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Breaking Cellular Symmetry along Planar Axes in *Drosophila* and Vertebrates

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In many organs, epithelial cells are polarized not only along the apicobasal axis, but also along a second axis within a plane. Acquisition of the latter polarity, known as planar cell polarity (PCP) or tissue polarity, is crucial for specialized cellular functions. Genetic programming of PCP has been most thoroughly studied in *Drosophila*, which has allowed identification of a number of regulatory molecules that are evolutionally conserved. One group of the regulators is responsible for interpreting a hypothetical polarity cue and directing local cytoskeletal reorganization. This group includes a seven-pass transmembrane cadherin known as Flamingo (also known as Starry night), other receptors, and downstream components; and many of those molecules are redistributed to restricted subcellular compartments. Recent studies on a trio of cell-surface molecules challenge a previous hypothesis about the identity of the polarity cue and prompt a novel hypothesis about a global input. Studies on vertebrate systems support the notion that the molecular mechanisms demonstrated in *Drosophila* are applicable to at least two classes of polarized behaviors of vertebrate cells: sensory hair morphogenesis in the inner ear epithelium, and convergent extension movements during gastrulation.

Key words: *Drosophila*, Flamingo, Frizzled, inner ear, planar cell polarity.

Abbreviations: PCP, planar cell polarity; Fz, Frizzled; Fmi, Flamingo; Dsh, Dishevelled.

Polarization along apicobasal or planar axis: how different are they?

A typical example of PCP is seen in the sensory epithelium of the inner ear, where stereocilia that protrude from the apical surfaces of hair cells are uniformly oriented (Fig. 1, A and B). This coordinated alignment maximizes the ear's sensitivity to sound and acceleration (*1*). As a line of Rapanui moais, the huge statues on Easter Island, fix their eyes in the same direction, stereocilia face unidirectionally throughout the sensory epithelium in the cochlea. From where does the polarity cue come? How does the hair cell interpret the cue and reorganize its cytoskeleton to break cellular symmetry?

Polarization along the apical-basal cell axis is mediated by cell-to-substrate and cell-to-cell adhesion. In these contexts, distinct environments, such as the basal surface and the apical free surface, surround each cell. These heterogeneous environments convey spatial information that is utilized to orient the cell (*2*). In contrast, cells at distinct coordinates along the planar axis make contact with a superficially homogenous environment, yet cells at all locations display remarkable fidelity to the axis. This feature indicates that the signaling mechanism of PCP operates over a long distance (*3*, *4*).

PCP can be readily visualized in animals that have landmarks exposed on their body surfaces, such as scales in fish, feathers in birds, and epidermal cuticular structures in insects including *Drosophila* (*4*, *5*). *Drosophila* adults are decorated by unipolar arrays of wing hairs (Fig. 1, C and D) and sensory bristles; numerous polarity mutants of *Drosophila* have been isolated, and their gene products controlling PCP were subsequently identified (*4*, *6*, *7*). Despite the long history of genetical analysis of the fly, the subcellular distributions of these regulatory molecules were not clearly shown until 1999. This minireview focuses on current views of the molecular mechanisms underlying PCP in the fly wing, summarizes recent discoveries in vertebrates, and discusses many unsolved questions.

Classification of polarity phenotypes of wing epidermal cells

PCP of wing epidermal cells becomes visible in the pupa (*7*). At around 30 h after pupal development begins, each epidermal cell, which is typically hexagonal in shape, assembles actin bundles at its distalmost vertex, producing a single prehair that extends away from the cell (Fig. 1, E and F). Thus cells acquire proximal-distal (P-D) polarity. Fly genes that control PCP in all organs (hairs on the wing, bristles on the notum, and ommatidia in the eye) are designated the "core" group genes and they include *frizzled* (*fz*), *dishevelled* (*dsh*), *prickle-spiny legs* (*pk*), *Van Gogh/strabismus* (*Vang/stbm*), and *flamingo /starry night* [*fmi/stan*, summarized in Fig. 2A (*8–14*)]. A seven-pass transmembrane receptor, Fz, and its downstream component, Dsh, also transduce the canonical pathway of the Wnt signaling which controls cell fate

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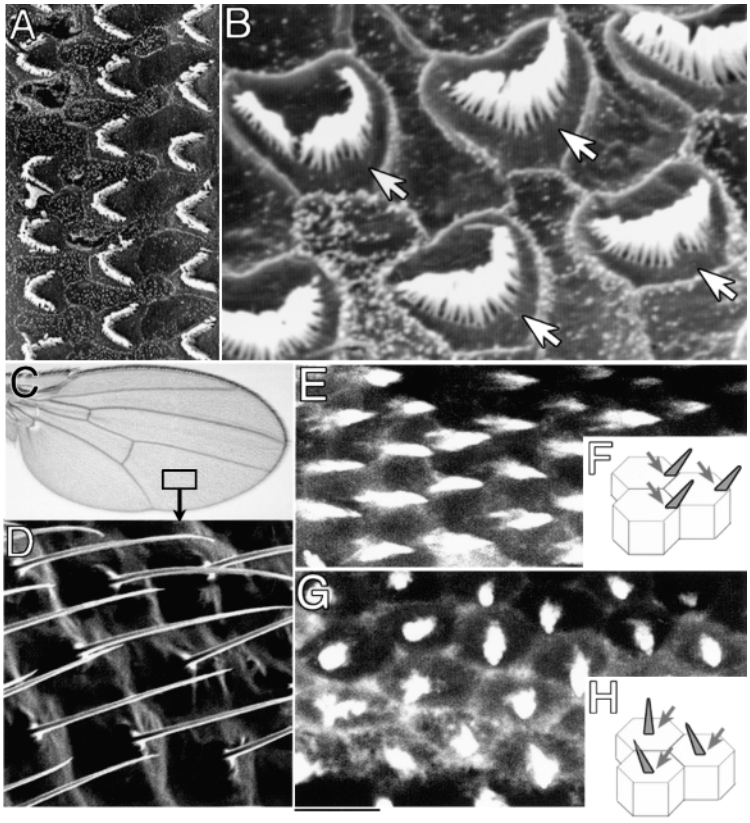

Fig. 1. **Examples of PCP in vertebrates and *Drosophila*.** (A) and (B) Images of outer hair cells in mouse cochlea obtained by scanning electron microscopy (SEM). Stereocilia protrude from the apical surfaces of the hair cells and they are uniformly oriented (arrows in B). (C–H) *Drosophila* wing epidermis. In each panel, the proximal-distal axis runs from left to right. (C) A wing of a *Drosophila* adult. (D) SEM image of the wing surface. Each cell has a single hair that points distally. (E) and (G) Prehair formation was visualized at 34 h after initiation of pupal development in the wild type (E) and a *fz* mutant (G), which both express GFP::actin. In contrast to prehair formation at distal cell edges in the wild type (E), the *fz* mutant cell generated a hair at the cell center (G). (F) and (H) Diagrams of epidermal cells in the wild type (F) and the *fz* mutant (H). Arrows point to sites for prehair formation. This figure is adapted from those in Ref. *49*.

determination and proliferation; thus the PCP pathway and the canonical one branch at Dsh (*15–17*).

A wing cell that has a mutation for any of the core group genes mislocalizes the prehair formation; it produces a prehair near the cell center (Fig. 1, G and H). Therefore, the core members are required to restrict the site to the distal edge of the cell. Genes of another group [*RhoA*, *inturned* (*in*), *fuzzy* (*fy*), and *multiple wing hairs* (*mwh*) in Fig. 2A] prevent the assembly of actin bundles outside the distal cell edge, as shown by the fact that hairs emerge at multiple locations along the periphery of those mutant cells (*4*, *7*).

Interdependent "zigzag" distributions of regulatory proteins

Over the last four years, striking evidence of the intracellular localization of the core member proteins has been reported, and this information has opened a door to building a working hypothesis of molecular mechanisms (*4*, *12*, *18–22*). Several hours before prehair formation, the regulatory proteins become concentrated at proximal/distal (P/D) cell boundaries rather than at the anterior/posterior (A/P) boundaries; and this biased localization becomes most prominent just before the onset of prehair morphogenesis. At this stage, X-Y views of epidermal planes provide typical zigzag patterns that run orthogonal to the P-D axis (compare Fig. 2, C and D). Whether each core member is present bilaterally (at both proximal and distal boundaries) or in a unipolar manner (at either proximal or distal boundary) is different from one to another (see Fig. 3, described next). For Fz and Dsh, only active protein molecules accumulate at the distal boundary, suggesting that these redistributions depend on Fz signal transduction through Dsh.

Curiously, the distributions of these proteins are interdependent. For example, Fmi is present evenly around the entire cell periphery and also in the cytoplasm without active Fz molecules (*12*); conversely, in the absence of Fmi, the transmembrane protein Fz is no longer localized at cell boundaries (*18*). This reciprocal dependency suggests that the core members constitute a signaling complex and that this complex formation at the P/D boundary is prerequisite for normal cell polarization, although physical interaction between Fmi, Dsh, and Fz has not been demonstrated under the immunoprecipitation conditions we employed (Y.S. and T. U., unpublished result).

Models of planar polarization of wing epidermal cells

How does each core member function at P/D boundaries to polarize cells? One tentative scenario of the sequence of events is described below. Essentially, an initial small imbalance in Fz activity between proximal and distal cell edges is amplified by a complicated feedback loop (*4*, *17*, *23–25*).

Initially regulatory molecules are present evenly at the cell periphery (Fig. 3A). The seven-pass transmembrane cadherin Fmi takes advantage of its homophilic binding property to become localized at cell boundaries, and this Fmi localization is required for recruitment of Fz and Dsh to the cell-cell contact site (*12*, *18–20*). Subsequently a ligand of Fz is produced by and secreted from the distalmost cells, and a shallow concentration gradient is made along the P-D axis of the wing by extracellular diffusion;

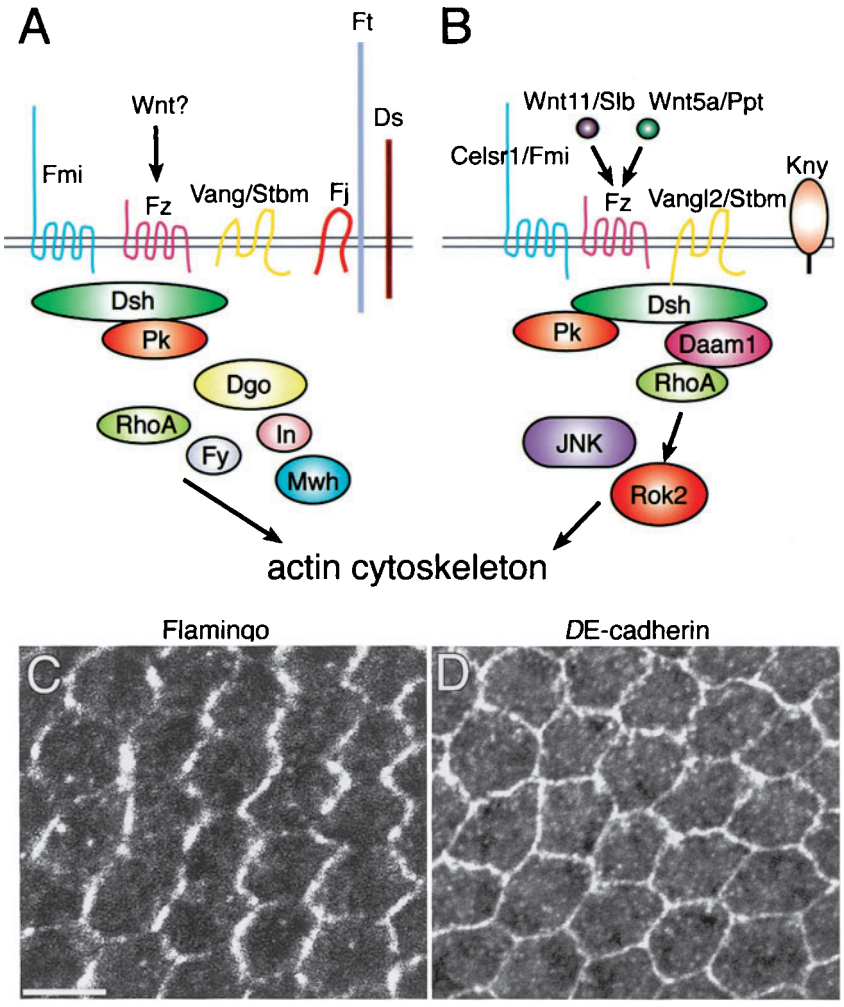

Fig. 2. **Regulatory molecules of PCP in *Drosophila* and vertebrates.** (A) and (B) Secreted molecules, a single membrane-pass or multimembrane-pass proteins, and intracellular components that control PCP in *Drosophila* (A) and in vertebrates (B). See details in the text. Molecules that are not discussed in the text are Diego (Dgo in A, Ref. *21*), Knypek (Kny in B, Ref. *47*), vertebrate Prickle (Pk in B, Ref. *43*) and Jun-N-terminal kinase (JNK in B, Ref. *48*). (C) and (D) Confocal images of wing epidermis just before the onset of prehair formation. This epidermis was doubly stained for Flamingo (Fmi, C) and *D*E-cadherin (D). Scale bar: 5 μm. This figure is adapted from those in Ref. *49*.

alternatively, the ligand could be propagated from cell to cell by intercellular transcytosis (*23*, *26*). In any case, this graded distribution is thought to act as a polarity cue.

The shallow gradient leads to a small difference in the level of Fz activation between the proximal and distal cell edges (Fig. 3B). This in turn causes a subtle imbalance in the intensity of Fz signal transduction through Dsh, which drives redistribution of Fz, Dsh, and Fmi towards the distal boundary, where the signaling level is slightly higher. Fz-Dsh and the LIM domain protein Pk localize in a mutually exclusive fashion; thus Pk accumulates at the proximal boundary, where the Fz-Dsh level is lower (*22*).

The redistribution of the Fz-Dsh complex, together with Pk's inhibitory action towards Dsh at the proximal boundary, amplifies the small difference in the signaling along the P-D axis within the cell, which further accelerates intracellular segregation of Fz-Dsh and Pk (Fig. 3, C and D). During this amplification, Fmi molecules that are redistributed to the distal boundary of one cell interact with Fmi molecules on the proximal boundary of the neighboring cell. This bilateral Fmi "zipper" helps to stabilize the uneven accumulation of the other proteins (*12*). Ultimately this positive feedback loop generates a steep peak of the signaling at the distal cell vertex; and this peak initiates cytoskeletal reorganization for prehair formation (Fig. 3E). In the above scenario, the feedback loop operates between proximal and distal cell vertexes in each cell; but another possibility is amplification of a small imbalance across the P/D boundary by intercellular looping.

A long-standing riddle: reconsideration of the identity of the polarity cue

The above model fits into the following framework for discussing cell polarity in general: (i) An extrinsic spatial cue is provided locally on the cell surface to instruct cells to orient the axis. (ii) Receptors and downstream components interpret the cue and reinforce the asymmetry defined by the cue. Many questions remain to be answered. A long-standing riddle of PCP is the identity of the polarity cue, in other words, what initiates the imbalance of Fz activity along the P-D axis. In analogy to the Wnt canonical pathway, it was postulated that a ligand for Fz may be one of the *Drosophila* Wnts and that its graded distribution is the cue. An obvious prediction is that loss-of-function mutants of that *Wnt* gene would show a PCP phenotype; however, no such fly Wnt has been reported so far (*27*).

Alternatively, the cue may not be provided by a secreted protein that travels over a long distance, but by a cell-by-cell mechanism. It has recently been proposed

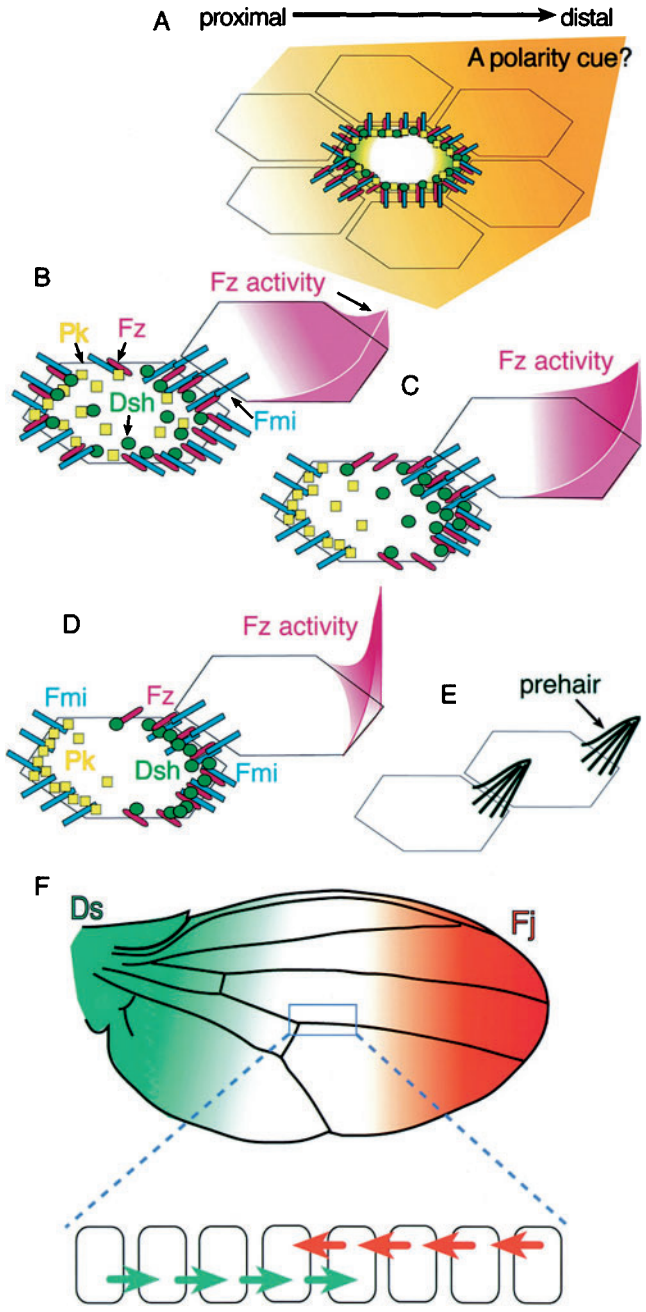

Fig. 3. **The feedback loop model and candidates for global cues.** In every panel, the proximal-distal axis runs from left to right. (A–E) A model of the feedback loop that amplifies an initial small difference in the level of Fz signaling. Each hexagon represents a wing epidermal cell. Fz (pink bar), Fmi (blue bar), Dsh (green circle), and Pk (yellow square) are illustrated. Along the apicobasal axis, all of the molecules are localized to the level of the adherens junction. See details in the text. A–E are adapted from those in Ref. *49*. (F) Fj and Ds are expressed in opposing gradients along the P–D axis of the wing. See details in the text.

that a cascade of interactions among a set of transmembrane proteins transmits directional information (*28–30*). These molecules are a transmembrane/secreted protein, Four-jointed (Fj), and atypical cadherins, Dachsous (Ds) and Fat (Ft, Fig. 2A). Fj and Ds are expressed in opposing gradients along the P-D axis of the wing [Fig. 3F (*30*, *31*)], which may be the source of information. Fj and Ds are then thought to generate a gradient of Ft activity (but not a gradient of Ft expression), possibly through a series of juxtacrine interactions (arrows in Fig. 3F). This cascade might resemble a "domino effect," which could explain the long-range operation of these molecules (i.e., non-cell autonomous effects of mutations of *fj*, *ds*, and *ft*). Cells would respond to this global directional, but subtle, cue mediated by Ft. If a fraction of cells were to interpret this input erroneously, they could correct such errors with the help of the Fz-dependent feedback loop, resulting in a high-fidelity response (*30*). This model also raises many questions. Are the opposing gradients of Fj and Ds relevant to PCP? If so, how are those gradients of gene expression generated? What kind of signal does Ft transduce and how does it influence Fz activity (*32*)?

Novel cell biological questions and findings that are relevant to the feedback loop model

The Fz-dependent feedback model provides several interesting subjects of cell biological or biochemical investigations. How are the core member proteins asymmetrically distributed along the P-D axis in each cell? This can be explained by two mechanisms that are not mutually exclusive. One is preferential sorting to the P/D cell boundary, and the other involves selective retention at the P/D boundary following initial uniform transport to the plasma membrane. To distinguish between these possibilities, we have followed examples of studies on asymmetrical cell division (*33*, *34*) and developed a protocol for time-lapse *in vivo* observation of the P/D accumulation of the regulatory molecules. We are observing cells of transgenic animals expressing GFP-tagged Fz, which was previously shown to be functional (*18*). This imaging approach may contribute to clarification of mechanisms by which a feedback loop amplifies an initially small signal.

How exactly does signaling mediated by Dsh reorganize actin cytoskeleton? A formin homology domain protein, Daam1 was identified as a bridging factor between Dsh and RhoA from a study using *Xenopus* (*35*). Daam1 binds both a Dsh homolog and RhoA and activates RhoA in a Wnt/Fz signaling-dependent manner during gastrulation (see below). A *Daam 1* homolog has been found in the fly genome and awaits genetic characterization.

Finally it should be mentioned that we probably do not yet understand all of the molecular functions of Fmi. In addition to the likely model that bilateral distribution of Fmi at cell boundaries anchors signaling components, Fmi itself may also possess a signaling function. This speculation emerges from experiments of ectopic gradient expression of Fmi and sequence similarity of the 7-pass transmembrane domain to those of a subfamily of G protein-coupled receptors (*12*). It remains to be demonstrated that Fmi is coupled to G protein and that any of the G proteins is involved in PCP in the wing.

What are known and unknown at the molecular level about PCP in vertebrates

Although many mouse mutants with morphological defects of hair cells in their inner ear have been examined, none of the mutations appeared to affect the initial

establishment of PCP. All three of the mouse homologs of *fmi* are expressed in the developing organ of Corti (*36*); and it was reported very recently that two mutant mice with abnormal head-shaking behavior, *spin cycle* and *crash*, carry independent mutations within one of the homologs, *Celsr1*. In addition, a mutation in *Vangl2*, a homolog of the fly PCP gene *Vang/stbm*, results in disruptions in the polarization of stereocilia (*37*, *38*). It should be emphasized that the phenotypes of the above mutant mice do not involve general or progressive disorganization, but appear to be specific to the establishment of polarity of the hair bundle, supporting strong conservation of molecular mechanisms between fly and mammals. Unexpectedly a LAP protein family gene, *Scrb1*, was also identified as a PCP gene in the mouse (*38*). This is a homolog of a fly tumor suppressor gene, *scribble* (*scrib*), which controls the epithelial lateral domain along the apicobasal axis (*39*).

In vertebrate gastrulation, elongation of the body axis is driven by mesenchymal cell rearrangement called convergent extension (CE) (*40*). In mediolateral intercalation, cells take a characteristic bipolar shape with polarized protrusive activity and exert forces that align their neighbors. Several of the genes implicated in the regulation of CE are homologs of fly PCP genes, such as Fz family members, homologs of Dsh, Stbm, Pk, and RhoA [Fig. 2B (*35*, *41–43*)]. PCP in *Drosophila* and CE in vertebrate embryos both lead to coordinate cytoskeletal reorganization in masses of cells that are in contact with each other, and this would explain the partial overlapping of the molecular machinery (*24*). In contrast to PCP in the fly wing, in which none of the *Wnt* genes have been implicated, Wnt11 (Silberblick) and Wnt5a (Pipetail) control CE (*44–46*). Nevertheless it should be pointed out that analysis of expression patterns and rescue experiments indicate that those Wnts do not play the role of a directional cue in CE (*40*, *44*).

Although the underlying molecular mechanisms are unknown, other interesting examples of PCP in vertebrates include directional beating of cilia in the respiratory epithelia. Those cilia are constructed in a way that all beat in the same direction and sweep mucus up and out of airways. Malformation or malfunction of this conveyor belt results in failure in the removal of trapped bacteria and debris and damages host defense. Does coordinated orientation of the "9+2" arrangement of microtubules inside individual cilia underlie this fixed mode of beating? If so, how can cells orchestrate orientation of the microtubule arrangement of the astronomical number of cilia throughout the epithelia? Future investigations of a whole variety of examples of PCP are expected to reveal well-conserved parts as well as context-dependent modifications of the system.

Note Added in Proof: Relevant references were published during preparation of the proof. See the Refs. *50–54*.

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