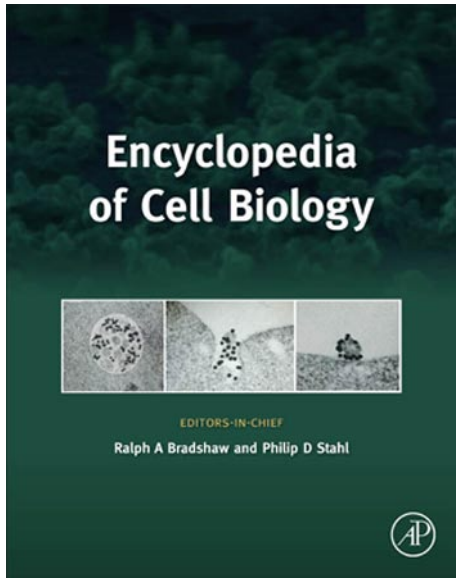

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CELL COMMUNICATION: CELLULAR OUTCOMES

Contents

Regulation of Cell Polarity

JD Axelrod, Stanford University School of Medicine, Stanford, CA, USA

Introduction

Defects in planar cell polarity (PCP) result in a range of developmental anomalies (birth defects) and diseases including neural tube closure defects (reviewed in Simons and Mlodzik, 2008; Copp and Greene, 2009), polycystic kidneys (reviewed in Simons and Walz, 2006; Wallingford, 2006; Wang and Nathans, 2007; Simons and Mlodzik, 2008), conotruncal heart defects (Garriock *et al.*, 2005; Phillips *et al.*, 2005, 2007; Henderson *et al.*, 2006), deafness (Curtin *et al.*, 2003; Montcouquiol *et al.*, 2003, 2006; Lu *et al.*, 2004; Davies *et al.*, 2005; Wang *et al.*, 2005, 2006a,c; Deans *et al.*, 2007; Qian *et al.*, 2007; Jones *et al.*, 2008), and situs inversus (reviewed in Santos and Reiter, 2010). PCP polarizes skin and hair (Guo *et al.*, 2004; Wang *et al.*, 2006b,c; Devenport and Fuchs, 2008), and is also believed to underlie directed migration during wound healing (Lee and Adler, 2004; Caddy *et al.*, 2010) and invasion and metastasis of malignant cells (Weeraratna *et al.*, 2002; Lee *et al.*, 2004; Katoh, 2005; Coyle *et al.*, 2008; Kuriyama and Mayor, 2008). Despite the obvious importance of this pathway in human physiology and development, and considerable attention and progress in the past 15 years, major questions about the signaling mechanism remain to be answered.

Most of our mechanistic understanding of PCP signaling comes from work in *Drosophila*, in which numerous tissues, including the wing, eye, and abdomen display manifestations of PCP (Tree *et al.*, 2002a; Zallen, 2007; Simons and Mlodzik, 2008). Of these, the most thoroughly studied planar polarized tissue is the fly wing, in which each cell produces a trichome (or 'hair'), that in wild type emerges from the distal side of the cell and points distally (**Figure 1**; Wong and Adler, 1993). During polarization of hair cells, cytoskeletal regulators are recruited to proximal and distal sides of the cell and control the localization of actin polymerization and bundling to ensure distal localization of hair emergence (Wong and Adler, 1993; Strutt and Warrington, 2008; Yan *et al.*, 2009; Lu *et al.*, 2010). Mutants either fail to choose a side, thus producing a hair from the center of the cell, or choose an incorrect side, resulting in an incorrectly oriented hair. Cells of the abdominal epithelium produce multiple posteriorly oriented hairs that emerge from the posterior side of the cell and point posteriorly.

Polarity in the eye results from the differentiation of the initially equipotent R3/R4 photoreceptor progenitors into an equatorial R3 and a polar R4 (**Figure 1**). Here, the key distinction is not between opposite sides of the same cell, but between adjacent sides of this pair of progenitor cells. A competition for Notch signaling activation between the R3/R4 pair becomes biased by the PCP signal at the intercellular junction so that the equatorial cell always expresses low Notch levels and becomes R3. PCP mutants lead either to incorrect R3/R4 fate decisions, or in some cases, indistinctly differentiated pairs of R3/R4 cells (Zheng *et al.*, 1995; Cooper and Bray, 1999).

On the notum, PCP controls the orientation of an asymmetric cell division in the sensory organ precursor (pI) cells. pI cells differentiate within the epithelium and divide asymmetrically to produce an anterior pIIb daughter and a posterior pIIa daughter cell. The PCP pathway distinguishes anterior and posterior sides of the pI cell through asymmetric interactions with its anterior and posterior neighbors. The pI cell therefore seems to become polarized much like the surrounding epithelial cells do, but it uses this polarity to position cell fate determinants and the mitotic spindle prior to an asymmetric division. PCP mutants cause this division to be incorrectly oriented.

Mechanosensory organs are composed of a multicellular bristle, and an associated bract (**Figure 1**). These organs are arranged in precise patterns, and have an intrinsic polarity that is evident at several levels. The bract, elaborated by a single cell, resembles a hair, and points distally. The shaft of the bristle points distally, similar to the bracts and hairs. In addition, the base of each shaft is surrounded by a socket cell, and the vector defined by each socket-bract pair points proximally. Each of these polarities can be disturbed by PCP mutants, and may vary independently (Held *et al.*, 1986).

The molecular machinery that directs these morphogenetic events downstream of the core module is specific to the tissue. For example, during polarization of hair cells, cytoskeletal regulators are recruited to proximal and distal sides of the cell and control the localization of actin polymerization and

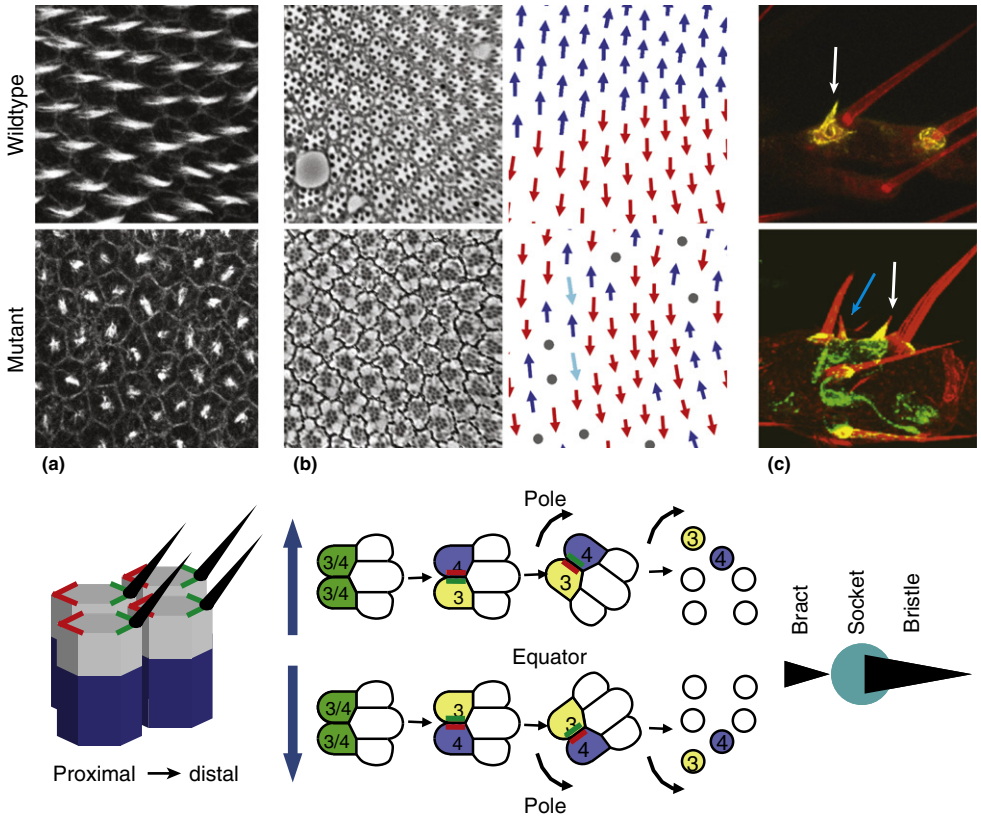

Figure 1 Manifestations of wild type and mutant PCP signaling. (a) Phalloidin stains showing the actin-based emerging hairs (prehairs) growing from the distal side of each cell and pointing distally in wild type, and growing from the center of the cell in a PCP mutant wing. Below, a cartoon of each cell, with green and red bars schematizing the subcellular localization of PCP proteins once cells are polarized. (b) Polarity in a wild-type and a mutant eye. Sections reveal the rhabdomeres of seven photoreceptor cells in each ommatidium, each forming a chiral structure with a particular orientation. In wild type, the two chiral forms are on opposite sides of an obvious equator, and point in opposite directions. In the mutant, chiralities are interspersed, and some ommatidia have symmetrical form. Many ommatidia are also misrotated. The schematic shows the PCP-dependent differentiation of the R3 and R4 cells, and subsequent rotation and morphogenesis of each ommatidium. (c) Bracts associated with mechanosensory bristles on the legs of a wild type and a PCP mutant fly. In wild type, the bract is always induced from the epithelial cell directly proximal to the socket and shaft (white arrow). In the mutant, one bract is correctly positioned (white arrow), while the other is incorrectly located on the distal side, and points proximally (blie arrow).

bundling to ensure distal localization of hair emergence (Wong and Adler, 1993; Strutt and Warrington, 2008; Yan *et al.*, 2009; Lu *et al.*, 2010). In contrast, tissue-specific control of bristle and bract polarization represents the interaction of the PCP modules with a more complex multicellular system (Peng *et al.*, 2012).

Clones of cells that are either mutant for a core PCP component or that overexpress a core component stereotypically perturb, or fail to perturb, the polarity of cells in nearby nonmutant tissue (Gubb and Garcia-Bellido, 1982; Vinson and Adler, 1987; Taylor *et al.*, 1998; Adler *et al.*, 2000). This is most obvious in the wing and eye, where arrays of polarizing cells are present (**Figure 2**). In the cases when polarity is perturbed, polarities are reversed to either abnormally point toward or away from the clone. This phenomenon is referred to as domineering nonautonomy, and together with the corresponding abilities of these clones to reorganize the localization of core PCP proteins in these cells (see below) has provided fertile ground for experiments aimed at understanding the mechanism of core PCP signaling.

In vertebrates, many aspects of PCP signaling identified in flies are conserved, but genetic analyses indicate that a more diverse array of morphologic events is controlled by the same components together with additional regulators not present in flies (Jones and Chen, 2007; Wang and Nathans, 2007; Zallen, 2007; Simons and Mlodzik, 2008). Here, we will focus on our emerging understanding of PCP signaling mechanisms derived from studies in flies.

A Modular Signaling System

Genetic and molecular analyses in several *Drosophila* tissues have identified components of the PCP signaling mechanism, and have suggested that they may be divided into three classes of functional modules: global directional modules, a core module, and a suite of tissue-specific effector modules that respond to the upstream modules to produce morphological asymmetry in individual tissues (Tree *et al.*, 2002a). The global directional modules link tissue-level directional information

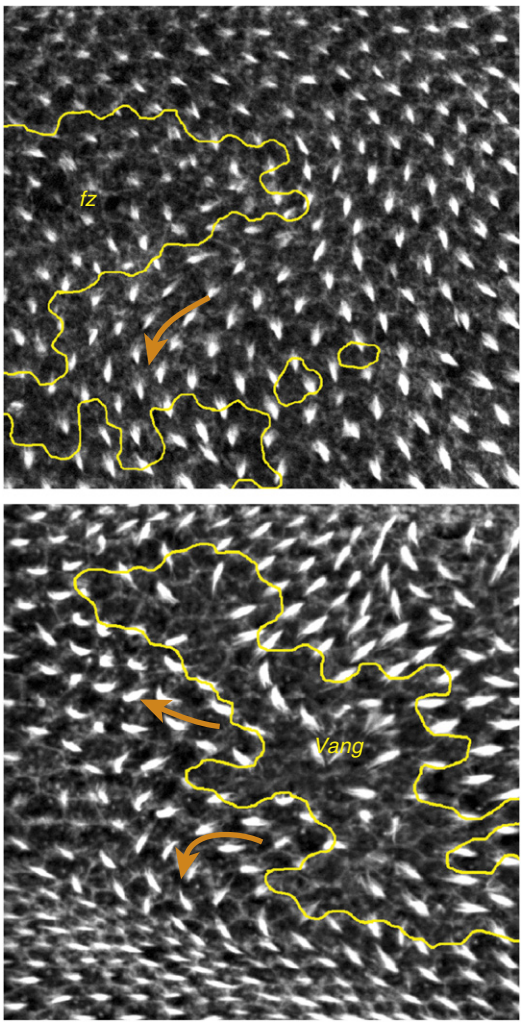

Figure 2 Domineering nonautonomy near a *fz* and a *vang* mutant clone in the wing, visualizing the emerging prehairs with phalloidin stain. Clones were genetically marked (not shown) and are surrounded by the yellow lines. In a wild-type wing, prehairs point distally. Note that prehairs are reoriented to point toward the *fz* clone and away from the *vang* clone (orange arrows). They therefore perturb polarity on opposite sides of the clone.

to local cell polarization. The core module amplifies molecular asymmetry within cells while linking the polarity of cells with their neighbors, producing a coordinated polarization across the tissue. The tissue-specific modules act as effectors for a diverse group of morphological readouts of the molecular polarity produced by the upstream modules.

The first recognized and best understood global module is the Fat/Dachsous/Four-jointed (Ft/Ds/Fj) module (**Figure 3**). This module serves to convert tissue-level expression gradients to subcellular gradients of Ft–Ds heterodimer localization (Mahoney *et al.*, 1991; Clark *et al.*, 1995, 2002; Adler *et al.*, 1998; Yang *et al.*, 2002; Ma *et al.*, 2003; Lawrence *et al.*, 2004). It consists of the atypical cadherins Ft and Ds, that form heterodimers which may orient in either of two directions at any apical cell–cell boundary, and the Golgi resident protein Four-jointed (Fj) (Villano and Katz, 1995; Zeidler *et al.*, 2000; Yang *et al.*, 2002; Ma *et al.*, 2003). Fj acts as an ectokinase on both Ft and Ds (Ishikawa *et al.*, 2008), to make Ft a stronger ligand, and Ds a weaker ligand, for the other (Brittle *et al.*, 2010; Simon *et al.*, 2010). As Fj and Ds are expressed in gradients across tissues (Zeidler *et al.*, 1999; Casal *et al.*, 2002; Yang *et al.*, 2002; Ma *et al.*, 2003; Lawrence *et al.*, 2004), the result is a larger fraction of Ft–Ds heterodimers in one orientation relative to the other (Ma *et al.*, 2003). This molecular asymmetry is predicted to be subtle, but can be detected at early stages of development when the Ds and Fj gradients are steeper (Ambegaonkar *et al.*, 2012; Bosveld *et al.*, 2012; Brittle *et al.*, 2012). Many elements of this relatively elegant and simple model are likely to be correct, yet it is clear that it is far from a complete picture, and important puzzles remain. This mechanism will not be discussed at length here, as it was recently reviewed (Matis and Axelrod, 2013).

For some time, Wnts have been known to participate in PCP signaling in vertebrates (Vladar *et al.*, 2009; Goodrich and Strutt, 2011; Wallingford, 2012), and recently, a potential role for Wnts, likely as global signals, has been proposed in flies, where Wnt4 and Wg have been suggested to function as redundant signals that act near the wing margin (Wu and Mlodzik, 2008). The localized expression of these diffusible molecules at the wing margin suggests the possibility that they may signal by forming gradients, but little is yet known about their mechanism of action. Studies of the *Drosophila* abdomen have led to the suggestion of yet another type of global signaling information. The Ft/Ds/Fj mechanism clearly contributes to PCP in the abdomen, but may not explain all of global signaling function. To date, there is no firm evidence pointing to the identity of an additional global signal (Lawrence *et al.*, 2002).

The core module comprises the first recognized molecular components of PCP signaling. Several decades of study have led to the understanding that it acts both to amplify asymmetry, and to coordinate polarization between neighboring cells, producing a local alignment of polarity. Proteins in the core signaling module, including the seven-pass transmembrane protein Frizzled (Fz) (Vinson and Adler, 1987; Vinson *et al.*, 1989), the multi-domain protein Dishevelled (Dsh) (Klingensmith *et al.*, 1994; Thiesen *et al.*, 1994), the Ankryin repeat protein Diego (Dgo) (Feiguin *et al.*, 2001), the four-pass transmembrane protein Van Gogh (Vang; a.k.a. Strabismus) (Taylor *et al.*, 1998; Wolff and Rubin, 1998), the Lim domain protein Prickle (Pk) (Gubb *et al.*, 1999), and the seven-transmembrane atypical cadherin Flamingo (Fmi; aka Starry night) (Chae *et al.*, 1999; Usui *et al.*, 1999; reviewed in Zallen, 2007), adopt asymmetric subcellular localizations that predict the morphological polarity pattern such as hairs in the fly wing (Usui *et al.*, 1999; Axelrod, 2001; Feiguin *et al.*, 2001; Strutt, 2001; Tree *et al.*, 2002b; Bastock *et al.*, 2003). These proteins form intercellular complexes that communicate at cell boundaries, recruiting one group to the distal side of cells, and the other to the proximal side, through the action of a poorly understood feedback mechanism, thus aligning the polarity of adjacent cells (Tree *et al.*, 2002b; Amonlirdviman *et al.*, 2005). Though not formally established, this mechanism has all the hallmarks of bistability. The unpolarized state is predicted to be metastable and an input bias, or fluctuations caused by

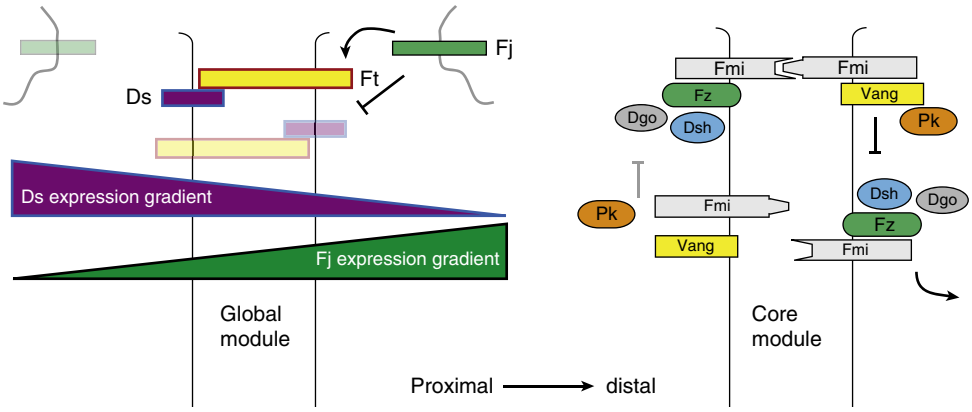

Figure 3 Schematics of the Ft/Ds/Fj global and the core modules. Organization of components at the junction between two cells is depicted. Gradients of Fj and Ds expression lead to a slight excess of Ft–Ds heterodimers at each interface. The core module is depicted as undergoing mutual inhibition, with the proximal components Vang and Pk disrupting the Fz-Dsh distal components. This particular competition was won by the upper complex, in the wild-type orientation.

noise, is expected to bias a coordinated polarization that will then amplify in magnitude. Indeed, this behavior has been captured by a variety of mathematical modeling frameworks for PCP signaling (Lawrence *et al.*, 2004; Amonlirdviman *et al.*, 2005; Le Garrec *et al.*, 2006; Le Garrec and Kerszberg, 2008; reviewed in Axelrod and Tomlin, 2011).

It is important to point out that the core module mechanism has no intrinsic directionality; allowed to polarize in the absence of a global directional signal, it is expected (and indeed seen in experiments and in simulations; reviewed in Axelrod and Tomlin, 2011) to achieve locally coordinated polarity that produces swirling patterns not respecting the global tissue axes. The global signals are therefore envisaged as providing subtle directional inputs that would both bias the initiation of polarization in a given direction and sustain the orientation of polarization during disrupting events such as cell divisions and morphogenetic rearrangements that require realignment of the polarization axis.

The segregation of proximal and distal core PCP proteins to opposite sides of the cell is a molecular marker of cell polarization, and correlates intimately with the various morphological polarization responses. For example, trichomes develop at the side of the cell where the distal proteins Fz and Dsh localize in wing cells, and Delta is activated and Notch repressed in the prospective R3 cell where Fz and Dsh localize (**Figure 1**).

Principles of Collective Polarization

On theoretical grounds, one can posit that generation of cell polarity requires two coordinated signaling events. First, accumulation of a cell polarity factor, P, must be self-enhancing, and second a long-range signal is required to inhibit accumulation of the same factor (**Figure 4**; Meinhardt, 2007). This has been modeled in single cells, and studied experimentally in systems such as budding yeast and migrating neutrophils, where, by definition, both signals are intracellular.

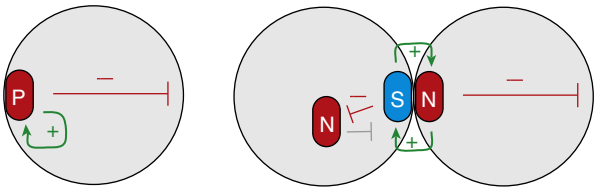

Figure 4 Cartoons of activities required for cell polarization in a single cell using only intracellular interactions (left) and using both intracellular and intercellular interactions (right).

Intracellular local self-enhancement can result from cooperative interactions between components of the polarity factor, for example. Long-range intracellular inhibition may result from a separate diffusing inhibitory molecule, or perhaps more simply, by limiting the amounts of one or more components of the polarity factor, thereby causing depletion and suppression of accumulation across the cell as a single locus stochastically becomes predominant and more rapidly accumulates the factor.

While the same principles apply in polarization of multicellular assemblies, the possibility for intercellular signaling provides additional routes to fulfill these two functions. Given a system with two polarity complexes that have the ability to recruit each other across intercellular boundaries like North and South poles of magnets, one can hypothesize that the intracellular long-range inhibition can be complemented, or even replaced, by an intercellular signal in which accumulation of North on one side of a given cell attracts components of South to the adjacent side of the neighboring cell. Since South and North repel each other, this will inhibit North from accumulating adjacent to it's location in the first cell, thus providing a long-range inhibition, but in the neighbor rather than in the original cell. Furthermore, local self-enhancement can proceed by a related mechanism. North in the first cell attracts South in the neighbor, which repels North. By repelling North, accumulation of additional South in the first cell is

diminished. Physicists have thoroughly modeled these types of systems.

Feedback Control of Core Amplification

Experimental evidence suggests that the core PCP proteins function, at least in part, through intercellular interactions akin to those described above. The wild-type distributions of proximal and distal core proteins to opposite sides of the cell, and the rearrangements observed around mutant or overexpressing clones have long suggested just such a North–South relationship between proximal and distal proteins (see e.g., Tree *et al.*, 2002b; Strutt and Warrington, 2008; Wu and Mlodzik, 2008), and this was eventually demonstrated formally (Chen *et al.*, 2008). Here, North and South can be equated to Fz and Vang. Their interaction requires an additional factor, the atypical cadherin Fmi that forms homodimers that participate in the complex. Of the core PCP proteins, only Fmi is required, in both cells, to mediate this interaction.

The asymmetrically localized subcellular complexes, with Fz on the distal side and Vang on the proximal side of adjacent cells, communicate information bidirectionally between those cells (Strutt and Strutt, 2007; Chen *et al.*, 2008). This is perhaps most simply illustrated by the observation that cells on either side of adjacent *vang* and *fz* mutant clones both strongly polarize, indicating that cells with only the Fz complex and cells with only the Vang complex can strongly polarize a neighboring cell (Strutt and Strutt, 2007). Fmi homodimers are essential for this communication (Usui *et al.*, 1999; Bastock *et al.*, 2003; Lawrence *et al.*, 2004; Strutt and Strutt, 2007; Chen *et al.*, 2008). It has been shown that, rather than acting simply as a scaffold for complex assembly, information passes bidirectionally through the Fmi bridge that, although a homodimer, is functionally, and presumably structurally, asymmetric (Chen *et al.*, 2008). This is evident from the observation that clones of cells overexpressing Fmi, but lacking both Fz and Vang retain the ability to repolarize neighboring cells. Competing models have alternately suggested that information only need flow through the Fmi homodimers (Chen *et al.*, 2008), or that Fz and Vang directly interact to mediate signal transmission (Wu and Mlodzik, 2008).

According to this understanding, these components can provide the mutual recruitment needed, while the mutual inhibition needed for the North–South repulsion is thought to be provided by the cytosolic PCP factors Pk, Dsh, and Dgo. A more detailed discussion of how these interactions might occur follows below.

The recruitment of North and South across intercellular boundaries into complexes, in the form of Fz–Fmi:Fmi–Vang complexes, can occur in either orientation at any given intercellular boundary. Long-range intercellular inhibition requires that, in addition, North exclude South, or South exclude North, or both, within each cell. Only indirect evidence for this mechanism currently exists. This kind of model, on a conceptual level, was presciently proposed by Adler *et al.* (1997), but at the time, little molecular context was available (Taylor *et al.*, 1998). A somewhat more explicit model was subsequently proposed based on the observation that Pk, which accumulates with Vang (on the proximal side, in wild type), was able to block Fz-dependent recruitment of Dsh to the cell cortex in cell cultures. Coupled with the phenomenological observations that proximal and distal proteins always seem to segregate to opposite sides when polarization occurs, one could infer that mutual inhibition occurs (Tree *et al.*, 2002b; Bastock *et al.*, 2003; Amonlirdviman *et al.*, 2005). However, the network of interactions has not been demonstrated, and it is difficult to parse out whether, at a wild-type intercellular junction, the exclusion of Fz/Dsh by Vang/Pk relies on exclusion within one cell or the loss of recruitment by the neighbor.

Asymmetric Fz–Fmi:Fmi–Vang complexes can form in the absence of the cytosolic factors, and can transmit polarity information under conditions in which differences are enforced between cells. When differences are not enforced between cells, Dsh, Pk, and Dgo functions are required for the feedback-mediated amplification of the asymmetry that develops at proximal–distal intercellular boundaries (Lawrence *et al.*, 2004; Strutt and Strutt, 2007; Chen *et al.*, 2008). In their absence, asymmetry is not amplified, and core PCP components remain more or less uniformly distributed around the cell.

As seen in wild type, core PCP proteins are not evenly distributed at intercellular junctions, but exist in uneven distributions, giving the appearance of being concentrated into aggregates, or puncta in some locations. This punctate appearance is greatly exaggerated with overexpression of Pk, one of the cytosolic proximal factors, and overall levels are increased (Tree *et al.*, 2002b; Bastock *et al.*, 2003). Fluorescence recovery after photobleaching (FRAP) has been used to demonstrate that the puncta are indeed much more stable aggregates, at least for Fmi and Fz (Strutt *et al.*, 2011). While membrane localization requires only Fz, Fmi, and Vang, the cytosolic factors are needed to induce stable aggregates. Unstable Fmi and Fz, or the fractions not in puncta, are subject to internalization and either recycling or degradation. Thus, the pools of core PCP components appear to exist in steady states of stable, aggregated complete complexes, less stable complexes consisting of Fz–Fmi:Fmi–Vang, and lower order, less stable subcomplexes. Pools of the unstable complexes are regulated by internalization. While additional detail about these processes is known, there is still no clear understanding of how the cytosolic factors produce amplification.

One hypothesis is that the cytosolic factors induce clustering, thereby providing the local cooperativity needed for polarization. The mechanism for clustering, or how it is enhanced by Pk, is not known. As previously proposed by Strutt *et al.* (2011), clustering may result from a scaffolding effect. These investigators dismissed the possibility of decreased endocytosis accounting for clustering.

The proximal protein Pk and the distal proteins Dgo and Dsh have been shown to engage in competitive binding interactions (Tree *et al.*, 2002b; Jenny *et al.*, 2003, 2005; Das *et al.*, 2004). This suggests, first, that oppositely oriented complexes come into contact, and second, suggests the possibility that these interactions might result in disruption of one or the other complex. At present, this potential mechanism is speculative, but is appealing, and consistent with the early proposal by Tree *et al.* (2002b). Such a model would provide long-range intercellular inhibition that is needed for polarization.

System Architecture

Studies of polarity in the wing and eye first led to the proposal that the Ft/Ds/Fj global module provides directional information that orients the activity of the core module (Yang *et al.*, 2002; Ma *et al.*, 2003; **Figure 5**). This hierarchical, or series, architectural scheme derived from the observation that orientation of core PCP proteins and morphological polarity are coordinately disturbed in global mutant clones (Ma *et al.*, 2003), and from mosaic analyses in the fly eye showing that boundaries between cells expressing and not expressing *ft*, *ds*, or *fj* lost the ability to influence polarity in the absence of *fz* (Yang *et al.*, 2002). In contrast, others have argued for a parallel system architecture, with the proposal of a bypass pathway (green arrow) resting upon observations in the abdomen that clones overexpressing global components (Ds or Ds[ecto], a more active form of Ds) produce domineering non-autonomy and therefore influence polarity within tissue lacking either Fz or Fmi (Casal *et al.*, 2006; Lawrence *et al.*, 2007). The argument supporting this scheme is also not definitive (discussed at length in Axelrod, 2009). Furthermore, it was suggested that PCP in the larval epidermis depends on the global module, while the core module has no function in this context (Repiso *et al.*, 2010), although a more detailed study found that the core module does become important in this tissue as it grows (Donoughe and DiNardo, 2011). Thus, the extent to which the blue, green, and black pathways (**Figure 5**) contribute has been proposed to differ in different contexts. The extents to which they contribute, or whether they in fact contribute at all in some tissues, remain controversial. Furthermore, since the data leading to alternate architectures derive from different tissues, one must consider the possibility that the architecture differs in different tissues. For the purposes of this discussion, only the Ft/Ds/Fj global module will be considered, as there is little data connecting Wnt4/Wg to other systems, and the identity of other potential global systems is not known.

The Ft/Ds/Fj system has features that make it an attractive candidate for providing directional information in multiple tissues. The direction of ommatidial polarization in the *Drosophila* eye depends on Ds and Fj gradients, and these effects require an intact core module (Yang *et al.*, 2002). In the eye, flattening the gradients leads to near randomization of local polarity, and inversion of the gradients leads to reversal of local polarity (Simon, 2004). In the wing, the core PCP proteins lose their orientation and polarize in swirling patterns in *ft* mutant clones (Ma *et al.*, 2003), and altering Ds expression patterns can reorient wing polarity (Matakatsu and Blair, 2004; Harumoto *et al.*, 2010). In the abdomen, opposing gradients of Ds and Fj are also observed, and these have opposite directions in anterior and posterior compartments of each segment (Casal *et al.*, 2002), and mutants demonstrate that they are needed for normal polarization. These observations are all consistent with a global directional function for the Ft/Ds/Fj module, acting upstream of, and in series with, the core module.

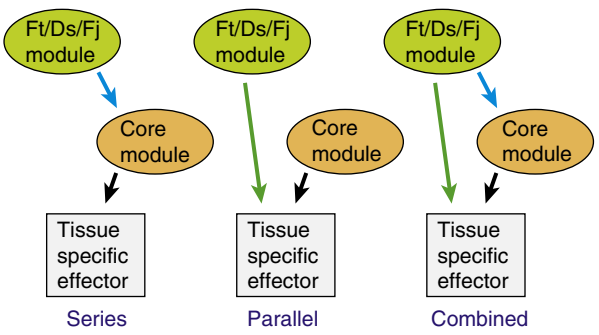

Figure 5 Possible architectures of the Ft/Ds/Fj global and the core modules in relation to the effector modules.

However, several observations are less simply reconciled with this model. When Ds and Fj, normally expressed in gradients along the proximal–distal (P/D) wing axis, are instead expressed uniformly, polarity is disrupted only in the proximal part of the wing (Matakatsu and Blair, 2004; Simon, 2004). In the abdomen, ectopic Ds expression can reorient tissue mutant for the core factors *fz* and *fmi* (Casal *et al.*, 2006). This would not be expected if the role of the Ft/Ds/Fj module is to provide directional information to the core module. Hence, this model is controversial, and others have proposed instead that the Ft/Ds/Fj and core modules function in parallel, acting independently on downstream effectors, and leaving open the question of what cues might orient core module function (Casal *et al.*, 2006).

In the face of the uncertainty about the relationship between the Ft/Ds/Fj module and the core module, the outlines of a unifying hypothesis that connects them in series have begun to emerge.

The first important observation is that microtubules appear to play a central role in the global alignment of PCP in the developing *Drosophila* wing. An unusual apical microtubule cytoskeleton (Eaton *et al.*, 1996; Shimada *et al.*, 2006; Harumoto *et al.*, 2010) can be seen in cells of the fly wing during polarization. During efforts to study the dynamics of Fz using a Fz::GFP transgene and live imaging, Shimada *et al.* (2006) noticed that what appeared to be vesicles can be seen departing the apical membrane, traversing the cell, and fusing to another side. Correlation to immuno-electron micrographs lends support to the notion that these were indeed Fz-containing vesicles that are associated with microtubules. A quantitative analysis showed that these vesicles move with an overall distal bias. Remarkably, using EB1::GFP, a marker of microtubule plus-ends, it was seen that the microtubules have a corresponding bias of distal plus-ends.

Vesicle movement was most active during the most dynamic period of polarization, and vesicle production depended on other core PCP proteins (Shimada *et al.*, 2006). From these data, biased trafficking could be inferred to be important in PCP acquisition, but whether this process was intrinsic to the core mechanism, or perhaps reflected a directional input, could not be discerned. However, a telltale clue was that the microtubule structure itself appeared not to depend on the core module. In a subsequent report, Harumoto *et al.* (2010) showed that the polarity of the microtubules depends on Ds, a component of the Ft/Ds/Fj module. This was consistent with evidence that Ft influences apical microtubule organization in another context (Marcinkevicius and Zallen, 2013). Plus-end bias was perturbed in *ds* mutants, and misexpression of Ds could reorganize microtubule polarity. These experiments were

complicated by the lethality associated with *ft* mutants, precluding a more thorough analysis, but suggested the possibility that the Ft/Ds/Fj global module organizes microtubules that in turn directionally bias core module polarization.

It is therefore tempting to hypothesize that polarized apical microtubules that transport Fz might comprise the Ft/Ds/Fj global directional signal that orients core PCP protein segregation. This hypothesis makes a number of predictions that remain to be tested. First, the oriented microtubules should appear and be polarized prior to the onset of core polarization. Second, there should be a spatiotemporal relationship between the orientation of apical microtubules and core polarization. This is of greatest interest in the wing, where substantial morphogenetic changes occur between third instar, when polarization begins, to the conclusion of polarization in the pupal stage, when hairs begin to grow. Finally, a more detailed analysis of the contributions of Ft/Ds/Fj to microtubule organization is needed.

The above hypothesis is based on data from the wing, yet the phenotypes and expression patterns, in particular the graded expression, of Ds and Fj suggest that they might have similar roles in other compartments. However, at first glance, there is an important inconsistency. If one imagines that the gradients of Ds and Fj organize microtubules, and thereby vesicle transport, in such a way that Fz accumulates toward low Ds and high Fj, this is observed in the wing and posterior abdomen, but the relative orientations are opposite in anterior abdomen and eye (Zeidler *et al.*, 2000; Casal *et al.*, 2002; Ma *et al.*, 2003; Matakatsu and Blair, 2004; Rogulja *et al.*, 2008; Axelrod, 2009).

Because the relative orientations of the Fj and Ds gradients with respect to the direction of core protein polarization is not conserved in wing, eye, and abdomen, universality of the model described above requires that one explain how oppositely oriented inputs can be rectified to produce similarly polarized outcomes. A clue to this rectification puzzle comes from the observation that tissues in which Fz and Dsh accumulate toward high Fj (wing and posterior abdomen (P-abd)) rely on the Pk but not the Sple isoform of Pk-Sple, while tissues in which Fz and Dsh accumulate away from high Fj (eye and anterior abdomen (A-abd)) rely on the Sple isoform; in wing and P-abd, polarity is disturbed in mutants of the pk^{pk} but not pk^{sple} isoform of the *pk* gene, whereas eye and A-abd are sensitive to pk^{sple} but not pk^{pk} (Gubb *et al.*, 1999; Lawrence *et al.*, 2004). One can therefore infer that Pk is the predominantly expressed or active isoform in wing and P-abd, while Sple is predominant in A-abd and eye.

Furthermore, clues suggest that the direction of gradient interpretation might depend on the predominant isoform present in each tissue. Manipulating *pk* and *sple* expression in wing and abodmen can alter the direction of polarization with respect to the Ft/Ds/Fj gradients. More specifically, overexpression of the non-predominant isoform in wing or either abdominal compartment can at least partially reverse polarity (Lawrence *et al.*, 2004; Lin and Gubb, 2009; Doyle *et al.*, 2008; Hogan *et al.*, 2011). This suggests that Pk causes hairs to point toward high Fj, while Sple caused them to point toward low Fj. Indeed, a subsequent analysis has shown that Pk and Sple cause the opposite orientation of microtubules with respect to the Fj and Ds gradients, and therefore the trafficking of Fz vesicles that could orient the core module is opposite (Olofsson *et al.*, 2014). The relative expression of these isoforms therefore can rectify the upstream signal to orient core module polarization.

Outlook

The past two decades have witnessed a leap in understanding the signals that control PCP, with the advances powered primarily by standard approaches employed in genetic models. Continued progress is likely to require the deployment of other approaches less commonly combined with traditional genetics, including biophysical, proteomic, cell biological, and biochemical studies. Meanwhile, the complex relationship between mutation and phenotype will demand the continued use of mathematical modeling to relate molecular interventions to pattern outcomes for a given network signaling model.

See also: Cell Communication: Growth Factor Mediated Cell Signaling: The Hippo Pathway. Cytoskeleton and Motors: Complex Cytoskeletal Structures: Cell Polarity. Cytoskeleton and Motors: Cytoskeletal Components: Microtubules and Microtubule-Associated Proteins (MAPs). Vertical Integration: Applications: Multiscale Analysis of Morphogenesis. Vertical Integration: Modeling: Computational Approaches for Multiscale Modeling

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