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Pointing in the right direction: new developments in the field of planar cell polarity

Roy Bayly¹ and Jeffrey D. Axelrod^{1,*}

¹Department of Pathology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5324

Abstract

Planar Cell Polarity (PCP) is observed in an array of developmental processes involving collective cell movement and tissue organization, and its disruption can lead to severe developmental defects. Recent studies in both flies and vertebrates have identified new functions for PCP, new signaling components, and proposed new mechanistic models. However, despite this progress, the search for simplifying principles of understanding continues and important mechanistic uncertainties still pose formidable challenges.

Sheets of cells often acquire a polarity that orients cells along an axis within the plane of the sheet, orthogonal to the apical-basal axis. PCP was originally described in epithelial cells, but is also seen in non-epithelial cell sheets. Its disruption can lead to developmental defects including deafness, neural tube and heart defects, and polycystic kidney disease.^{1, 2}

Much of our understanding of PCP comes from the fly, where powerful approaches have provided important mechanistic insights. In epithelia across species, mechanistic features appear to be conserved; however, in non-epithelial cells, while the same genes are involved, conservation of mechanism is less clear². Adding to the complexity of vertebrate PCP signaling is an intimate link with cilia that cannot exist is not observed in fly PCP³.

Here, we review some of the recent progress in the field of PCP. We discuss new models for how polarity of *Drosophila* PCP components is established in relation to the tissue axis. We also describe newly identified roles for PCP in vertebrate developmental processes including the collective cell movement phenomena of epidermal wound repair, the orientation of motile cilia and the breaking of left/right symmetry by polarized subcellular localization of cilia.

The Fundamental Machinery of PCP

Genetic and molecular analyses in *Drosophila* wing, eye and abdomen have provided a framework for understanding PCP. These studies have suggested a signaling mechanism that consists of several distinct sets, or modules, of proteins⁴ (Figure 1). A core module coordinates polarity between adjacent cells and amplifies subcellular asymmetry. Through a

*jaxelrod@stanford.edu.

feedback mechanism functioning at cell boundaries, these proteins develop subcellular asymmetry, accumulating in proximal [Flamingo (Fmi), Prickle (Pk), and Van Gogh (Vang)] and distal [Fmi, Frizzled (Fz), Dishevelled (Dsh), Diego (Dgo)] subsets on opposite sides of cell-cell junctions (reviewed in^{5, 6}). A second module consists of Fat (Ft), Dachshous (Ds), and Four-jointed (Fj). Opposing expression gradients of Ds and Fj are thought to provide global directional information^{7–9} (reviewed in⁶). In response to signals from the global and core modules, distinct downstream effector modules execute tissue-specific polarization events. A classic example is the distally-oriented polymerization of actin observed in hair formation during wing development¹⁰.

It is unclear to what extent PCP relies on similar mechanisms in different tissues. For example, asymmetric localization of core proteins has not been examined in the abdomen. In addition, while the global module is needed in all tissues so far examined, graded expression of Ds and Fj needed to provide directional information in the eye are at least partially dispensable in the wing, suggesting the possibility of another unidentified and redundant source of directional information in the wing. Furthermore, the connectivity between the modules is controversial. We have proposed that the global module signals directionality to the core module, while others have proposed that the global and core modules each signal independently to the downstream effector modules^{6, 11}.

Recent insights into *Drosophila* Fat and Dachshous function

Much discussion has attended the nature of signals that orient PCP with respect to the tissue axes. Two recent studies propose fundamentally different mechanisms by which this might occur.

Eaton and colleagues previously reported that polarization of PCP components can be detected very early in fly wing development, even in the larval wing discs¹² [G]. More recently, they showed that in the early pupal period, polarity is observed in a roughly radial pattern, with proximal sides of cells oriented toward the center of the wing and distal sides oriented toward the wing margin. However, toward the end of the polarization period, cell polarities are nearly parallel, in a proximal to distal direction (¹³; Figure 2). In the intervening period, exogenously applied tension, driven by wing hinge contraction, leads to cell elongation, oriented cell divisions, coordinated changes in spatial relationships between neighbouring cells and anisotropic [G] cell junction remodeling that together appear to reorient polarity. Inferred patterns of mechanical stress suggest that hinge contraction drives these movements. Indeed, severing the wing from the hinge alters both the cell flows and the reorganization of polarity, strongly suggesting that the cell flows cause the changes in polarity. These events can be approximated by a computational model relating mechanical stress to polarity¹³.

If bulk cell movement and rearrangement can reorganize polarity, might the “global” polarity regulators Fat, Ds and Fj orient polarization through such a mechanism? In support of this possibility, perturbing Ds, either by loss or gain of function, alters both the patterns of cell neighbor exchange and polarity¹³. Implying that this may be the sole mechanism by which the “global” regulators affect PCP, the authors of this study also suggest that the early,

radial pattern of polarity might arise by spontaneous alignment of local polarity, a property predicted by several mathematical models of polarity, including their own^{13–17}.

The idea that Fat, Ds and Fj might influence polarity by strictly mechanical means is a dramatic departure from alternative models. One previously proposed model suggests that opposing gradients of Ds and Fj act via Fat to orient microtubules with a distal plus-end bias that traffic Fz containing vesicles toward the distal cell cortex [G], providing the necessary input bias to allow the core module to polarize in a specified direction^{6, 18}. Furthermore, these components orient polarity in the eye, abdomen, and larval body wall^{7–9}, where no morphogenetic event similar to wing hinge contraction is known to occur. An alternative to Eaton's proposal is that Fat, Ds and Fj simultaneously modify both mechanical properties and polarization, but by different mechanisms. In line with this possibility, the expression of Ds changes over time during pupal wing development in patterns consistent with opposing gradients of Fj and Ds directing both the early radial and late parallel patterns of polarity (^{19–21}; Figure 2).

Another recent paper provides additional evidence for this gradient-based model. Harumoto and colleagues mapped the orientation of the apical microtubule network in the wing at several locations²² and found reorganization of microtubules consistent with the reorganization of polarity observed by the Eaton group. Not surprisingly, in a *ds* mutant wing, microtubule reorganization did not occur correctly. More dramatically, ectopic reversal of the *ds* gradient in the distal portion of the wing both reversed hair polarity and that of the microtubule cytoskeleton. Wing morphology was not significantly altered, and it is hard to imagine how the observed effects might occur through alteration of mechanical properties. However, neither study provides definitive proof for the respective models. More detailed mechanistic descriptions of how this module either modulates mechanical properties, or how it biases core module function, will allow their selective disruption, enabling assessment of their relative contributions to polarization. Furthermore, it is important to keep in mind that neither model is likely to tell the whole story, since the gradients of Ds and Fj are partially dispensable in the wing.

While studies in *Drosophila* have continued to improve our understanding of the fundamental PCP machinery, recent studies in vertebrates have uncovered previously unexplored roles for PCP, as discussed below.

Collective cell movement

In addition to polarizing cells within epithelia, vertebrate homologs of fly PCP genes are implicated in controlling a range of collective cell movements, including convergent extension (CE) during gastrulation, CE in the organ of Corti, and a variety of other events in vertebrates. Although there is extensive genetic evidence that a conserved group of PCP genes control these events, it is unclear to what extent their mechanism of action is conserved, using asymmetric subcellular localization as an indicator of similar mechanism. In the organ of Corti, CE is accompanied by a hallmark pattern of asymmetric subcellular localization[*]. During gastrulation, several examples of asymmetric subcellular localization have been reported, although these are different in character from the hallmark pattern

observed in flies^{23, 24}. In yet other cases, no asymmetric subcellular localization has been reported, leaving open the possibility of differing mechanisms². Additional characterization of PCP homologues in vertebrates has led to the identification of numerous other developmental processes involving planar polarized cell behaviors^{1, 2}, including other examples of collective cell movement discussed below.

Epidermal wound repair and Grainy head transcription factors

The integument is one of the more visually evident examples of PCP, as animal hairs, feathers and scales are oriented with respect to the body or limb axes. Orientation of mammalian hairs has been shown to depend upon the PCP pathway^{25, 26}, and indeed, the entire basal layer of the mouse epidermis shows molecular PCP, as evidenced by asymmetric subcellular localization of PCP proteins²⁶.

When the skin is wounded, keratinocytes undergo coordinated cell movement by crawling from the wound edge to close the gap²⁷. Several lines of evidence suggest a role for PCP signaling in vertebrate wound healing. Caddy and colleagues recently showed that effective wound healing in the mouse depends on *Celsr1*, *Scrib1*, (homologues of the fly PCP proteins *Fmi* and *Scrib*, respectively), and the vertebrate PCP component *PTK7*^{28, 29}. Additional links come from studies of Grainy head-like 3 (*Grhl3*), a transcription factor associated with epithelial integrity in mice, the *Drosophila* homologue of which (*Grh*) is involved in wound healing in flies^{30, 31}. Compound heterozygotes of *Vangl2* (homologue of *Drosophila* core protein *Vang*) and *Grhl3* implicate both of these genes in mouse wound healing²⁸. Polarized migration of keratinocytes during wound healing requires regulation of the actin cytoskeleton by members of the Rho subfamily of GTPases, *RhoA* and *Rac1*, as well as the Rho-associated kinase. Although it is unclear precisely how their activity becomes polarized³², members of the Rho GTPase family have been shown to interact with the PCP pathway^{33, 34}. It appears that the requirement for *Grhl3* in mouse wound healing is to promote transcription of *RhoGEF19*. *Grhl3* directly binds to the proximal promoter region and activates transcription of *RhoGEF19*, the overexpression of which is sufficient to rescue the phenotype observed in *Grhl3*-deficient keratinocytes²⁸.

Despite common roles as regulators of actin dynamics in wound healing, it is unclear whether murine *Grhl3* and *Drosophila grh*³⁰ share a common pathway. A function for fly *Grh* analogous to the regulation of *RhoGEF19* by murine *Grhl3* has not been tested. In contrast, although fly *grh* was found to regulate PCP, at least partly, by controlling *fmi* transcription³⁵, Caddy et al. found no evidence for regulation of *Celsr1-3* by *Grhl3* in the mouse²⁸.

Vertebrate *Grhl3* functions in collective cell movement in other tissues too. *Grhl3*^{-/-} mouse mutants display defects in neural tube closure³⁶, a phenotype similar to that of many PCP pathway mutants. Again, *Grhl3* genetically interacts with the PCP pathway gene *Vangl2* during neural tube closure and in development of hair cells within the inner ear²⁸. Should *Grhl3* therefore be considered a new component of the PCP pathway? Confounding such a conclusion, *Grhl3* is constitutively expressed in the mouse integument³⁷, and no evidence of wound specific activation of *RhoGEF19* has been demonstrated²⁸. In the neural tube and inner ear, the nature of the requirement for *Grhl3* is not known. *Grhl3* might therefore best

be thought of as a constitutive regulator of a required downstream effector for at least some PCP-dependent events. However, Grh-dependent target genes are induced during *Drosophila* wound healing³⁰, and the conserved requirement but divergent function for Grh in mouse and fly PCP may be more than a remarkable coincidence. These interesting findings should motivate further characterization of Grhl3 in PCP signaling.

Convergent extension and Septins

A recent report has revealed a requirement for the PCP effector Fritz (homologous to *Drosophila* Fritz³⁸), a coiled-coil WD40 repeat protein, in CE, and identified an interaction between the PCP pathway and Septins³⁹, a family of proteins that provide resilience to the plasma membrane and increase the overall structural integrity of the cell^{40, 41}.

Kim et al. showed that in the absence of *Xenopus* Fritz, CE is perturbed. The observed disruption of CE resulted not from the loss of individual cell polarity along the medial-lateral axis, but from the inadequate lengthening of polarized cells. Although it is unclear how Fritz regulates cell lengthening, *fritz* morphants [G] display dynamically undulating cell cortices and significant gaps between neighboring cells³⁹. The latter phenotypes suggested a possible role for Septins in CE, and indeed Septin knockdown or inhibition causes CE defects and a specific failure of cell elongation. It was then found that Fritz physically interacts with and is required for the proper cortical localization and function of Septin2 and Septin7.

Symmetry breaking by motile cilia

PCP and ciliogenesis

Recent work has revealed an intriguing interdependence between PCP and primary cilia in vertebrates. Though general conclusions cannot yet be drawn, an apparent requirement for primary cilia in at least some examples of PCP has been proposed. Conversely, a requirement for some Fritz-associated PCP components, including vertebrate homologs of *Drosophila* Inturned and Fuzzy, in ciliogenesis of both primary and motile cilia has also been observed[*], reviewed in³.

In addition to their cortical localization, Fritz and Septin7 localize to the axoneme [G] and base of cilia, with Septin7 appearing in a ring-like structure at the base³⁹. Hu et al. also observed Septin2 in rings at the base of primary cilia *in vitro*, where it contributes to a diffusion barrier for the trafficking of particles into and out of the primary cilium⁴². In the absence of Fritz, the Septin ring is altered in size and location, but not disrupted³⁹. It is unclear whether Fritz and Septins have a regulatory or structural function in controlling trafficking in and out of the primary cilium, but the observation that frog Fuzzy is required for trafficking at least one cargo into cilia suggests that this may be a function of this group of PCP pathway effectors. In an additional parallel, Vangl2 was recently shown to genetically and physically interact with BBS8, a member of the BBSome [G], which is known to traffic membrane proteins to the cilium^{43, 44}. The possibility of shared mechanisms between CE and regulation of the primary cilium is supported by the involvement of both Fritz and Septins in these processes.

Orientation and migration of cilia in multiciliated cells

Along the lateral ventricles of the brain, multiciliated ependymal cells [G] beat in a concerted fashion to propel cerebrospinal fluid (CSF) in a rostral [G] direction. Impairment of CSF flow results in hydrocephalus [G]. The beating orientation of each cilium correlates with the orientation of its basal foot [G], an appendage associated with the centrosome [G] of each cilium. Ependymal motile cilia are randomly oriented within each cell in the first few days of postnatal life, but subsequently align among themselves in each cell, and orient to beat rostrally⁴⁵.

Reminiscent of the multiciliated cells on frog skin⁴⁶, this rostral orientation has recently been shown to depend on both PCP signaling, and on fluid flow generated by the cilia themselves, or from an exogenous source (Figure 3). Loss of Vangl2, Celsr2, Celsr2 and 3, or disruption of Dishevelled2 (homologue of *Drosophila dsh*) function results in misoriented cilia^{47–49}. Loss of Celsr2 and 3 interferes with the normal asymmetric localization of Vangl2 and Fz3, and surprisingly, also impairs ciliogenesis⁴⁹. However, PCP signaling alone is insufficient for ciliary orientation, because interfering with flow, and likely the ability of cilia to sense flow, by knocking down Kif3a (required for ciliogenesis), disrupts basal foot orientation, but leaves the asymmetric localization of Vangl2 intact⁴⁷. How might the PCP system contribute to orientation of cilia? Vangl2 localizes throughout the axoneme of ependymal motile cilia in addition to its asymmetric localization at the cell cortex, suggesting a possible direct role in ciliary function or orientation⁴⁷. Experiments to dissociate a ciliary vs. cortical function for Vangl2 will be very challenging, yet the ability to separately test potentially distinct localized functions of PCP components within cells will be critical for our understanding of what is mechanistically responsible for the coupling of flow and ciliary reorientation.

In addition to their directional orientation and beating, the motile cilia are found in clusters that are localized asymmetrically at the rostral end of ependymal cells^{45, 48}. This ‘translational polarity’ found within ependymal cells depends on events that occur much earlier in development. Before they differentiate into ependymal cells, neural progenitors (radial glia), which line the ventricular surface of the brain, possess a single primary cilium asymmetrically localized to the rostral side of the apical cell surface (⁴⁵; Figure 3). Similar to the orientation of ependymal motile cilia, the rostral positioning of the basal body of primary cilium within radial glial cells requires the cilium to be intact, although a role for the PCP pathway in translational polarity remains unclear⁴⁵.

Migration of single motile cilia

The planar polarized migration of cilia within radial glial cells is reminiscent of recent observations in the nodal cells [G] of the mouse. Left/right (L/R) asymmetry is acquired very early during development and involves a leftward flow of nodal fluid hypothesized to cause an asymmetric accumulation of an unknown signal on the left side of the embryo, ultimately resulting in the asymmetric expression of developmental control genes and a body plan with L/R asymmetry⁵⁰. Most nodal cells possess a single motile cilium that beats with an intrinsic clock-wise motion. Migration of cilia towards the posterior side of each cell is thought to be required to achieve leftward fluid flow⁵⁰.

Recently, several studies have demonstrated a role for the PCP pathway in the posterior migration of motile cilia in mice, frogs and fish. In the absence of *Vangl1*, *Vangl1* and *Vangl2*, and in *Dvl1-3* compound mutant mice with five of six mutant alleles, the posterior migration of motile cilia within nodal cells was disrupted, resulting in impaired leftward flow and L/R patterning^{43, 51-53}. The same was observed in frog *Vangl2* morphants⁵¹. In mouse, *Vangl1*, *Vangl2*, and *Pk2* (homologue of *Drosophila pk*) were shown to localize asymmetrically at the anterior side while *Dvl2* localizes to the posterior side of nodal cells before the posterior migration of motile cilia⁵¹⁻⁵³. Surprisingly, despite the apparent importance of Vang proteins in other species, only modest laterality defects were seen in *Trilobite* (*Vang*) mutant zebrafish, but these were made much more profound with accompanying knockdown of *Bbs8*⁴³. However, in this case, reduced numbers of shortened motile cilia were observed, and it is unclear whether asymmetric ciliary positioning is a factor in this phenotype. Thus, at least in the mouse and frog, planar polarization of nodal cells appears to direct posterior positioning of the cilium. It will be interesting to learn how the asymmetric accumulation of PCP components at the cell cortex enables the directed migration of motile cilia within nodal cells.

Concluding remarks and further questions

Despite substantial advances in our understanding of the PCP signaling mechanism, important unresolved questions remain. Advances will require mechanistic dissection of the various signaling modules, and determination of how they interact with each other. In the last several years, conservation of at least some features of the PCP pathway between flies and vertebrates has been widely demonstrated, yet the puzzling relationship between primary cilia and PCP signaling observed in vertebrates is absent from flies. Of additional interest will be understanding the apparent differences between epithelial and non-epithelial PCP. Future advances will therefore depend both upon detailed mechanistic studies harnessing the power of *Drosophila* genetics, and upon intensified characterization and mechanistic investigation of vertebrate PCP, with a particular focus on the relationship between cilia and PCP. It is as yet unclear whether unifying principles will emerge, or whether we will discover that adaptations of a basic mechanism have resulted in a diversity of distinct processes that retain varying degrees of similarity to the mechanism originally characterized in flies. Because of the substantial list of developmental defects associated with PCP, as well as the recently recognized and phenotypically overlapping group of ciliopathies⁵⁴ [G], these areas are bound to attract considerable attention.

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Glossary Terms

Wing disc	Single layered, sac-like epithelial structure in the larvae that, in holometabolous insects such as <i>D. melanogaster</i> , gives rise to an adult wing after metamorphosis in the pupal stage
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Anisotropic	Having properties that depend on the direction of measurement
Cell cortex	Region of the cytoplasm lying just interior to the plasma membrane
Morphant	An organism treated with an antisense morpholino oligonucleotide resulting in a partial or total loss-of-function mutant
Axoneme	The portion of the cilium projecting into the extracellular space. It is composed of a circular array of nine microtubule doublets plus many other proteins, and is enveloped by a specialized region of plasma membrane
BBSome	The stable complex of seven Bardet-Biedl Syndrome proteins involved in trafficking proteins to cilia
Ependymal cells	Cells of the ependyma, the epithelial lining of the ventricles of the brain
Rostral	In the direction of the top of the head
Basal foot	An appendage protruding asymmetrically from one side of the basal body (centriole) of motile cilia. The direction in which the basal foot points indicates the direction of the active stroke in the ciliary beat cycle
Centrosome	An organelle consisting of a pair of centrioles that can nucleate cilia, and pericentriolar material that nucleates and organizes cytoplasmic and spindle microtubules
Hydrocephalus	The inappropriate accumulation of cerebrospinal fluid in the brain ventricles
Nodal cells	The transient structure at the caudal end of the basal streak of a mammalian embryo, in which left-right asymmetry is established
Ciliopathies	A large group of diseases and developmental anomalies, with overlapping manifestations, that result from defects in cilia structure or function

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Figure 1.

A model of the PCP signalling mechanism based on work in *Drosophila*. The PCP signalling mechanism is proposed to consist of three functional modules: a core module (a), a global directional cue (b), and one of many tissue specific effector modules that respond to the upstream modules to produce morphological asymmetry in individual tissues. **a.** The core module acts both to amplify asymmetry, and to coordinate polarization between neighboring cells, producing a local alignment of polarity (reviewed in^{5, 6}). Proteins in the core signaling module, including the serpentine receptor Fz, the multi-domain protein Dsh, the Ankyrin repeat protein Dgo, the 4-pass transmembrane protein Vang (a.k.a. Strabismus), the Lim domain protein Pk and the seven-transmembrane atypical cadherin Fmi (a.k.a. Starry night), adopt asymmetric subcellular localizations that predict and have been proposed (in the case of wing, demonstrated) to determine the eventual morphological asymmetry by orienting downstream effectors. These proteins communicate at cell boundaries, recruiting one group to the distal side of cells, and the other to the proximal side, through a feedback mechanism that likely involves mutual antagonism of oppositely oriented complexes, thereby aligning the polarity of adjacent cells.

b. The global module serves to convert tissue level expression gradients to subcellular gradients of Ft-Ds heterodimer expression^{8, 9, 20, 55}. It consists of the atypical cadherins Ft and Ds that form heterodimers which may orient in either of two directions at any cell-cell boundary, and the golgi resident protein Fj. Fj acts on both Ft and Ds, as an ectokinase⁵⁶, to make Ft a stronger ligand, and Ds a weaker ligand, for the other^{57, 58}. Thus, the graded expression of Fj and Ds result in a larger fraction of Ft-Ds heterodimers in one orientation relative to the other. **c.** Asymmetric core protein localization, with proximal proteins (orange and red) and distal proteins (blue and green) on opposite sides of cells. Localization of proteins corresponds to morphological polarity; in this example, polarized hair growth is shown.

Figure 2.

Reorganization of PCP in the pupal fly wing. **a.** Polarity, as detected by the asymmetric orientation of PCP proteins, is in a radial pattern during early pupal stages, but reorganizes to a more parallel, proximal-distal pattern later in development (¹³; zigzags represent polarized PCP proteins that localize to the proximal/distal cell boundaries; direction of cell polarity from proximal to distal is indicated by arrows). **b.** Tension, resulting from contraction of the wing hinge, cause cell flows (arrows), cell elongation, and junctional rearrangements (not shown). The resulting shear is proposed to cause reorientation of PCP domains. **c.** The relationship between Ds (red) and Fj (green) expression domains changes during pupal development^{19–21}. The corresponding gradients might also be responsible for the difference in orientation of PCP from early to later stages.

Figure 3.

Development of endymal PCP during mouse brain development. In the developing cortex, progenitor cells called radial glia line the ventricular surface of the lateral ventricles, and some of these differentiate into endymal cells. **a.** Each radial glial cell possesses a primary cilium which extends from the apical surface. From approximately E16 until P1, the apical surface area of radial glial cells increases and the primary cilium migrates towards the rostral end of each cell⁴⁵. **b.** From approximately P1 to P5, radial glia begin to differentiate into endymal cells, characterized by the continued increase in apical surface and the appearance of clusters of motile cilia⁴⁵. The observed clusters are asymmetrically localized to the rostral side of the cell except when ciliary function is disrupted⁴⁵. At this stage, motile cilia are not aligned in any one direction as determined by the orientation of their basal feet. In the absence of *Celsr2* or *Celsr2* and *Celsr3*, ciliogenesis is partially disrupted, and most cilia that do form are improperly docked at the apical surface⁴⁹. **c.** From approximately P5 until P20, the clusters of motile cilia become more densely packed, align with one another, and orient in a caudal to rostral direction. The alignment of motile cilia is dependent upon the PCP proteins *Vangl2*, *Dvl2*, *Celsr2* and *Celsr3*^{47–49}. Additionally, the rostral flow of CSF is required for their proper orientation in a process that is cilia-dependent⁴⁷. E: days of *in utero* gestation, post fertilization. P: postnatal age, in days.