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Cell biology in development

The cell biology of planar cell polarity

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Planar cell polarity (PCP) refers to the coordinated alignment of cell polarity across the tissue plane. Key to the establishment of PCP is asymmetric partitioning of cortical PCP components and intercellular communication to coordinate polarity between neighboring cells. Recent progress has been made toward understanding how protein transport, endocytosis, and intercellular interactions contribute to asymmetric PCP protein localization. Additionally, the functions of gradients and mechanical forces as global cues that bias PCP orientation are beginning to be elucidated. Together, these findings are shedding light on how global cues integrate with local cell interactions to organize cellular polarity at the tissue level.

The collective alignment of cell polarity across the tissue plane is a phenomenon known as planar cell polarity (PCP). Exemplified by the uniform orientation of bristles covering the insect epidermis or of the hairs covering the mammalian body surface (Fig. 1 A), PCP patterns can align over thousands, even billions of cells. This phenomenon is controlled by the so-called PCP pathway, which integrates global directional cues to produce locally polarized cell behaviors. There has been a recent surge in interest in PCP after discoveries that various processes such as vertebrate gastrulation, mammalian ear patterning and hearing, and neural tube closure all require a conserved set of PCP genes (Heisenberg et al., 2000; Tada and Smith, 2000; Wallingford et al., 2000; Kibar et al., 2001; Murdoch et al., 2001; Curtin et al., 2003; Montcouquiol et al., 2003; Copley et al., 2013). Since that time, the PCP pathway has been found to coordinate cell behaviors in numerous diverse settings including polarized ciliary beating in the trachea and brain ventricles (Tissir et al., 2010; Vladar et al., 2012), oriented cell divisions (Gong et al., 2004; Baena-López et al., 2005; Ségalen et al., 2010; Mao et al., 2011), lung branching (Yates et al., 2010), and hair follicle alignment (Guo et al., 2004; Devenport and Fuchs, 2008), to name a few (Fig. 1). Genetic disruptions to PCP cause severe developmental abnormalities in vertebrates, notably neural tube defects, left/right patterning defects, and ciliopathies, which highlights the essential requirement for PCP in development (Kibar et al., 2001; Murdoch et al., 2001; Curtin et al., 2003; Wang et al., 2006a,b; Kim et al., 2010; Song et al., 2010).

Like many types of cell polarity, the establishment of PCP involves (1) a global orienting cue, (2) asymmetric segregation of dedicated polarity proteins, and (3) translation of polarity information into polarized outputs. But unlike other types of cell polarity, the PCP mechanisms we currently understand involve coupling between adjacent cells, allowing for the alignment of polarity over many cell distances.

First described in insects and then genetically dissected in *Drosophila melanogaster*, PCP was long confined to the realm of experimental embryology and genetics until the discovery that the protein products of several PCP genes were localized asymmetrically within the cell, thrusting PCP into the domain of cell biology (for review see Strutt and Strutt, 2009). The challenge to understanding PCP on a molecular level is that long-range PCP is, in essence, an in vivo phenomenon that is difficult to recapitulate in a tissue culture dish. However, recent advances in imaging technology combined with increasingly sophisticated genetic tools are helping us to decipher the in vivo cell biology of PCP. In this review, I highlight some of the recent advances made toward understanding the cell biology underlying the establishment of coordinated polarized cell behaviors. For clarity, I limit discussions of PCP phenomena that meet the definition of PCP proposed by Goodrich and Strutt (2011): namely, that "cell–cell communication causes two or more cells to adopt coordinated polarity" in a process that is mechanistically "dependent upon planar polarity proteins." Other aligned cellular patterns or examples of noncanonical Wnt signaling, sometimes described as "Wnt/PCP" signaling, will not be discussed.

PCP components and molecular asymmetries

Two molecular systems control PCP behavior, the "core" and the "Fat–Dachsous (Ft–Ds)" PCP pathways. A key feature of both is the asymmetric distribution of their constituents (Fig. 2). The

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Abbreviations used in this paper: A-P, anterior–posterior; CE, convergent extension; Dgo, Diego; Ds, Dachsous; Dsh, Dishevelled; Fj, Four-jointed; Fmi, Flamingo; Ft, Fat; Fz, Frizzled; MT, microtubule; PCP, planar cell polarity; Pk, Prickle; TGN, trans-Golgi network; Vang, Van Gogh; Wg, Wingless.

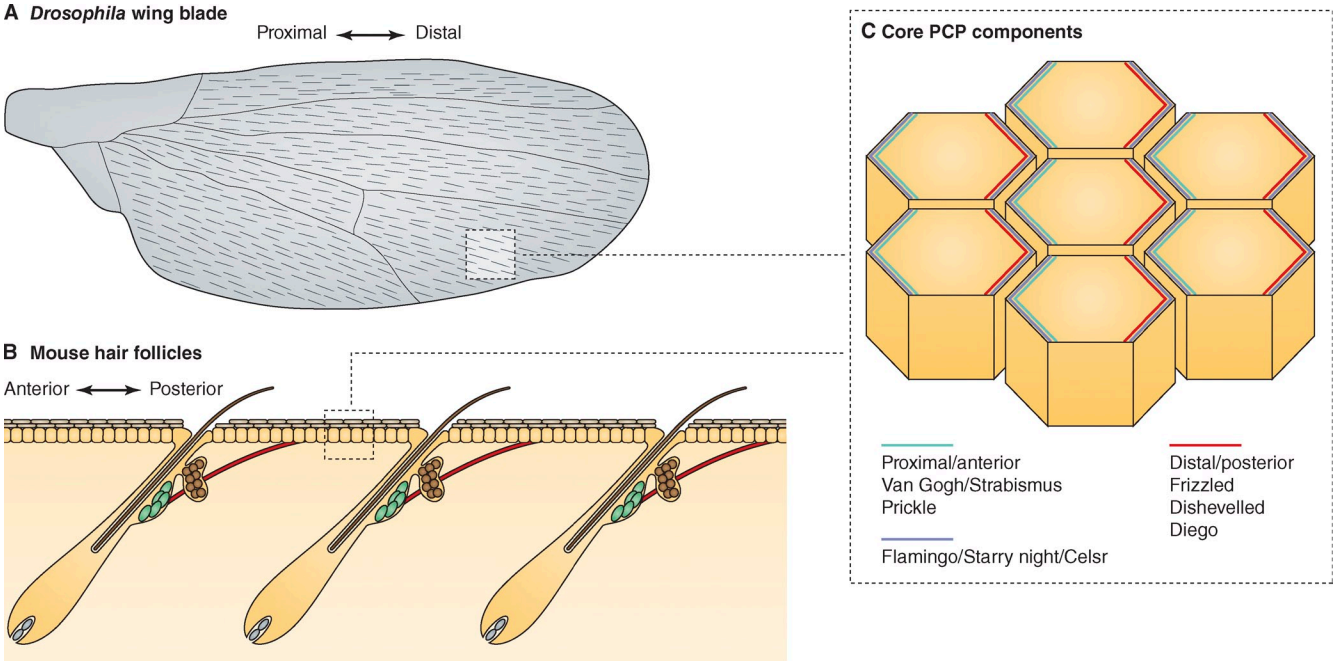

Figure 1. **Planar cell polarity and the core PCP components.** (A and B) The *Drosophila* wing blade and mammalian epidermis illustrate the phenomenon of PCP. In both cases, hairs point in a single direction along the tissue axis, where they align locally with neighboring hairs and globally across the tissue. Whereas *Drosophila* wing hairs are produced by single cells, mammalian hairs emerge from multicellular hair follicles, which orient as a unit. A conserved PCP pathway controls the collective alignment of both types of structures. (C) Core PCP components localize to the plasma membrane and asymmetrically segregate along the epithelial plane as indicated.

core PCP pathway is composed of the multipass transmembrane proteins Frizzled (Fz), Van Gogh (Vang; also known as Strabismus/Stbm), and Flamingo (Fmi; also known as Starry night/Stan), and the cytosolic components Dishevelled (Dsh), Prickle (Pk), and Diego (Dgo). On one edge of the cell reside Fz, Dsh, and Dgo, and on the opposite side lie Vang and Pk (Figs. 1 C and 2 B; Axelrod, 2001; Strutt, 2001; Feiguin et al., 2001; Tree et al., 2002; Bastock et al., 2003). The atypical cadherin, Fmi, resides on both sides, where it forms homodimers between neighboring cells (Usui et al., 1999; Shimada et al., 2001). These molecular asymmetries are observed in sensory hair cells of the vertebrate inner ear (Wang et al., 2005, 2006a,b; Montcouquiol et al., 2006; Deans et al., 2007; Song et al., 2010), the mammalian epidermis (Devenport and Fuchs, 2008; Devenport et al., 2011), brain ventricles (Tissir et al., 2010), and trachea (Vladar et al., 2012). Mutations in core PCP components lead to a loss or randomization of polarity and misalignment of cellular structures along the tissues axis.

The Ft–Ds pathway includes the large protocadherins Ft and Ds and the Golgi resident transmembrane kinase, Four-jointed (Fj; for review see Matis and Axelrod, 2013; Thomas and Strutt, 2012). Similar to the core system, Ft–Ds also displays molecular asymmetries in flies. Ds and its ligand Ft accumulate on opposite cell edges, where they form intercellular heterophilic interactions (Fig. 2 D; Matakatsu and Blair 2004; Ambegaonkar et al., 2012; Brittle et al., 2012). Unlike the core components, Ds and Fj are expressed in complementary gradients in the *Drosophila* eye and developing wing, which contribute to the cellular asymmetries of Ds and Ft (Fig. 2, C and D). Whether Ft–Ds–Fj gradients and asymmetries are conserved in vertebrate systems has yet to be determined.

Segregation of cortical polarity proteins: Shaking hands with the enemy

The asymmetric segregation of Fz–Dsh–Fmi and Vang–Pk–Fmi complexes to opposite sides of the cell relies on their mutual exclusion intracellularly and their preferential binding between neighboring cells (Fig. 2 B; for review see Strutt and Strutt, 2009). There is mutual interdependence among core PCP components for their asymmetric localization. Depletion of any one core PCP component results in a loss of asymmetry of all the others. In addition, PCP asymmetry develops progressively from initially uniform distributions (Fig. 2 A). Thus, PCP asymmetry can be thought of not as a simple hierarchy of interactions, but the result of feedback amplification of an initial directional bias.

Intercellular interactions. PCP requires cell–cell communication, mediated by the transmembrane components of the core system, where it is thought that Fz–Fmi on one cell interacts with Vang–Fmi on its neighbor. These interactions are best understood in the *Drosophila* wing blade, where PCP controls the alignment of wing hairs along the proximal–distal axis (Figs. 1 A and 2, A and B). In the wing, Vang–Pk localize to the proximal face of each cell, whereas Fz–Dsh–Dgo localize distally adjacent to the wing hair (Figs. 1 C and 2, A and B; Axelrod, 2001; Strutt, 2001; Tree et al., 2002; Bastock et al., 2003; Das et al., 2004). By generating mutant clones and examining PCP localization at the clone border, the intercellular interactions between neighboring cells can be assessed in vivo. For example, when Fz is lacking within a clone, leaving only Vang–Fmi available at cell junctions, then Fz–Fmi in adjacent wild-type cells is recruited to the clone border (Chen et al., 2008). Vang mutant clones produce a similar effect, but in this case the excess Fz

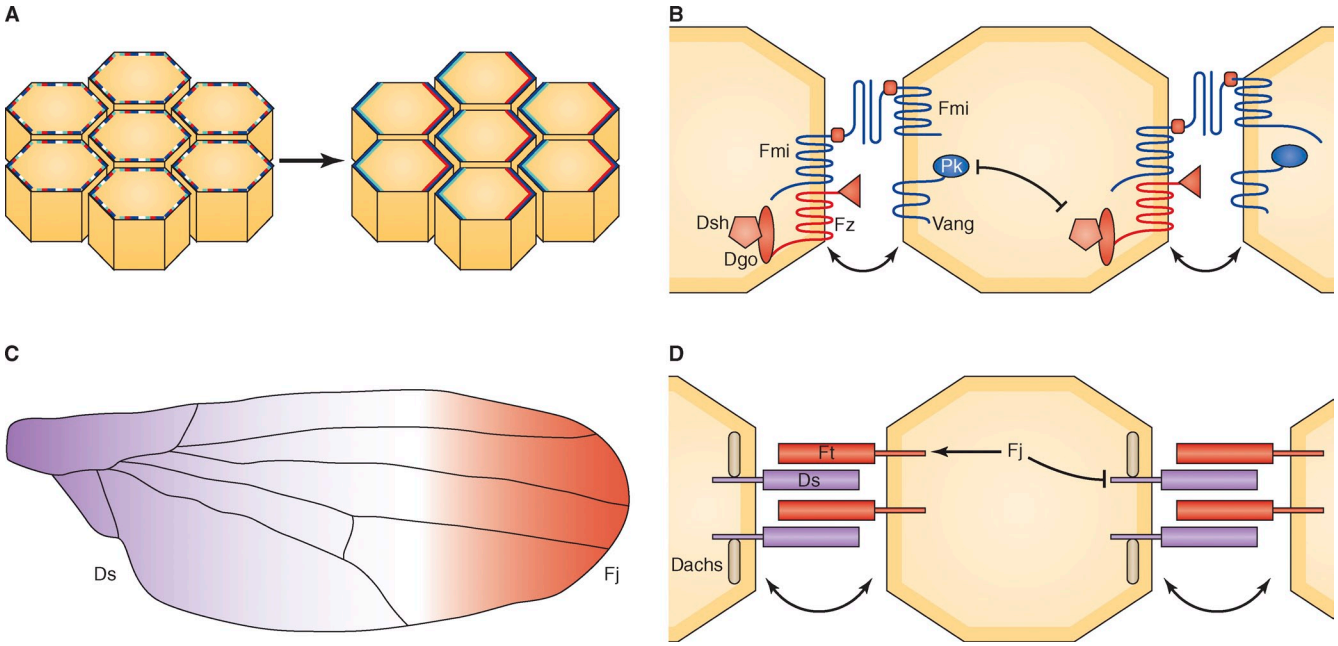

Figure 2. **Asymmetric localization of PCP components.** (A) PCP asymmetry develops progressively from an initially uniform distribution of core PCP proteins. Fz, Dsh, and Dgo (red) localize to the distal/posterior edge, whereas Vang and Pk (turquoise) localize to the proximal/anterior side. Fmi (dark blue) localizes to both sides, where it forms homodimers between neighboring cells. (B) Feedback interactions between core PCP components. A Fz–Fmi complex interacts preferentially with a Vang–Fmi complex between cells, whereas proximal and distal complexes antagonize one another within the cell. (C) Ds and Fj are expressed in opposing gradients in the *Drosophila* wing blade. Fj positively modulates Ft activity, leading to a gradient of Ft activity across the wing (not depicted). (D) Graded expression of Ds and Fj leads to asymmetric cellular localization of Ds and Ft, which form heterodimers between adjacent cells. Dachs, a downstream component of the Ft–Ds pathway, also localizes asymmetrically in association with Ds.

recruits Vang to clone borders (Bastock et al., 2003). What mediates these intercellular asymmetric interactions? One possibility is that Vang and Fz interact directly, and in vitro binding assays between the Fz extracellular domain and Vang suggest that this mechanism is possible (Wu and Mlodzik, 2008). However, mutants of Fz or Vang lacking their extracellular domains can still recruit one another between cells, which suggests that something else must bridge the two proteins (Chen et al., 2008). The seven-pass transmembrane cadherin, Fmi, likely performs this function. Fmi is essential for the junctional recruitment of Fz and Vang, and Fmi homodimers appear to be functionally asymmetric (Chen et al., 2008; Strutt and Strutt, 2008; Struhl et al., 2012). Clonal overexpression of Fmi preferentially recruits Fz to the clone border, even in the absence of Vang, which suggests that excess or unpaired Fmi is in a configuration that has higher affinity for Fmi–Fz than Fmi–Vang (Chen et al., 2008; Strutt and Strutt, 2008). Thus, Fmi may exist in two forms depending on whether it is paired with Fz or Vang, but the molecular basis for this difference is not known (Chen et al., 2008; Strutt and Strutt, 2008; Struhl et al., 2012).

Amplification of asymmetry. Intercellular Fz–Fmi and Vang–Fmi complexes can form between cells in any orientation, so how do they resolve into discrete and opposed asymmetric domains? One way is through clustering of Fz–Fmi and Vang–Fmi complexes of the same orientation, and the cytoplasmic PCP components are particularly important for this function. As PCP complexes grow increasingly asymmetric, they cluster into discrete puncta that are stably associated with the plasma membrane and are resistant to endocytosis (Strutt et al., 2011). FRAP analysis of Fz-containing puncta demonstrated that they are highly stable compared with diffuse Fz-GFP, and have limited lateral mobility within the membrane. In the absence of Dsh, Pk, or Dgo, the size, intensity, and stability of Fz-containing puncta are diminished (Strutt et al., 2011), whereas overexpression causes Fz accumulation and coalescence into larger puncta (Feiguin et al., 2001; Tree et al., 2002; Bastock et al., 2003). Although the precise mechanisms driving PCP puncta formation are not known, the cytoplasmic components do not affect endocytosis, which suggests that they contribute to puncta formation by clustering intercellular complexes (Strutt et al., 2011). Pk can interact homophilically (Jenny et al., 2003; Ayukawa et al., 2014), which might promote clustering of proximal Vang–Pk–Fmi complexes. It will also be interesting to determine whether the cytoskeleton is directly connected to PCP complexes to minimize lateral mobility within the membrane.

A second mechanism contributing to PCP asymmetry is directed transport. Live imaging of fluorescently tagged PCP proteins in pupal wings showed that Fz- and Dsh-containing particles travel across the cell in a proximal-to-distal direction (Shimada et al., 2006; Matis et al., 2014; Olofsson et al., 2014). These particles most likely represent endosomes undergoing transcytosis, as they arise from the proximal cortex and are labeled by the endocytic tracer FM4-64. This mechanism could serve to amplify asymmetry or even provide the initial polarity bias by removing proximal Fz–Dsh–Fmi complexes and transporting them to the distal side. Directed PCP transport is mediated by an array of subapical, noncentrosomal microtubules (MTs) that align along the proximal–distal axis, with the plus

ends oriented with a slight distal bias (Hannus et al., 2002; Shimada et al., 2006; Harumoto et al., 2010; Matis et al., 2014; Olofsson et al., 2014). Ft and Ds are required for proximal–distal MT alignment (Harumoto et al., 2010), which suggests that the Ft-Ds system may feed into the core PCP system by orienting cytoskeletal architecture to deliver Fz–Dsh–Fmi complexes to the distal edge of the cell.

Directed transport of Vang-containing endosomes has not been reported in flies, but selective trafficking could target Vang to specific membrane domains. In mammalian cells, exit of the Vang homologue Vangl2 from the trans-Golgi network (TGN) requires Arfrp1 (an Arf-like GTPase) and the clathrin adaptor complex AP-1, neither of which are required for the transport of a mammalian Fz homologue Fz6 or Fmi/Celsr1, which suggests that the differential sorting of PCP complexes to opposite sides of the cell could initiate at TGN export (Guo et al., 2013). Whether newly synthesized Vang and Fz proteins are transported to opposing cell surfaces from the TGN has not yet been explored.

Microtubule orientation also correlates with PCP asymmetry in mouse trachea epithelial cells, where PCP coordinates the alignment of motile cilia (Vladar et al., 2012). MTs are planar polarized with their plus ends oriented toward the Fz–Dvl domain, and disruption of MTs with nocodazole impairs core PCP localization. Similarly, MTs are needed to establish Pk asymmetry in gastrulating zebrafish embryos (Sepich et al., 2011). However, in the skin epithelium, MTs align perpendicular to the axis of PCP asymmetry (unpublished data). Thus, directed transport along MTs may not be required in all tissue types for the establishment of PCP asymmetry.

Negative regulation. Repulsive interactions between Vang- and Fz-containing complexes may also contribute to the amplification of asymmetry, and cytoplasmic proteins have been proposed to perform this function. Pk and Dgo both bind to Dsh in vitro, interacting with the same domain on Dsh in a mutually exclusive manner (Jenny et al., 2005). In addition, overexpression of Pk can prevent Dsh translocation to the membrane (Tree et al., 2002; Carreira-Barbosa et al., 2003), which suggests that Pk binding to Dsh could displace it from the proximal side of the cell. On the distal side, Dgo binding to Dsh would prevent association with Pk, thus enhancing Dsh distal localization. This increase in Dsh and Pk asymmetry would then positively feed back by clustering the transmembrane components into stable membrane domains.

Modulation of PCP protein levels by ubiquitin-mediated degradation also leads to feedback by restricting the amount of one PCP protein to antagonize another. In flies, regulation of Dsh by a Cullin-3-BTB E3 ubiquitin ligase complex limits its levels at cell junctions (Strutt et al., 2013a). Reduction of Cullin-3 leads to an increase in overall core PCP protein levels, a reduction of asymmetry, and defects in wing hair polarity, which is consistent with Dsh overexpression phenotypes (Strutt et al., 2013a). SkpA, a subunit of the SCF E3 ligase, regulates Pk levels by promoting its degradation in a Vang-dependent manner (Strutt et al., 2013b). In mice, Smurf E3 ligases ubiquitinate Pk and promote its local degradation by binding to phosphorylated Dvl2 (a mammalian homologue of Dsh; Narimatsu et al., 2009). Smurfs are required for Pk localization in the inner ear and floor plate, and their removal leads to defects in convergent extension (CE) and stereocilia alignment (Narimatsu et al., 2009). Thus, targeting Pk for degradation either balances total Pk protein levels or targets a specific pool of Pk for ubiquitination and proteasome degradation.

Tissue-level polarity cues: This way or that?

What provides the tissue-level polarity cue that biases core PCP asymmetry in one direction over another? This is perhaps the most fundamental, yet poorly understood, element of PCP. Current models propose that an upstream, graded cue provides an initial bias in PCP asymmetry by regulating the levels, localization, or activity of one or more of the core proteins. Gradients are attractive candidates for providing global polarity cues, as they can act across many cells and define the tissue boundaries over which polarity must be oriented.

Ft–Ds–Fj. Unlike the core proteins, Ds and Fj are nonuniformly expressed in the *Drosophila* eye, wing, and abdominal segments, and as such, the Ft–Ds module has been proposed to provide a global polarity cue (Fig. 2, C and D; for review see Ma et al., 2003; Yang et al., 2002; Thomas and Strutt, 2012; Matis and Axelrod, 2013). Ft and Ds are heterodimeric cadherins, regulated by the Golgi kinase Fj (Ishikawa et al., 2008; Brittle et al., 2010; Simon et al., 2010). The complementary expression patterns of Ds and Fj are thought to give rise to asymmetric Ft and Ds protein localization, with Ft and Ds localizing to opposite sides of each cell (Fig. 2 D; Ambegaonkar et al., 2012; Bosveld et al., 2012; Brittle et al., 2012). Because Fj positively regulates the activity of Ft, a gradient of Ft activity is expressed across the wing complementary to that of its ligand, Ds (Simon et al., 2010). Mutations in the Ft–Ds system give rise to swirling wing hair patterns, and disrupt the global alignment of core PCP proteins, but not their asymmetric distributions.

An appealing model for symmetry breaking in the early *Drosophila* wing is that cellular asymmetries of Ft–Ds polarize MT organization and promote the distal transport of Fz–Dsh–Fmi vesicles (Shimada et al., 2001, Harumoto et al., 2010; Matis and Axelrod, 2013; Matis et al., 2014). This would produce an initial bias in Fz–Dsh localization, which would then be amplified by feedback interactions. However, several pieces of evidence have prevented the model from gaining universal acceptance. First, Ds and Fj gradients are oriented in opposite directions with respect to the core PCP proteins in the wing compared with the eye and abdomen. This discrepancy has been rectified with the finding by two independent groups that cells interpret Ft–Ds–Fj gradients differently depending on which of two Pk isoforms is expressed (Ayukawa et al., 2014; Olofsson et al., 2014). Second, the Ft–Ds system can orient PCP independently of the core pathway, and thus the two systems orient polarity in parallel, as opposed to in a single, common pathway (Casal et al., 2006). Third, Ft–Ds mutations affect core PCP orientation only regionally in the wing, which suggests that, if Ft–Ds provides a global bias, other, redundant cues must also exist (Matakatsu and Blair, 2006; Matis et al., 2014). Finally, the direction of Ft–Ds and core PCP asymmetry diverges late in wing development, where

the two systems become completely uncoupled. Intriguingly, the extent of coupling depends on which isoform of Pk is expressed (Merkel et al., 2014). Perhaps the simplest explanation for Ft–Ds function is that it can both transmit polarity information independent of the core system and organize the cytoskeleton to provide an initial bias of core PCP asymmetry, but which mechanism predominates depends on the tissue and developmental stage.

Wnts. Wnt proteins have long been considered attractive candidates to provide tissue-level polarity cues because Fz and Dsh are primary components of the Wnt–β-catenin signaling pathway. Wnts are secreted glycoproteins that bind to Fz and other receptors, and often display graded expression. In vertebrates, Wnts are clearly important regulators of PCP, but whether they act instructively or permissively is unclear. In zebrafish, Wnt5a and Wnt11 are required for CE movements during gastrulation, but uniform expression of Wnt11 rescues the mutant phenotype, which suggests that it is permissive rather than instructive (Heisenberg et al., 2000; Kilian et al., 2003). Wnt5a is expressed in a gradient along the axis of polarity in the mouse inner ear, where it interacts genetically with Vangl2 in cochlear hair cell orientation (Qian et al., 2007). In the mouse limb, Wnt5a and its atypical receptor Ror2 are required for limb elongation and the asymmetric localization of Vangl2 at the proximal face of converging and extending chondrocytes (Gao et al., 2011). Wnt5a is expressed in a distal-to-proximal gradient, which induces a gradient of Vangl2 phosphorylation. The functional consequences of Vangl2 phosphorylation are unknown but Vangl2 cellular asymmetry appears to be strongest distally, where Wnt5a and Vangl2 phosphorylation levels are highest (Gao et al., 2011).

While several studies had argued against the involvement of Wnt proteins in *Drosophila* PCP (Lawrence et al., 2002; Chen et al., 2008), it was recently discovered that Wingless (Wg) and Wnt4a act redundantly to orient PCP in the wing, particularly near the wing margin (Wu et al., 2013). Misexpression of Wg or Wnt4a reorients wing hair polarity in a pattern reminiscent of Fz loss of function, which suggests that Wnt gradients may orient polarity by antagonizing Fz. Consistently, the ability of Fz and Vang to recruit one another between adjacent cells in culture was inhibited by the addition of Wg or Wnt4a, which suggests that Wnts could provide a polarizing cue by diminishing Fz–Vang interactions at the margin of the wing, where Wnt expression is highest (Wu et al., 2013). However, Wnt4a overexpression also reorients MT alignment, suggesting that Wnts may act as polarity cues thorough an effect on the cytoskeleton (Matis et. al, 2014). Alternatively, Sagner et al. (2012) suggest that Wg orients core PCP indirectly through its effects on wing patterning and growth. Although the evidence for Wnt gradients as global PCP cues is accumulating, the mechanisms by which they regulate core protein levels or activity remain to be elucidated.

Mechanical forces. Anisotropic mechanical forces that accompany growth and morphogenesis can also provide global polarizing cues. During wing development, PCP reorients in response to extensive morphogenetic changes that elongate the wing along the proximal–distal axis. In early pupal wings, PCP aligns toward the wing margin and then reorients during wing elongation and contraction of the wing hinge (Aigouy et al., 2010). These morphogenetic changes have broad effects on cell behavior, inducing cell elongation, oriented divisions, and cell rearrangements with a concomitant reorientation of PCP. Severing the wing pouch from the hinge blocks cell flows and PCP reorientation, which suggests that the anisotropic tension from hinge contraction drives tissue flow and the reorientation of polarity (Aigouy et al., 2010). Although this model doesn't explain what initially biases PCP, it does demonstrate how the morphogenetic processes that shape tissues can completely remodel global PCP alignment. This is an attractive model to explain how PCP aligns over very large tissues, like the mammalian skin, where hairs consistently reorient along regions of extensive tissue elongation such as the face, limbs, and ears.

Downstream effectors of PCP: Steering the wheel

If PCP is the cell's compass, it is also the steering wheel, directing downstream, polarized cell behaviors in response to global directional cues. PCP can polarize a wide range of cell behaviors, which suggests that it can intersect with numerous downstream effectors. We focus here on three examples where the molecular mechanisms linking core PCP to their polarized outputs have recently been elucidated.

Distal positioning of wing hairs. Each cell of the *Drosophila* wing blade emits a single actin-rich protrusion from its distal edge. The placement of the wing hair strongly correlates with the position of Fz–Dsh–Fmi, which suggests that core proteins may localize cytoskeletal regulators to distinct positions within the cell (Strutt and Warrington, 2008). On the proximal side, Vang recruits a group of proteins that negatively regulate actin prehair formation: Inturned, Fuzzy, and Fritz (Adler et al., 2004; Strutt and Warrington, 2008). These three proteins regulate Multiple Wing Hairs, a GTPase-binding/formin-homology 3 (GBD/FH3) domain protein thought to repress actin polymerization (Strutt and Warrington, 2008; Yan et al., 2008). This restricts actin nucleation to distal positions within the cell, and in the absence of Multiple Wing Hairs, ectopic actin bundles form across the apical surface (Wong and Adler, 1993). On the distal side, casein kinase 1 γ CK1g/gilamesh is required to further refine prehair nucleation to a single site through a parallel mechanism involving Rab11-dependent vesicle traffic to the site of prehair formation (Gault et al., 2012). Rho and Rho kinase (Drok) have also been implicated in wing hair formation, but their roles are difficult to dissect due to the numerous functions of Rho in cell shape and cell division (Winter et al., 2001; Yan et al., 2009).

Actomyosin contraction and convergent extension (CE). CE was the first vertebrate process to be linked molecularly to PCP (Wallingford et al., 2000). During CE, mesenchymal cells elongate, form mediolateral-directed protrusions, and intercalate mediolaterally, narrowing the mediolateral axis while simultaneously lengthening the anterior–posterior (A-P) axis (Fig. 3 A; Keller, 2002). Mediolateral polarization, elongation, and intercalation are lost when core PCP components are disrupted, leading to a failure in CE (Tada and Smith,

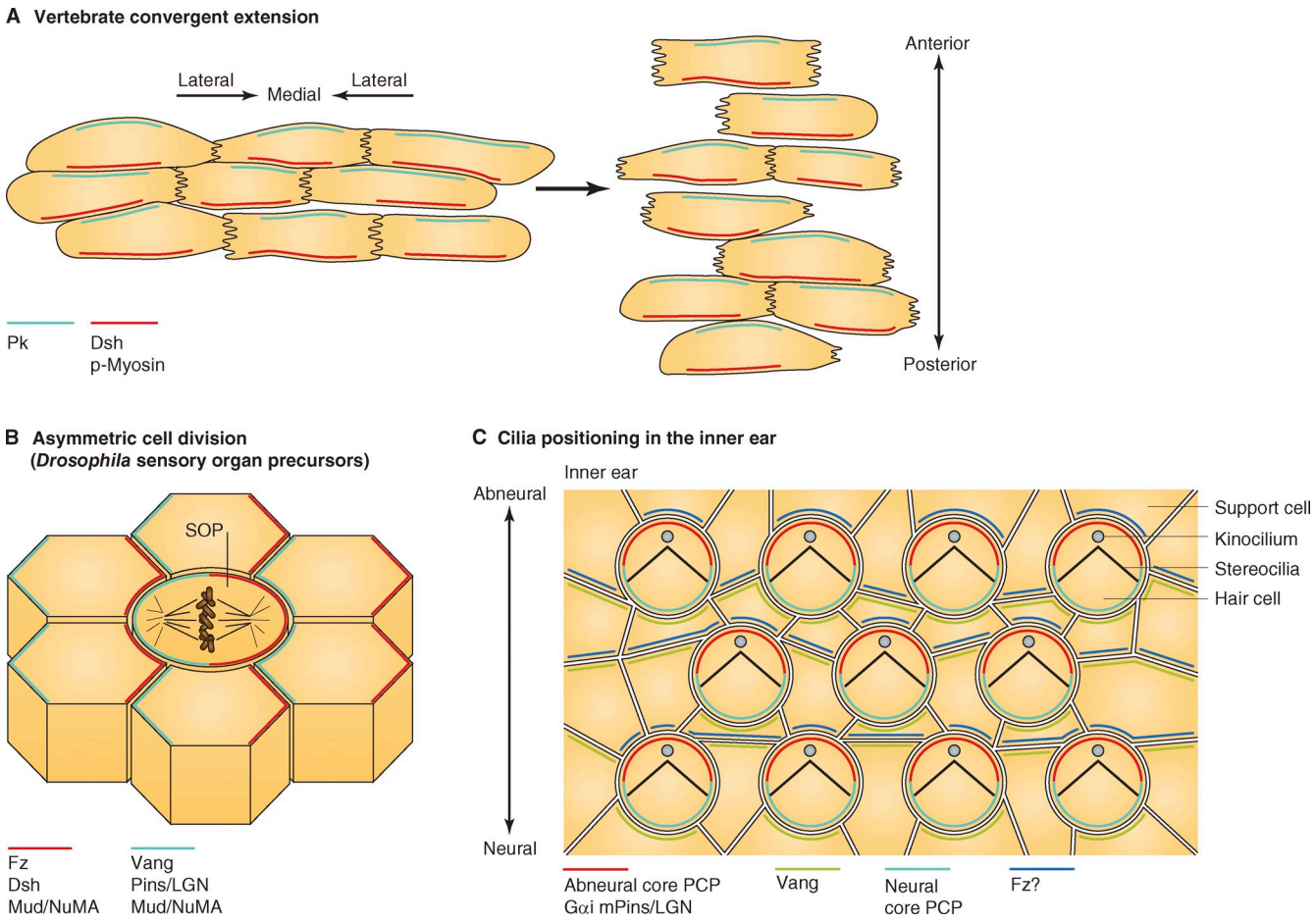

Figure 3. **Polarized cell behaviors controlled by PCP.** (A) PCP drives convergent extension (CE). CE in vertebrates is driven by mediolateral intercalation, which narrows the mediolateral axis while simultaneously lengthening the A-P axis. Mediolateral intercalation is accompanied by cell polarization and elongation and the formation of mediolateral protrusions, all of which require core PCP function. Pk localizes anteriorly (Ciruna et al., 2006; Yin et al., 2008), whereas Dsh localizes posteriorly (Yin et al., 2008). In addition, PCP proteins recruit myosin to A-P cell borders, leading to actomyosin contractility and junctional shrinking. (B) Asymmetric cell division. *Drosophila* sensory organ precursors (SOPs) divide asymmetrically along the epithelial plane, giving rise to distinct anterior and posterior daughters. Spindle alignment along the A-P axis is PCP dependent. Dsh interacts with Mud/NuMA and the dynein complex posteriorly while Vang links Pins/LGN-Mud/NuMA-dynein on the anterior. This links astral MTs to the A-P cortex, bringing the spindle into register with the A-P axis. (C) Positioning of the kinocilium in the inner ear. The placement of kinocilium in sensory hair cells of the inner ear determines the position of V-shaped stereocilia bundles. Gαi and mPins/LGN localize on the abneural side on the hair cell, where they are required for abneural positioning the MT-based kinocilium. The collective alignment of kinocilia and stereocilia bundles across the epithelium requires the core PCP component Vangl2. Vangl2 (light green) localizes to the abneural side of supporting cells. Whether Fz (dark blue) associates on the opposite face is not yet clear (Ezan et al., 2013).

2000; Wallingford et al., 2000; Goto and Keller, 2002; Jessen et al., 2002). While several PCP-dependent mechanisms have been proposed to mediate CE movements, two recent studies provide direct mechanistic links between asymmetrically localized core PCP components and CE behaviors. In neuroepithelial cells, PCP specifies the localization of myosin to the A-P faces of intercalating cells. Fmi/Celsr1 and Dvl recruit the formin DAAM1 to the A-P junction, which in turn binds and activates PDZ-RhoGEF. This likely activates RhoA and myosin contractility specifically at A-P junctions, resulting in medial-directed cell intercalation and neural plate bending (Nishimura et al., 2012). A similar mechanism was found to drive CE movements of mesenchymal cells during *Xenopus* gastrulation. In this case, Fritz and Dsh help to localize septins to mediolateral vertices, where they spatially restrict cortical actomyosin contractility and junctional shrinking to A-P cell edges, thus driving cell intercalation (Fig. 3 A; Kim et al., 2010; Shindo and Wallingford, 2014). Together these studies show how asymmetric PCP localization produces collectively polarized cell behaviors through spatial modulation of the cytoskeleton.

Positioning of centrosomes and cilia. PCP regulates the positioning of MT-based structures including the mitotic spindle and cilia. In *Drosophila* sensory organ precursors and early zebrafish embryos, PCP controls mitotic spindle orientation along the epithelial plane by interacting with the highly conserved spindle orientation complex, which links astral MTs to the cell cortex through Mud/NuMA-mediated recruitment of the dynein complex (Ségalen et al., 2010). To orient the spindle, posteriorly localized Dsh binds to Mud/NuMA, which recruits the dynein complex and astral MTs to the posterior cortex. On the anterior side, Pins/LGN recruits Mud/NuMA, bringing the spindle into A-P alignment (Fig. 3 B). Similarly, PCP was recently shown to interact with the spindle orientation machinery to position the kinocilium in nondividing cells of the inner ear

(Ezan et al., 2013; Tarchini et al., 2013). In vestibular hair cells, Gαi and mPins/LGN localize to the abneural cortex, opposite Vangl2, where they are required for kinocilium positioning and subsequent alignment of stereocilia bundles (Fig. 3 C; Ezan et al., 2013). MT plus ends and dynein also show an abneural bias suggesting that Gαi-mPins/LGN induces pulling on MTs by a similar mechanism that orients the centrosome during spindle orientation. Vangl2 is required for the alignment of Gαi-Pins/LGN crescents between cells, coordinating kinocilia positioning and stereocilia polarity across the tissue (Fig. 3 C; Ezan et al., 2013). Thus the PCP pathway co-opts the spindle orientation machinery to specify not only the division plane but also cilia position in nondividing cells. As PCP is required for asymmetric cilia positioning in a wide range of cell types, including the node (Antic et al., 2010; Borovina et al., 2010; Song et al., 2010; Hashimoto et al., 2010), it will be interesting to determine whether this mechanism is conserved.

Concluding remarks

PCP is a fundamental and highly conserved process coordinating a vast number of polarized cell behaviors. While the number of functions ascribed to PCP continues to grow, an understanding of the mechanisms establishing PCP is still far from complete. The development of cellular asymmetry from uniform distributions is not well understood, and will benefit from recent advances in high-resolution, time-lapse imaging with photoconvertible fluorescent tags. Other important issues to resolve include deciphering the structural domains and biochemical interactions mediating intercellular communication, identifying the global cues that orient PCP especially in vertebrates, and deciphering the mechanisms by which complex multicellular structures, like lung branches and hair follicles, are oriented by the PCP machinery.

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