the distal side, the four-pass transmembrane protein Van Gogh (Vang or Strabismus/Stbm)⁴, accumulates on the proximal side, whereas the seven-transmembrane atypical cadherin Flamingo (Fmi or Starry night/Stan)⁵, accumulates on both sides. The axis of these asymmetric subcellular distributions predicts the trichome polarity pattern². These proteins are thought to communicate across intercellular boundaries, recruiting one group to the distal side of cells, and the other to the proximal side, through the function of a poorly understood feedback mechanism⁶. The results are the tendency of adjacent cells to polarize in the same direction, like dominoes, and the local propagation of polarity from cell to cell. The

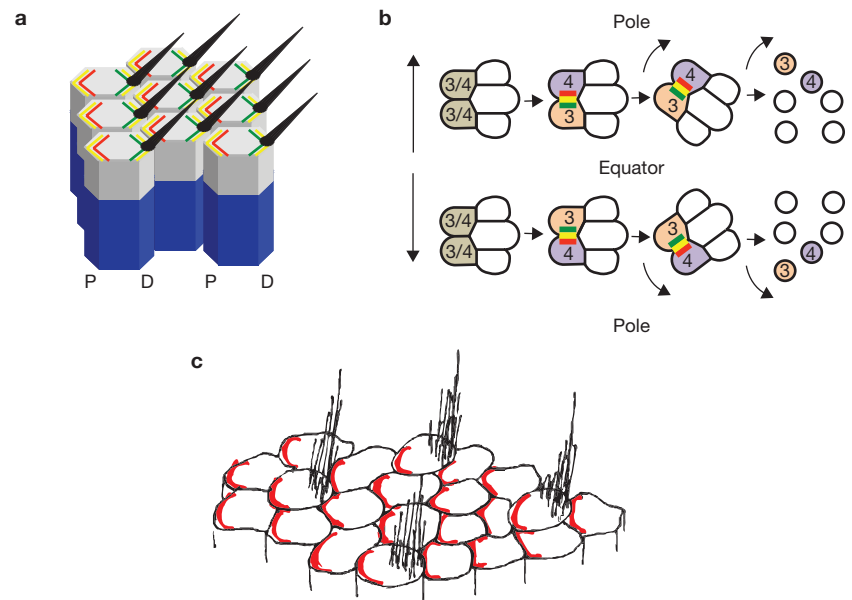


Figure 1 PCP in the *Drosophila* wing and eye, and the mammalian vestibular epithelium. **(a)** *Drosophila* wing epithelial cells elaborate a trichome from their distal vertex. The PCP proteins Fmi (yellow), Fz (green) and Vang (red) accumulate at proximal (P) and distal (D) cell boundaries and are thought to participate in distinct proximal (Fmi and Vang) and distal (Fmi and Fz) complexes that communicate with and stabilize each other across the boundary. **(b)** In the *Drosophila* eye, the prospective R3/R4 photoreceptors are recruited into developing ommatidia. The same PCP protein complex establishes an asymmetric complex between the prospective R3 and R4 cells, biasing a Notch signal that directs adoption of the R3 fate in the equatorial cell and the R4 fate in the polar cell. Subsequent differentiation and rotation of the ommatidium depends on the relative positions of R3 and R4. **(c)** In the mammalian vestibular epithelium, sensory hair cells differentiate within a supporting epithelium. The sensory hair cells elaborate asymmetrically placed ciliary bundles whose orientation is determined by the PCP mechanism. The entire epithelium shows polarized distributions of PCP proteins before sensory hair cell differentiation.

same proteins adopt asymmetric subcellular distributions in specific cells of the ommatidia of the *Drosophila* eye, where they polarize an intercellular signal that determines differential cell fates (Fig. 1b). Although the specifics are controversial, a global directional cue must guide the directionality of the self-organizing system mediated by Fz/Vang/Fmi^{7,8}.

In vertebrates, PCP is readily apparent in the sensory epithelium of the inner ear, where the sensory hair cells show a striking planar polarity evident in their asymmetric placement of ciliary bundles on their apical surfaces. Asymmetric localization of Fz, Vangl2, Celsr1/Fmi and other PCP proteins seems to recapitulate that seen in *Drosophila*, and

disruption of genes encoding these proteins produces abnormal PCP of the sensory hair cells (Fig. 1c), suggesting a well conserved mechanism⁹. Genetic analyses indicate that PCP is involved in a growing list of developmental events, and its disruption is associated with open neural tube defects, polycystic kidney disease, deafness syndromes, ciliary dyskinesia, situs inversus and conotruncal heart defects. In addition, PCP is involved in normal vasculogenesis and wound healing, and is implicated in the invasive and metastatic behaviour of malignant neoplasms¹⁰.

An earlier study had shown that mouse Fz6 is required for normal body hair polarity, as mutants show abnormal swirling hair patterns¹¹.

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