



Published in final edited form as:

Annu Rev Genet. 2008 ; 42: 517. doi:10.1146/annurev.genet.42.110807.091432.

Planar Cell Polarity Signaling: From Fly Development to Human Disease

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Abstract

Most, if not all, cell types and tissues display several aspects of polarization. In addition to the ubiquitous epithelial cell polarity along the apical-basolateral axis, many epithelial tissues and organs are also polarized within the plane of the epithelium. This is generally referred to as planar cell polarity (PCP; or historically, tissue polarity). Genetic screens in *Drosophila* pioneered the discovery of core PCP factors, and subsequent work in vertebrates has established that the respective pathways are evolutionarily conserved. PCP is not restricted only to epithelial tissues but is also found in mesenchymal cells, where it can regulate cell migration and cell intercalation. Moreover, particularly in vertebrates, the conserved core PCP signaling factors have recently been found to be associated with the orientation or formation of cilia. This review discusses new developments in the molecular understanding of PCP establishment in *Drosophila* and vertebrates; these developments are integrated with new evidence that links PCP signaling to human disease.

Keywords

cell polarity; drosophila; organ patterning; frizzled-pcp signaling; ciliopathies

HISTORY OF PLANAR CELL POLARITY STUDIES

The coordination of cellular polarization is an important feature of development and critical for organ function. Epithelial apical-basolateral polarity enables organs and tissues to perform vectorial functions, including transport of fluid or directed secretion of specialized components. In addition, most epithelial tissues require a second axis of polarity, commonly referred to as planar cell polarity (PCP), which is within the plane of an epithelium. This type of polarity is, however, not restricted to epithelial tissues, but is also found in mesenchymal cell types throughout animal development.

Historically, the study of PCP originated from work in arthropods (e.g., 45,75; then referred to as tissue polarity), and elegant genetic analyses in *Drosophila*, where most adult cuticular structures show PCP-type polarization, put the problem firmly on the map some 25 years ago (45,144). PCP studies in *Drosophila* have been most prominently studied in the fly wing, eye, abdomen, and notum (for reviews on *Drosophila* PCP, see References ^{1,73,74,91}; see also examples in Figure 1). The initial studies were soon followed by systematic genetic screens, molecular cloning, and functional analyses of *Drosophila* PCP factors (Table 1) (reviewed in References 1,73,128).

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DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

More recently, many vertebrate tissues and developmental processes have been shown to display typical PCP features (for reviews on PCP features, see References 65,142,145,152). First, analyses in *Xenopus* (133,148) and zebrafish (62,84) of the process of convergent extension (CE) during gastrulation and neurulation indicated that orthologues of *Drosophila* PCP factors are key players in this context. For example, several CE mutants identified in forward genetic screens in zebrafish turned out to be orthologues of *Drosophila* PCP genes (reviewed in Reference 97). Thus most of the core PCP genes are now known to be important for both epithelial polarization and CE during gastrulation, supporting the commonality of PCP establishment not only across species but also between different polarized cell types and organs. In addition, in mammals, “hairy” organs such as the inner ear and skin/epidermis are beautiful examples of epithelia with PCP features (e.g., 47,95,151). In particular, the PCP hair pattern defects in the mouse are strikingly reminiscent of the actin–hair pattern defects in *Drosophila* wings, and PCP abnormalities in the inner ear are very similar to those in the fly retina (Figure 2) (e.g., 152). Taken together, the study of PCP generation has come full circle—from studying hair patterns on flies, to the studies of eye development, convergent extension, and cochlear development, and now back to studying hair patterns, only this time in mammals.

The evolutionary conservation and parallels of the *Drosophila* PCP factors during vertebrate development and homeostasis made the analysis of PCP generation an important and mainstream feature of developmental studies in many organisms and medical contexts. Unraveling the molecular and cellular mechanisms of the establishment of PCP is presently one of the frontiers in developmental genetics and cell biology. How individual cells that are hundreds of cell diameters apart acquire the same orientation within an organ (or the plane of an epithelial field) or how mesenchymal cells generate uniform polarization leading to ordered cellular migration and intercalation are fascinating biological and biomedical problems. In addition, recent discoveries suggest that the PCP factors play a critical role in many diseases, and these factors in particular have been linked to genetic syndromes associated with ciliary functions.

Despite significant progress in dissecting the molecular aspects of PCP establishment over the past 10 years, our mechanistic and cellular understanding of this process is still very rudimentary. Several good reviews have been published recently addressing specific PCP issues in *Drosophila* (e.g., 1,76,118,165) and in vertebrates (e.g., 65,142,145,152). We thus first summarize only the key features of PCP generation and then focus on recent findings of potential links of PCP factors to ciliary morphogenesis and function, and to human disease. We apologize for the omission of research areas and viewpoints that have not been included here.

CONSERVED FACTORS IN PLANAR CELL POLARITY SIGNALING

The current data indicate that there are two evolutionarily conserved sets of PCP factors that act together to coordinate PCP establishment: the Frizzled (Fz)/Flamingo (Fmi) core genes (Table 1; see below) and the Fat/Dachsous (Ds) PCP system (Table 1 and see below). The relationship between the two sets of factors is unresolved, and views and models of their interaction and integration differ (see below).

The Frizzled/Flamingo Core Group

The core Fz/PCP gene cassette is highly conserved across species and tissues and is now understood in more detail than that of the Fat/Ds system. The components of the Fz/Fmi system include Fz and Fmi (a.k.a. Starry night/Stan), Dishevelled (Dsh; Dvl in mammals), Prickle (Pk), Strabismus/Van Gogh (Stbm/Vang), and Diego (Dgo; Diversin and Inversin in vertebrates) (reviewed in References 1,73,128,142,152). In brief, historically Fz and Dsh have been the central PCP signaling molecules (potentially acting on the downstream effectors of,

for example, the Rho subfamily of GTPases; see also Table 1), with the other core Fz-Fmi/PCP factors that regulate Fz-Dsh localization and/or signaling activity. For example, Stbm/Vang and Pk antagonize Fz-Dsh activity (60,61,136,140,155). Pk is recruited to the membrane by Stbm (60), binds Dsh, and antagonizes its Fz-mediated membrane recruitment (140). Stbm also binds Dsh and thus might affect its function directly (8,104). In general, as deduced from the *Drosophila* data the Fz-Dsh and Stbm/Vang-Pk pairs are thought to antagonize each other, and their localization becomes resolved to mutually exclusive domains at opposite poles of each cell (Figure 3; see below). In addition, Diego promotes Fz-Dsh activity, colocalizes with Fz-Dsh, and binds Dsh directly (29,40,61). This interaction is thought to protect Dsh from the antagonistic effect of the Stbm-Pk complex (61).

The role of the atypical cadherin Fmi is the least understood in this group (30,120,141). Fmi is thought to serve a homophilic adhesion function; it colocalizes with both the Fz-Dsh and the Stbm/Vang-Pk complexes, and is also genetically required in both complexes. The role of Fmi needs to be addressed in more detail. In particular, Fmi still has no known molecular PCP interaction partner.

It remains an open question how the localization and interactions will play out in the vertebrate Fz/PCP system. Although the asymmetric localization of some of the PCP factors has been documented in some vertebrate tissues (e.g., in the mouse inner ear or during zebrafish gastrulation and neurulation), a complete data set and thus an equivalent model to *Drosophila* do not yet exist. The current examples include the asymmetric localization of Vangl2, Dvl2, and mFz3 and mFz6 in the mouse inner ear (95,150,151), and the localization of Pk and Dsh during zebrafish convergent extension processes (20,162; see below).

Genetic studies in *Drosophila* have identified additional genes that act within the Fz/PCP group as either downstream effectors or regulatory genes. The CKIε kinase has emerged as a potential regulator of Fz/PCP signaling in *Drosophila* (72,131), and a related PCP function has been proposed in vertebrates (89). Genetic interactions indicate that CKIε acts positively on Fz-Dsh activity (72,131). CKIε is apically enriched like Fz and Dsh and required for asymmetric Dsh localization, but it is itself not asymmetrically localized within the proximo-distal axis in wing cells (131). Surprisingly, its kinase activity is dispensable for Fz/PCP signaling (72).

An additional factor thought to participate in Fz-Dsh/PCP signaling is the heterotrimeric G protein subunit Gao. Genetic evidence supports its role in both canonical Fz-Dsh/β-catenin signaling and Fz-Dsh/PCP signaling (64). Biochemical studies in heterologous cell culture systems also support a role of heterotrimeric G proteins in both Fz signaling pathways (3,79,149). However, the mechanistic role of the G proteins (and their associated regulators) remains unclear for either Fz-Dsh/PCP or canonical Fz-Dsh/β-catenin signaling. Importantly, the physical interaction of the candidate G protein(s) with Fz family receptors, a hallmark feature of seven pass-transmembrane G protein coupled receptors, has not been demonstrated. Moreover, in *Drosophila*, Gao does not colocalize with the Fz-Dsh complex (or the Stbm-Pk complex) in wing cells, but it displays a diffuse proximally enriched localization (64). Thus, the role(s) of the G proteins in Fz-Dsh signaling remains to be resolved.

The Fat/Dachsous PCP Group

A second group of regulators has been shown in *Drosophila* to affect PCP establishment in all tissues analyzed. Its main components are the very large protocadherins Fat (Ft) and Dachsous (Ds) (82,114,160), as well as Four-jointed (Fj) (130,166,167). Fat and Ds can interact heterophilically across cell boundaries (86,87). In addition to Fat, Ds, and Fj, the Atrophin (Atro; a.k.a. Grunge/Gug) protein has been linked to this group (37,38). Although *atro* shows similar genetic behavior to Fat in the eye, how it is linked to Fat mechanistically is unclear. Atro has been shown to associate with the intracellular domain of Fat (38). However, it is a

transcriptional corepressor in all other contexts and thus this might suggest that the Fat-Ds interaction could act via transcriptional regulation.

Fj is thought to modulate the activity of Ds and possibly its interaction with Fat (130). Fj appears to be acting in the Golgi and, based on phenotypic similarities and genetic studies, is proposed to modulate the extracellular domain of Ds and thus affect its “activity” (130). This interpretation is supported by the observation that, while *fat* expression is uniform, *ds* and *fj* are expressed in opposing gradients in the eye (160) and also in the wing, albeit to a lesser extent. Moreover, it is sufficient that either Ds or Fj are expressed in a graded manner (122).

The functional relationship of the Fat/Ds group to the Fz/Fmi PCP core group remains an open question. It has been suggested that Fat/Ds acts upstream of Fz/PCP signaling (82,160), largely based on data in the fly eye. For this system it has been suggested that Fz/Fmi-PCP signaling loses its bias between the R3 and R4 cells in the *fat/ds* mutant situation and a random decision is made (160), whereas in wild type, higher Fz/PCP signaling in the R3 precursor relative to R4 is key to properly specifying it as R3; PCP establishment in the fly eye is determined by the interactions and specific fates of the R3/R4 precursors (91). However, more recently, a very detailed and complete set of results presented by Casal and colleagues (16), from analysis of PCP establishment and the interactions between the Fat/Ds and Fz/Fmi groups in the abdomen, strongly suggest that the two signaling cassettes act in parallel and reinforce correct PCP establishment through their independent parallel inputs. This analysis took advantage of the nonautonomous properties of some of the core PCP factors [first described for *fz* (144)] and established that, for example, the nonautonomous redirection of wild-type cells, as caused by either *fat* or *ds* mutant clones, does not require the presence of Fz or Fmi. The simplest interpretation of these very extensive data is that the two signaling cassettes act independently of each other in parallel (16; see also 76). This conclusion is further supported by the observation that in certain tissues (for example, the larval denticle belts) neither pathway shows defects in a single loss-of-function scenario, but PCP defects become apparent when components of both cassettes are mutant (16). This observation suggests that sometimes the two cassettes act redundantly in parallel, again supporting a parallel input. With these new data in hand, it is possible to reinterpret the available data in the eye (160) along the same lines and conclude that Fz/Fmi-PCP signaling is “normal” in *fat* mutant tissue, but as the two pathways act independently, in a nonredundant manner in the eye, a randomized R3/R4 fate decision is the result for mutants of either. Despite an active but unresolved debate, the evidence now clearly favors the parallel, independent function of the Fat/Ds and Fz/Fmi cassettes as proposed by Lawrence et al. (16,76).

TISSUE-SPECIFIC PCP SIGNALING EFFECTOR PROTEINS

Both signaling cassettes are required in many different tissues (from flies to mammals) and the associated cellular responses are very diverse, ranging from the regulation of cytoskeletal organization, cell adhesion and movement, nuclear signaling, and orientation of the mitotic spindle to probably more yet unknown cellular functions (reviewed in 118,152). Thus, besides the core PCP factors described above, many tissue-specific PCP signaling effectors have been identified in *Drosophila* (see also Table 1). Three main tissue responses are known in *Drosophila*: (a) formation of actin hairs (trichomes) on a specific side of the cell as a result of cytoskeletal rearrangements in, for example, the wing or the abdomen; (b) cell fate specification as a result of nuclear signaling in the eye; and (c) orientation of the mitotic spindle in sensory organ precursor cells on the thorax and abdomen (for detailed reviews, see References 1,73, 91,132). Each of these tissues is thought to have some tissue-specific PCP effectors. For example, the genes *fuzzy* and *inturned* appear to be specific to the cytoskeletal rearrangements occurring in wing cells (and related cellular polarization in other cells of the adult cuticle). They have no obvious effect in the eye. Similarly, the kinase encoded by *nemo* appears to be

an eye-specific effector for the ommatidial rotation process, and it has no obvious PCP phenotypes in the wing (90).

In contrast to these, there are also Fz/PCP effectors that function in all tissues analyzed. Most prominently, this group includes the Rho family GTPases (35,39,96,129) and *dROK*, the *Drosophila* orthologue of mammalian Rho-associated kinase ROCK (154). DRok, for example, appears to affect a specific step of PCP establishment in the wing and the eye, e.g., the number wing hairs formed per cell in the wing and ommatidial rotation in the eye.

Although the Rho-family GTPases are also required in several contexts for vertebrate PCP establishment (48,49), it is not yet established what the cellular effector pool will be in vertebrates. Note that in some vertebrate PCP contexts, some of these effectors from *Drosophila* have been implicated as well. For example, Fuzzy and Inturned appear critical for the formation of cilia (105), but here they act upstream of Dvl and Rho (105,106). Moreover, in zebrafish CE Nlk (Nemolike kinase) mutants enhance the CE-specific *Wnt11/silberblick*-associated cell movement defects (137). More studies are needed to correlate the respective functions between the different organisms.

PAR PROTEINS AND PCP ESTABLISHMENT

Several recent studies suggest that there is also a link between the PAR proteins and PCP establishment. A recent study has identified physical interactions between an ArfGAP (XGAP) and several PAR proteins as essential in the PCP context of convergent extension (CE) in *Xenopus* (58). The XGAP and the PAR proteins (PAR-6, 14-3-3e/PAR-5, and aPKC) localize to mediolateral ends of cells during the CE process, where they are mutually dependent on each other's localization, suggesting the existence of stable, polarized PAR complexes. These observations suggest an intriguing relationship between the PAR protein complexes and the core Fz/PCP factors. Although it requires the comparison of two different systems (*Xenopus* and zebrafish), it is intriguing to speculate that the PAR/aPKC complex and the Fz/PCP complexes display antagonistic interactions. For example in zebrafish, in cells undergoing CE, Pk and Dsh are asymmetrically localized within the anterior-posterior axis, with Pk localizing to the anterior end of cells (20) and Dsh localizing to the posterior of the same cells (162), whereas the XGAP-PAR-aPKC complex is localized to the mediolateral ends of cells during *Xenopus* CE. If these localizations are conserved across species, this would indeed suggest an antagonistic interaction between the complexes containing aPKC and core Fz/PCP factors. Support for this model comes from studies of PCP establishment in the *Drosophila* eye. Here, Fz/Fmi levels are selectively increased in the R3/R4 pair by antagonizing aPKC in the two critical cells for Fz/PCP signaling via PAR-3 (Bazooka). In other cells during eye patterning, where PCP signaling is low, aPKC phosphorylates Fz and thus reduces its levels by a yet unknown mechanism (33).

Taken together with the mutually inhibitory interactions between the Fz-Dsh and Stbm-Pk complexes (see above), antagonistic interactions among all three complexes (the aPKC complex and the two PCP complexes) lead in mesenchymal cells to an anterior Stbm-Pk complex, a posterior Fz-Dsh complex [as are both factually seen in zebrafish (20,162)], and a mediolateral aPKC/PAR complex. This would provide cells undergoing CE with all polarity information needed for convergence to and intercalation at the midline. Consistent with this model, the PAR-1 kinase can phosphorylate and positively regulate Dsh during CE (102) and PAR-1 localization appears to be mutually exclusive with that of aPKC/PAR-3/PAR-6 in several cellular contexts. However, this model remains speculative, and further experimental studies are needed to dissect these interactions in more detail.

HOW IS PCP GLOBALLY COORDINATED OR THE CELLULAR ASYMMETRY GENERATED ACROSS TISSUES?

Although much information has been gained by studying PCP in *Drosophila*, one question has not been answered. How is the global polarization—the initial asymmetry—within whole tissues established? The Fz receptor-family are the receptors of the secreted growth factors of the Wnt family, and functions as such in canonical Wnt/ β -catenin signaling (e.g., 80). Thus the *Drosophila* Wnts are good candidates to serve as a polarizing cue in PCP as well. However, to date no published experimental evidence supports this assumption, and it remains unknown how whole fields of cells are initially polarized in *Drosophila*. In vertebrates, the Wnt5a and Wnt11 family members have been clearly linked to PCP-type signaling; for example, the zebrafish mutants *silberblick* (Wnt11) and *pipetail* (Wnt5a) have typical convergent extension phenotypes (52,77). The experimental evidence, however, suggests a permissive role rather than an instructive role for these vertebrate Wnts. Recent additions to canonical Wnt signaling in vertebrates suggest that a Fz ligand could also be unrelated to Wnts. For example, Norrin is a high-affinity ligand for mammalian Fz4 (shown in mouse and human), activating canonical signaling (159). It shares no apparent sequence similarity to Wnts, and no homologues of Norrin are present in the fly genome. This observation might suggest, however, that other secreted factors might regulate the activity of Fz in PCP. Nevertheless, despite serious efforts by the *Drosophila* PCP community to find a Fz ligand for PCP signaling, it appears that the Fz signaling activity in PCP is largely ligand independent or, in other words, constitutive. This conclusion, although mainly based on gain-of-function data (12,17,113,127,157,158), taken together with the lack of any known ligand is rather compelling.

What then are the global polarizing signal(s) and mechanism(s)? As mentioned above, it has been proposed that the Fat/Ds system could serve as an upstream polarizing cue for the Fz/Fmi-PCP group. Members of the Fat/Ds group are expressed in gradients (e.g., Ds in the eye and the wing) and their graded expression is under the control of canonical Wg-signaling (86,160). As attractive as this model first appears, there are obvious shortcomings. First, the gradients of the Fat/Ds group have opposite slopes in the eye and wing relative to the presumed polarization of the field, as deduced through the analysis of the Fz/Fmi core factors (86,160), arguing against a general polarizing mechanism. Second, as discussed above, it appears likely that the Fat/Ds and Fz/Fmi “cassettes” function in parallel to each other (16,76). As there are no known Fz ligands in PCP in *Drosophila*, maybe extracellular ligands should be sought for the other transmembrane core PCP factors in that group, Vang/Stbm and/or Fmi. A global polarization of these would suffice to create a polarized field and maybe this could provide clues for the global polarization cue. Or can *Drosophila* learn a trick from vertebrates here?

PCP IN VERTEBRATES

Although the fly is amenable to phenotypic analysis of PCP, studying PCP in vertebrates remains difficult. Most PCP genes have only one isoform in *Drosophila*, whereas in vertebrates there are often numerous isoforms (for example 3 Dvls and 10 Fzs in the mouse). Furthermore, some isoforms have nonoverlapping expression patterns, with the result that knocking out one PCP mouse gene will most likely not lead to full PCP defects, as is the case in *Drosophila*. Therefore, the study of PCP generation in vertebrates has been hampered by redundancy and requires a detailed analysis of as many tissues as possible. Double and triple knockouts are very often inevitable, making it a tedious business (152).

In the fly, the tissues that are typically scored for PCP defects are mostly external epithelia and therefore easily accessible. So far, only a few vertebrate or mammalian tissues have been shown to involve clear aspects of PCP. At present, the tissues that require PCP genes to organize their cells in the plane are cells that undergo convergent extension during gastrulation, neurulation,

and possibly also cardiac outflow tract development (53). Inner ear sensory cells use PCP to organize their characteristic stereociliary bundles. In the skin, hair follicle orientation as well as eyelid closure requires PCP (152). Recent data also indicate that PCP signaling is involved in renal development and that defective PCP signaling leads to polycystic kidney disease (124).

The list of affected tissues in PCP mutants (Table 2) will likely grow. Most tissues, in particular epithelia, require a three-dimensional organization during development and also in adulthood to maintain their function. PCP controls organization in the planar dimension and should therefore be active at some point in most tissues. Likely candidates are, for example, tissues that perform a vectorial function in the plane of the epithelium, such as the respiratory epithelium that transports mucus aborally through coordinated ciliary beating, or the oviduct epithelium that transports the fertilized ovum to the uterus, as was already proposed 10 years ago (34).

Insight into mammalian PCP has mostly been obtained through analysis of the *Looptail* mouse, which harbors a truncating mutation of *Vangl2* (or *Strabismus*). There are only two *Vangl* genes and they often appear to act nonredundantly, the reason why *looptail* mice display a relatively broad spectrum of PCP defects. In contrast, individual knockouts of single *Dvl* genes (there are three) show minimal defects. The two *Vangl* (*strabismus*) genes were also found to be redundant in some contexts, for example, in the control of neural tube formation, orientation of the stereociliary bundles in cochlea, and organization of major extracardiac vessels (139). Homozygous double mutant mice could not be recovered, which represents another caveat of mammalian PCP analysis compared to the fly, where many PCP mutations produce viable animals.

PCP AND CILIA

PCP in vertebrates seems to be a strikingly connected with one particular organelle: the cilium. Cilia are cellular appendages that have recently attracted close attention due to their crucial involvement in human disease (54,85,110). In fact, although the primary cilium has long been studied, it was the province of only a small but dedicated group of researchers until its importance became clear early this decade. A new disease class has even been established, termed ciliopathies (6,54,85). Ciliopathies, which are caused by defects in cilia formation and function, mainly consist of genetic syndromes such as the autosomal-dominant polycystic kidney disease (ADPKD), Bardet-Biedl syndrome (BBS), Meckel-Gruber syndrome (MKS), Oro-facio-digital syndrome (OFD), and nephronophthisis (NPHP). Except for ADPKD, these syndromes are rare. However, the spectrum of clinical signs and symptoms includes such common and important features as obesity, retinitis pigmentosa, neural tube defects, and polycystic kidney disease (6).

The essential structure of cilia consists of nine peripheral microtubule doublets, the axoneme, which emerges from the basal body (i.e., the mother centriole in a centrosome). The axoneme is surrounded by a membrane lipid bilayer that is continuous with the plasma membrane. The assembly and maintenance of the cilium depends critically on the existence and function of a dedicated transport system, called intraflagellar transport (IFT), that transports cargo in and out of the cilium (85). Based on whether the axoneme includes an additional central pair of microtubules, cilia are classified as 9+2 or 9+0 cilia. 9+2 cilia tend to be motile, whereas 9+0 cilia tend to be immotile, sensory cilia (85). Also, in contrast to motile cilia, which are always numerous, only one non-motile cilium usually occurs per cell. Almost all cell types in the human body are ciliated, which also explains why so many tissues are affected in pleiotropic ciliopathies such as the Bardet-Biedl syndrome.

Motile cilia often function in fluid or mucus transport, whereas sensory cilia are mechanosensors and chemosensors. Recently, a number of signaling pathways have been shown to depend on ciliary function such as Hedgehog, PDGF, and Wnt signaling pathways. In particular, for the mammalian Hedgehog pathway the relationship between cilia, both transmembrane proteins in the Hedgehog pathway—Patched and Smoothed—and the processing of Gli transcription factors has been addressed in detail (reviewed in Reference 57). Impaired hedgehog signaling caused by ciliary defects also contributes to several clinical features included in the ciliopathies (e.g., poly-dactyly and rostral neural tube defects) (146).

The first hint that defective PCP signaling could be involved in ciliopathies came from studies on the nephronophthisis type II gene *inversin*. Inversin is a ciliary protein that shares sequence similarity and domain architecture with the PCP core component Diego. Inversin was found to directly interact with Dvl and also to regulate Dvl stability (123). Dsh/Dvl is shared by both Wnt signaling pathways, and both pathways are thought to require distinct subcellular pools of Dvl (158). Within the PCP pathway, Dsh/Dvl has to be tightly associated with the plasma membrane, whereas in canonical Wnt signaling, Dsh/Dvl shuttles between different subcellular compartments, including nucleus, cytoplasm, and plasma membrane (59,147). Inversin downregulates cytoplasmic but not membrane-bound Dvl pools. Both proteins also translocate together to the membrane during epithelial cell differentiation. Inversin thus appears to negatively regulate the canonical Wnt signaling pathway while promoting PCP signaling (123). This becomes manifest in impaired CE movements during gastrulation and cystic kidneys in *Xenopus* and zebrafish morphants, respectively. *Inv* mutant mice suffer from polycystic kidney disease, *situs inversus*, and hepatobiliary and cardiac abnormalities. They also display abnormal fur patterning reminiscent of *Fz6*^{-/-} mice (47,123).

Recently it was found that other proteins that belong to the ciliary and centrosomal machinery such as the Bardet-Biedl (BBS) proteins, the nephronophthisis protein NPHP3, the ciliary kinesin KIF3A and the oro-facial-digital syndrome protein OFD1, are also able to function as molecular switches in Wnt signaling pathways (11,26,42). For example, the disruption of basal bodies by knockdown of BBS proteins compromises proteasomal degradation of Dvl and β -catenin and, therefore, the intracellular Wnt response. The depletion of BBS proteins also impairs CE movements in zebrafish (42,115). These defects can be partially rescued by coinjection of mRNA for a membrane-bound version of Dvl, including a N-terminal myristoylation and palmitoylation signal. This suggests that the subcellular distribution and regulation of Dvl degradation might be influenced directly by the cilium and the basal body (42).

PCP AND NEURAL TUBE DEFECTS

BBS mouse models also interact genetically with the *looptail* mouse with respect to neural tube closure and stereociliary bundle orientation in the cochlea (115). These phenotypes are typical mammalian PCP defects, and should therefore be discussed in more detail.

Neural tube closure is the result of neurulation, a process in which the neural plate bends up and eventually fuses to form the hollow tube that will become the brain and the spinal cord. The driving force of neural tube closure is provided and maintained by cells undergoing CE movements. Neural tube closure normally initiates at three sites along the rostral-caudal axis but occurs in the brain in a manner very different from that in the spinal cord. Human neural tube defects (NTDs) are therefore classified based on their location in the rostral-caudal axis. Forebrain and midbrain closure defects are termed anencephaly or encephalocele, whereas hindbrain and spinal cord closure defects are referred to as craniorachischisis (146,161). Partial closure of the spinal cord, or spina bifida, represents the mildest and also most common human NTD. Combined with the other NTDs, it occurs in 1 to 2 infants per 1000 births, which makes

it the second most common human birth defect. Population- and family-based studies indicate a complex multigenic cause of NTDs.

This notion was challenged recently by Gros and colleagues, who found mutations in the PCP core component *Vangl1* in patients with familial and sporadic NTDs (66). The respective patients mainly exhibited defects in the caudal neural tube, including craniorachischisis. Moreover, it was shown that the *Vangl1* mutations disrupted the physical interaction with *Dvl*. These results, for the first time, place core PCP genes within the realm of human disease and suggest that screening for mutations in *Vangl1* and in other PCP components should be considered in affected families.

In light of the *looptail* mouse phenotype, these findings were, however, not so surprising. Like the patients, these mice suffer from more caudal defects such as craniorachischisis (67). Although *Dvl2*^{-/-} mice also display some rostral defects, it is believed that the PCP pathway is responsible for caudal NTDs (50). In contrast, the Hedgehog pathway accounts for most of the rostral defects (146). The distinction is not entirely consistent as, for example, in *Patched1* null mice both rostral and caudal defects are seen (44). It seems that both pathways act at different stages during neurulation. Whereas the Hedgehog pathway regulates neural plate bending and specification of ventral neural cell fates, the PCP pathway drives neural tube closure (31).

Since Hedgehog signaling critically depends on intact ciliary structure and function, there is a strong correlation of the neural tube phenotypes in mouse mutants with abnormal cilia, such as IFT mutant mice, with the Hedgehog signaling phenotypes (36). In the case of PCP signaling, the correlation is less clear, as null or partial loss-of-function IFT mutants typically do not display PCP-like NTDs. The role for cilia in PCP-dependent neural tube closure therefore remains obscure.

In *Xenopus* embryos, depletion of the PCP effector proteins *Inturned* and *Fuzzy* (see Table 1) leads to open neural tubes and defective cilia formation (105). Both proteins were found to be required for the organization of a subapical actin cytoskeletal network essential to anchor basal bodies to the apical membrane—a prerequisite for ciliogenesis. The conclusion from this observation would be that PCP signaling functions upstream of cilia signaling. This is, however, again in contrast with the observed phenotypes in mouse models. Mouse mutants in the core PCP factors have so far not been shown to display defects in ciliogenesis. However, as described above, the analysis might be impaired by redundancy between related PCP genes. Therefore, a more systematic approach is needed.

Recent studies have also shown that the subapical cytoskeleton is important for apical constriction. Apical constriction initiates cell shape changes that underlie neural tube bending and closure. Dominant-negative *Dsh*, for example, disrupts apical constriction by preventing apical Rho accumulation (70). As both ciliogenesis and apical constriction depend on an intact subapical cytoskeleton, it would be interesting to see whether disrupted PCP signaling affects both processes equally or whether one defect is the result of the other. A very interesting question is also whether cilia are required in cells undergoing CE movements and, if so, whether they perform motile or sensory functions.

PCP AND THE COCHLEA

The vertebrate system in which the relationship between cilia and PCP signaling is probably best understood is the mammalian inner ear, in particular the organ of Corti (94). In the organ of Corti the sensory hair cells form rows of cells with V-shaped organized stereociliary bundles on the apical surface (see Figure 3). The stereociliary bundles consist of a large single kinocilium (a true sensory cilium) located on the abneural side of the cell and an actin-based

stereociliary bundle organized in a staircase pattern, which points in the abneural direction. Hair bundle orientation is important for inner ear function as it allows the hair cells to sense the direction of mechanical stimulation.

The morphological polarization of sensory hair cells is under the control of the PCP signaling pathway. The first evidence for this came again from the *looptail* and the *circletail* mice (which affects the Scribble gene) (95). In both mouse mutants the precise arrangement of stereociliary bundles is disrupted. The picture resembles the situation in the *Drosophila* compound eye where the ommatidia are randomly organized in PCP mutants. Hair bundle orientation defects in the organ of Corti have since been described in Ptk7 and Celsr1/Flamingo knockout and Dvl1/Dvl2 and Fz3/Fz6 double knockout mice (27,81,150,151) (see also Table 2). The organ of Corti can also be explanted and cultured in vitro for several days. Using this system, it was shown that the application of Wnt ligands can influence the orientation of stereociliary bundles, suggesting Wnts as a permissive factor in the orientation process (28). However, this role has not been addressed in a loss-of-function experiment.

The inner ear has also emerged as a good vertebrate system to study asymmetric protein localization of PCP core factors. The respective studies have already produced some surprises: In contrast to the situation in *Drosophila* where Stbm and Fz are on opposite poles, Vangl2 and the Fz receptors mFz3 and mFz6 localize to the same side of the inner ear sensory cells (151). Fz3 and Fz6 displayed remarkable redundancy in this process where at the protein level one Fz can compensate for the loss of the other (151). As Dvl2 is found on the opposite side of Fz, the membrane protein that would anchor Dvl2 at the membrane is not yet known. Other Fz receptors may play a role in this context and/or another Dvl member may be involved. The PCP signaling pathway operating in the mammalian inner ear thus seems to have similarities to, but also clear differences from, the *Drosophila* PCP pathway.

A recent study by Chen and colleagues examined the relationship between PCP and IFT mutants in the context of sensory hair polarization (63). Using conditional knockout mice for IFT88/Polaris and Kif3a, the authors asked whether kinocilia are required for normal development of the mouse inner ear sensory epithelium. Loss of the kinocilium due to IFT88 and Kif3a inactivation caused a misorientation of stereociliary bundles similar to that in the core PCP mutants. However, in some cells the bundles appeared to be mislocalized to a more central location on the apical surface. This finding also correlated with a circular and symmetric arrangement of the bundles. When examining PCP protein localization in the IFT88 mutant cochlea, the PCP factors Fz3 and Vangl2 were found to retain their normal, asymmetric localization patterns in the mutant hair cells. These data have two important implications: first, the cilium is required for the actin-based stereociliary bundle positioning, and second, PCP protein localization does not appear to be downstream of ciliary function. One conclusion could also be that stereociliary bundles fail to respond to the positioning cues provided by PCP signaling when the cilium is missing (4).

Similar precise cilia and basal body positioning can be found in the mouse node, an embryonic tissue that regulates left-right body asymmetry (56). Here, the node cells place almost all of their basal bodies near the posterior end of their apical dome-like surface. The motile cilia formed by these basal bodies are tilted posteriorly in an angle that allows them to perform their characteristic rotation movements (101). The importance for this precise positioning is reflected in the phenotype of *inv* mutant mice. In the nodes of these mice basal bodies are mispositioned, leading to mistilting and uncoordinated beating of the cilia. As a consequence, the flow generated by these cilia is slower and has a meandering streamline (101).

It will be interesting to investigate core PCP mouse mutants with regard to basal body positioning and ciliary beating in the node and also other tissues that require coordinated ciliary

beating. This analysis should include close examination of the subapical actin cytoskeleton and its role in the anchoring of basal bodies. In zebrafish, Fz2 was found to be involved in left-right asymmetry regulation (100). Depletion of Fz2 by using morpholino oligonucleotides resulted in decreased cilia length and number. In addition, Fz2 morphants phenocopied the morphants for *duboraya*, a novel ciliogenesis factor (100). *Duboraya* function appeared to be dependent on Fz2-mediated noncanonical Wnt signaling and also required for an intact subapical actin cytoskeleton in cells lining the Kupffer's vesicle and the pronephric duct (100).

In summary, the PCP pathway seems to have a role in the organization of a subapical actin cytoskeleton, which in turn is a prerequisite for proper basal body and cilia positioning. Precise positioning could be required for coordinated beating of motile cilia populations and for the execution of selective sensory cilia function.

PCP AND POLYCYSTIC KIDNEY DISEASE

The question whether the PCP factors and PCP signaling act upstream or downstream of cilia function might be different and possibly more complicated in the kidney. Here, defective PCP signaling has been brought into connection with polycystic kidney disease (PKD) etiology (124,125).

PKD is one of the most common monogenic diseases. ADPKD occurs in 1 to 1000 individuals and accounts for up to 10% of all cases of end-stage renal disease. Due to lack of treatment options, affected individuals will inevitably undergo renal transplantation or require dialysis. The ADPKD symptom is caused by mutations in Polycystin-1 and -2 and is the main PKD type. Other PKD forms include autosomal-recessive PKD, nephronophthisis, BBS or MKS, in which PKD is part of a syndromic complex and typically affects infants or children (55).

The decisive pathogenetic events for all PKD forms are thought to occur during renal development (112). There is also strong evidence that defects in ciliary function cause PKD. All PKD gene products, for example, localize to the primary cilium and/or basal body, and for some specific ciliary functions have been identified (98,99). Moreover, the kidney-specific ablation of cilia leads to renal cysts (78). Cilia can be found on the apical surface of tubular epithelial cells where they are supposed to function as mechanosensors of fluid flow occurring in the tubular lumen. The mechanical stimulus is transduced by the calcium channel Polycystin-2 (probably with the help of Polycystin-1), which leads to an increase in cytosolic calcium (99). The signaling events triggered by this increase in calcium are poorly understood.

Cyst formation tends to occur during the proliferative phases in renal development (41,112). The cells still remain differentiated since even in cysts the epithelial barrier function is maintained. This factor distinguishes PKD from cancerous diseases. Presumably, a defect in the temporal control of differentiation or in the orientation of tubule growth occurs during renal development. Normal tubule growth is most likely driven by convergent extension movements and oriented cell division—two processes that are both controlled by the PCP pathway (7,9, 43,65) (see Figure 4). Although convergent extension movements have not yet been described for the developing kidney, oriented cell divisions were recently observed by Fischer and colleagues. They found that during postnatal life there is massive cell proliferation in the maturing nephron. Because of a strict alignment of the mitotic spindle with the tubule axis, this growth phase does not lead to an increase in tubule diameter. In contrast, cystic kidneys display a randomization of the mitotic angle of the dividing tubular epithelial cells that could account for cyst formation (41). Another group also demonstrated that in mouse models lacking cilia, spindle orientation defects can be seen during development and also during repair processes following kidney injury (108). Taken together, these results suggest that the PCP pathway might regulate the planar growth of developing and injured tubules in the kidney.

Aberrant PCP signaling could therefore cause uncoordinated growth, which might lead to an increase of tubular diameter and, thus, cyst formation. This hypothesis was strengthened recently by the finding that mice mutant for *Fat4*, an orthologue of *Drosophila* Fat, exhibit polycystic kidney disease in addition to PCP phenotypes in the cochlea and the neural tube. *mFat4* mutant kidneys also showed genetic interaction with *Vangl2* and *Fjx*, the orthologue of *Drosophila* *fj*. The mitotic angle was slightly randomized in dividing tubular epithelial cells of *Fat4*^{-/-} kidneys. In addition, *Fat4* localized to the primary cilia in interphase Madin-Darby canine kidney cells (116).

How could cilia be involved in setting up the division plane for tubular epithelial cells? Cilia may well sense and transmit the directional cues for spindle orientation before onset of mitosis. During mitosis, cilia are not present, as the centrosomes are required for the spindle apparatus by forming the spindle poles. Another possibility is therefore that the centrosomes but not the cilia are directly involved in spindle orientation. Centrosomes could also be involved in polarization events that occur right after mitosis. Ciruna et al. (20) found that in neuroepithelial cells in zebrafish the PCP pathway is necessary to reestablish cell polarity that is transiently lost during mitotic cell division and to reintegrate daughter cells into the tissue. Strikingly, neural tube defects in the *Vangl2/trilobite* mutants can be rescued by blocking cell division (20). Since the inhibition of the cell cycle is an effective treatment in murine models of PKD, this effect may be due, at least in part, to the PCP pathway performing similar functions in the mouse nephron as in the zebrafish neural tube (14).

A COMMON RIGHT DIRECTION FOR PCP IN DIFFERENT SPECIES

The diversity of tissues in mammals poses a challenge in the search for a unifying theme of the PCP pathway across species and organs. Each tissue has likely found its own variation on a theme in utilizing the PCP core pathway to develop and maintain its three-dimensional architecture. Cilia can be envisioned as global navigation devices providing each cell in a tissue with positional information (10). This characterization is especially true for sensory cilia, which could indeed be helping or even instructing the PCP pathway in its tissue-shaping task. Multiciliated cells, on the other hand, could be instructed by the PCP pathway to perform their vectorial functions across the plane of the epithelium. Park and colleagues recently demonstrated that Dsh functions in a ciliogenetic pathway together with Inturned and Rho to anchor basal bodies at the apical plasma membrane (106). Dsh was found to localize asymmetrically near the base of the cilia regulating the sort of planar polarization that underlies directional beating of cilia. These authors also reported that Dsh functions to link basal bodies with membraneous vesicles that then fuse with the plasma membrane and thus appear to govern the final step of basal body docking to the plasma membrane. The vesicles contain members of the Exocyst complex, which are involved in polarized membrane trafficking. The Exocyst complex has previously been shown to regulate the trafficking of PCP core factors such as Flamingo in the *Drosophila* wing (21). In the same system, the *dsh¹* mutation compromises the polarized distribution of Flamingo (141). Apart from the Exocyst complex, Dsh also seems to associate with other components of the vesicular trafficking machinery, suggesting that one mechanism for Dsh function might lie in the regulation of membrane trafficking (18,71,163).

Although several caveats still exist, these examples nicely demonstrate how work carried out in different systems—mammalian and *Drosophila*—can lead to a unifying hypothesis about the function of PCP core factors. It is hoped that we will see more of these examples, leading in the future to a more complete understanding of the molecular mechanisms underlying the roles of PCP signaling pathway(s).

PCP is a molecular pathway with big potential. Every tissue or organ can make use of it in one way or the other for coupling cell-cell communication with tissue development and function.

The PCP field has already worked its way into a number of tissues and diseases of different species. Nevertheless, much work is needed to find a common right direction.

Acknowledgments

We thank Carlo Iomini, William Gault, and Jennifer Zallen for careful reading of and comments on the manuscript. We are grateful to John Wallingford and Helen McNeill for sharing data prior to publication, and to Jeremy Nathans and Jennifer Zallen for pictures and drawings. We thank all members of the Mlodzik lab for continuous discussions and support. Work in the Mlodzik lab is supported by grants from the NIH/NIGMS and the NIH/NEI. M.S. is supported by a postdoctoral fellowship from the Deutsche Forschungsgemeinschaft.

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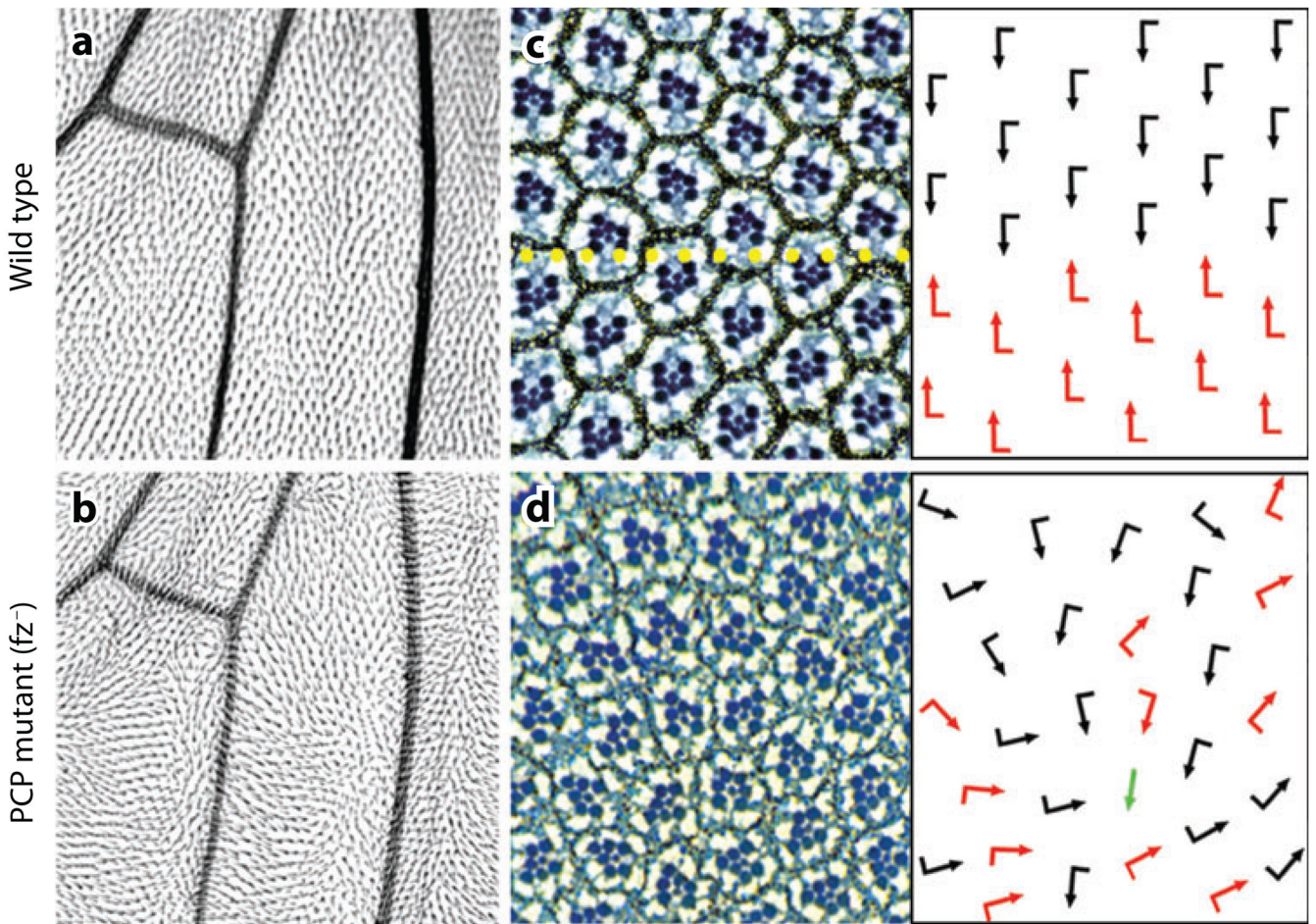


Figure 1. Typical examples of PCP features in *Drosophila*. PCP effects in the wing (*a,b*) and eye (*c,d*). Wild type is shown in panels *a* and *c* (note the regular arrangements in both tissues), and the mutant appearance (*fz⁻*) of same tissues is shown in *b* and *d*. (*c* and *d*) The right panels show the orientation of ommatidia schematically by arrows: black and red arrows represent the dorsal and ventral orientations (not mirror image symmetry in wild type/*c*) and loss of it in the mutant scenario. Occasional symmetrical ommatidia (*green arrow*) are also found in the mutants.

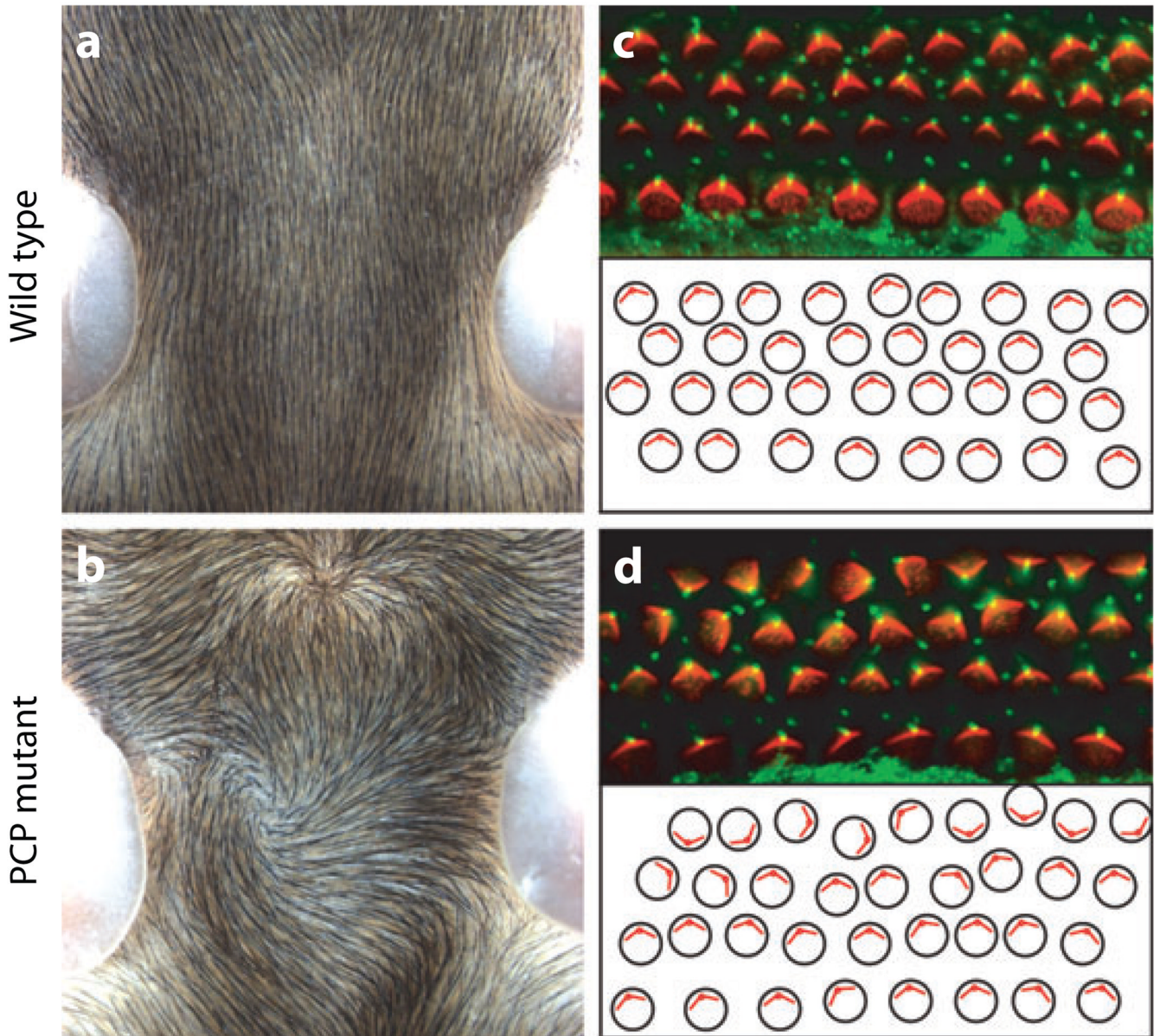


Figure 2. Examples of PCP features in mammals. PCP features of the mouse skin (*a,b*) and the inner ear (*c,d*). (*a,b*) Dorsal view of mouse neck and the orientation of the skin hair in wild-type mice (*a*) and *fz3* mutant mice (*b*). Note random whorls, swirls, and waves in the mutant genotype as compared to the normal anterior-posterior orientation in *a*. In *a* and *b* anterior is up. (*c,d*) Orientation of sensory hair cells of the mammalian (mouse) cochlea (inner ear). Each cell contains polarized bundles of actin-based stereocilia (labeled *red* with phalloidin) and a tubulin-based kinocilium (labeled with antiacetylated tubulin in *green*). In PCP mutants these bundles still form but their orientation becomes randomized [*d*; *Looptail/Vangl2* (*stbm*) mutant]. The lower panels in *c* and *d* show schematic representation of the cellular (actin bundle) orientation reflecting their randomized appearance in the mutant. The original pictures were kindly provided by Jeremy Nathans.

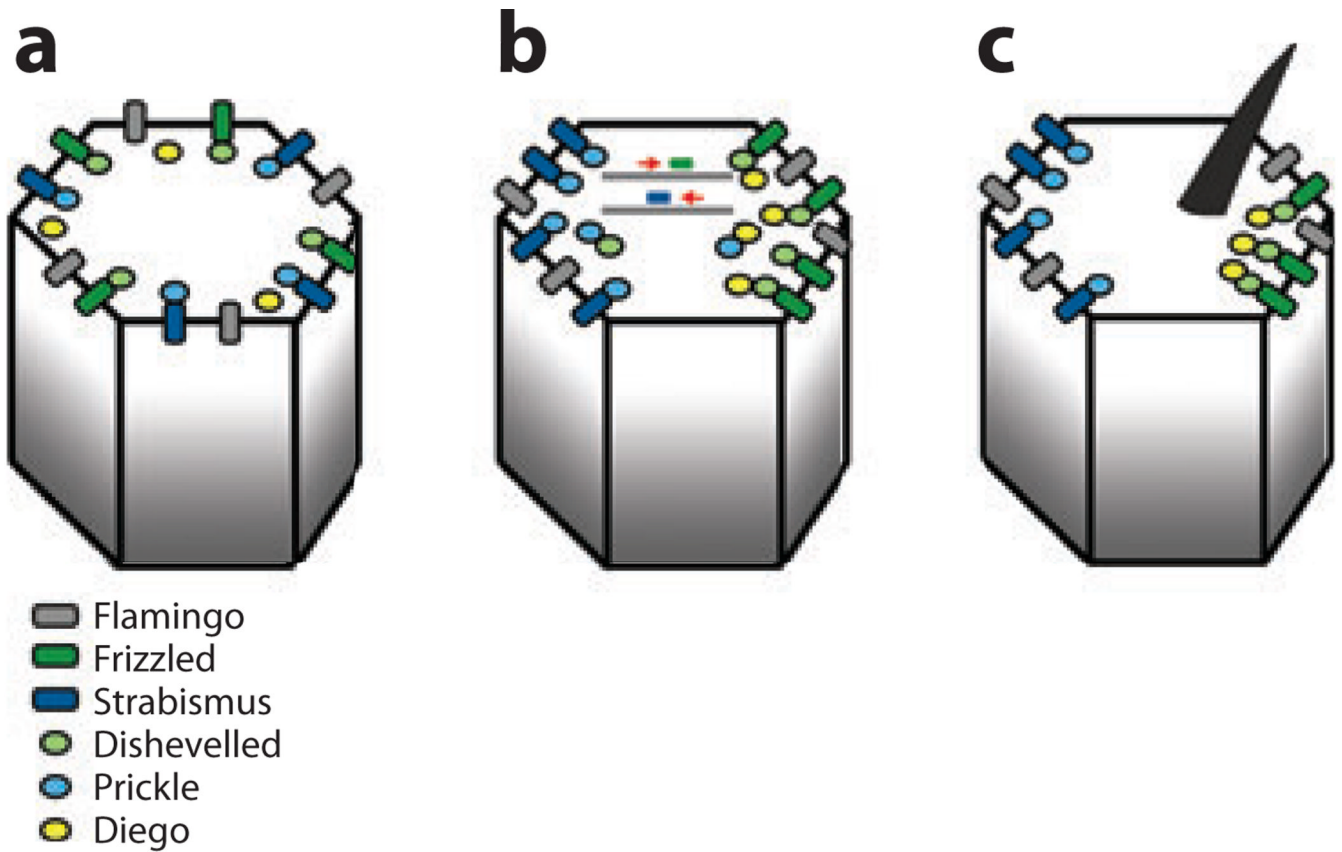


Figure 3.

Schematic presentation of the generation of asymmetric core PCP protein localization in *Drosophila* wing cells. In pupal wing cells, the core PCP proteins of the Fz/Fmi cassette become asymmetrically localized to proximal and distal cell membranes. Proximal is left and distal is right in all panels. A single cell at different stages maturing from left to right is shown in the respective panels *a–c*. (*a*) Schematic of the localization of the core PCP proteins prior to any asymmetry detection at the onset of their interactions. (*b*) During polarization the Fz-Dsh-Dgo complexes become enriched at the distal end of each cell, whereas the Stbm-Pk complexes concentrate proximally. Fz has been seen to travel distally on microtubule-associated particles (121), and something similar might also happen for Stbm/Vang. (*c*) Final stage of polarization with all complexes resolved in either distal (Fz-associated protein or proximal cell ends. An actin-based hair is formed close to the distal vertex of each cell (where Fz-Dsh are localized). The *Drosophila* pupal wing is the only tissue in which the localization of all core PCP proteins has been analyzed; all but Dsh have also been analyzed in the *Drosophila* eye.

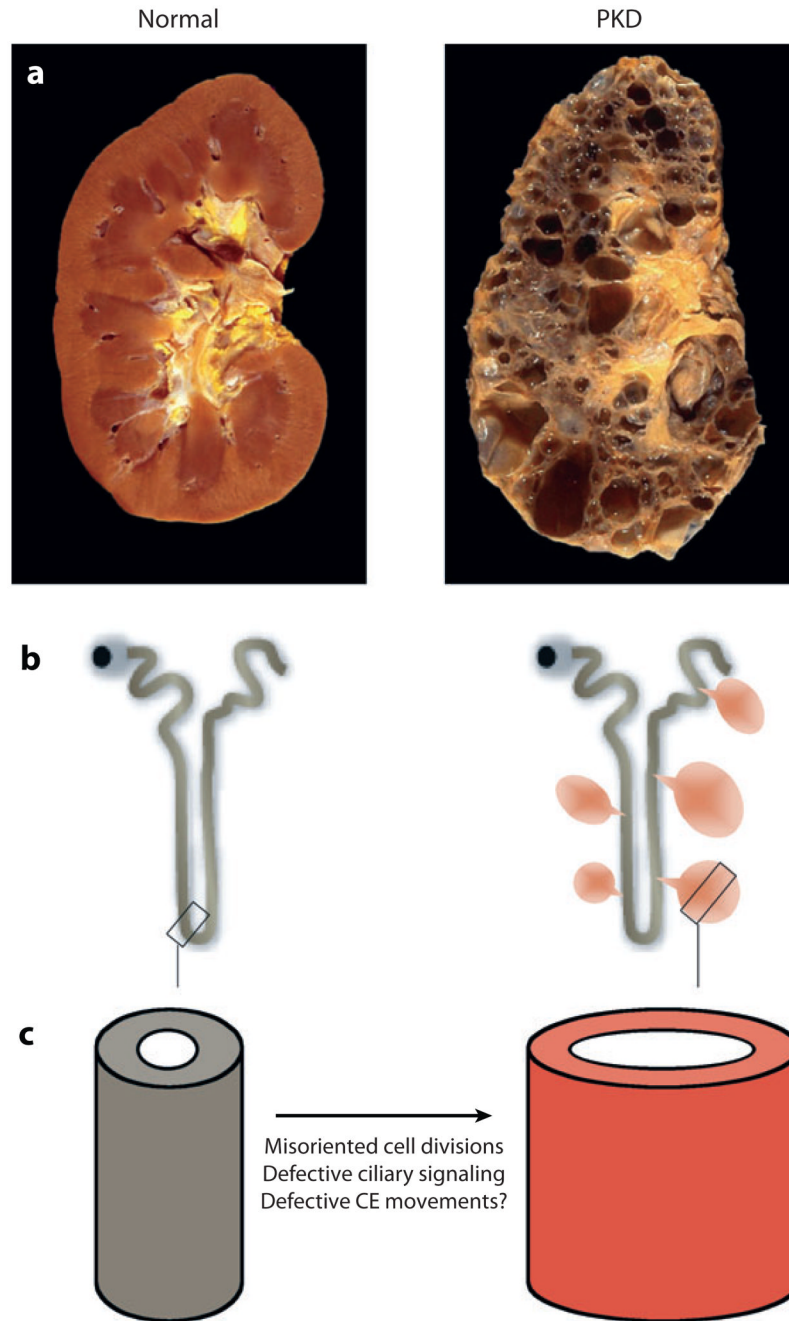


Figure 4. PCP and polycystic kidney disease (a) Photographs of a healthy (*left*) and a polycystic kidney (*right*). (b) Schematic diagram of the nephron, the functional unit of the kidney. In ADPKD, cysts arise from all segments of the nephron (*right panel*). (c) Cyst formation is thought to be caused, in part, by defective PCP signaling. The PCP pathway regulates the cell division plane of epithelial cells in the elongating tube during renal development. More speculatively, elongation of the growing tube could also be driven by convergent extension-like movements. The cilium might provide directional cues for the regulation of these two processes.

Table 1

PCP factors in *Drosophila* and vertebrates

<i>Drosophila</i> gene	Tissues affected in <i>Drosophila</i>	Molecular features	Vertebrate homologues involved in PCP (see also Table 2)	Selected associated PCP-specific references
Core Fz/PCP components				
frizzled (<i>fz</i>)	All adult tissues	Seven-pass transmembrane receptor; binds Wnt ligands; binds Dsh; recruits Dsh and Dgo to membrane	<i>Fz3</i> (mouse)	(32,47,144,151,153,168)
			<i>Fz6</i> (mouse)	
			<i>Fz7</i> (<i>Xenopus</i>)	
<i>dishevelled</i> (<i>dsh</i>)	All adult tissues	Cytoplasmic protein containing DIX, PDZ, DEP domains; recruited to membrane by Fz; binds Fz, Pk, Stbm, and Dgo; undergoes extensive phosphorylation	<i>Dvll</i> , 2, and 3 (mammals)	(5,13,126,133,148)
			<i>XDsh</i> (<i>Xenopus</i>)	
<i>prickle</i> (<i>pk</i>) (a.k.a. <i>prickle-spiny legs</i>)	All adult tissues	Cytoplasmic protein with 3 LIM domains and PET domain; recruited to membrane by Stbm; physically interacts with Dsh, Stbm, and Dgo; competes with Dgo for Dsh binding	<i>pk1</i> and 2 (mouse, zebrafish)	(15,46,61,135,140,143)
<i>strabismus</i> (<i>stbm</i>)/ Van Gogh (<i>Vang</i>)	All adult tissues	Novel 4-pass transmembrane protein; binds Pk, Dsh, and Dgo; recruits Pk to membrane	<i>trilobite</i> (<i>tri</i> ; zebrafish)	(20,60,62,95,136,155)
			<i>Vangl1</i> (mouse; function unknown)	
			<i>Vangl2</i> (<i>looptail</i> ; mouse)	
<i>flamingo</i> (<i>fmi</i>)/ <i>starry night</i> (<i>stan</i>)	All adult tissues	Cadherin with seven-pass transmembrane receptor features; capable of homophillic cell adhesion	<i>Celsr1</i> (mouse)	(27,30,141)
<i>diego</i> (<i>dgo</i>)	Most adult tissues, notum only in GOF	Cytoplasmic ankyrin repeat protein; recruited to membrane by Fz; binds Dsh, Stbm, and Pk; competes with Pk for Dsh binding	<i>Diversin</i> (<i>ankyrin repeat domain 6</i> ; <i>ankrd6</i>)	(29,40,61,93,117,123)
			<i>Inversin</i> (<i>invs</i>)	
Fz/PCP signaling regulators				
<i>Casein Kinase 1ε</i> (<i>CK1ε</i> ; <i>discs overgrown/dco</i>)	Eye and wing*	S/T protein kinase; acts positively on Fz/PCP signaling; regulates Dsh localization	<i>CK1 epsilon</i>	(24,72,131)
<i>widerborst</i> (<i>wdb</i>)	Wing, not eye	Regulatory subunit of the PP2A phosphatase	N.D.	(51)

<i>Drosophila</i> gene	Tissues affected in <i>Drosophila</i>	Molecular features	Vertebrate homologues involved in PCP (see also Table 2)	Selected associated PCP-specific references
<i>G protein o α47A</i> (<i>G-ou47A</i> ; <i>brokenheart</i> , <i>bkh</i>)	Wing*	The α subunit of the G _o protein; has asymmetric localization in the wing, which requires Fz. Also shown to regulate Fz localization in the wing	Galpa proteins	(3,64,79,149)
Fat/Dachsous PCP group factors				
<i>fat</i> (<i>ft</i>)	All adult tissues	Divergent member of the Cadherin superfamily; heterophillic interaction with Ds; cytoplasmic domain binds Atrophin	<i>mFat4</i>	(16,74,82,86,87, 116,122,160)
<i>dachsous</i> (<i>ds</i>)	All adult tissues	Divergent member of the Cadherin superfamily; heterophillic interaction with Fat	N.D.	(16,74,82,86,87, 122,160)
<i>four-jointed</i> (<i>ff</i>)	All adult tissues	Type-2 transmembrane protein; possibly functions in Golgi to modify Ds	N.D.	(122,130,166,167)
<i>atrophin</i> (<i>atro</i>)	Eye and wing	Transcriptional corepressor; binds to cytoplasmic domain of Fat	N.D.	(38)
PCP effectors				
Fz/PCP signaling effectors				
<i>dDAAM</i>	?	Formin-homology (FH) domain protein that binds both Dsh and RhoA. The <i>Drosophila</i> homolog is with other FH proteins	<i>XDaam1</i>	(49,88)
	PCP defects only observed in GOF			
<i>dRac1</i>	Eye and wing*	Small GTPase of Rho subfamily, acts downstream of Dsh	<i>Xrac1</i> (<i>Xenopus</i>)	(35,39,48,96)
<i>dRhoA</i>	Eye and wing*	Rho family of small GTPases, acts downstream of Dsh	<i>RhoA</i>	(39,49,96,129,134)
<i>misshapen</i> (<i>msn</i>)	Eye, wing and notum*	STE20-like S/T protein kinase acting downstream of Dsh		(103)
<i>Rho Kinase</i> (<i>drok</i>)	Eye and wing*	RhoA effector protein; S/T kinase	<i>rho kinase 2</i> (<i>rok</i> ; zebrafish)	(83,154)
Tissue-specific PCP effectors (in <i>Drosophila</i>)				
<i>inturned</i> (<i>in</i>)	Wing	A cytoplasmic protein with a	<i>inturned</i> (<i>Xint</i> ; <i>Xenopus</i>)	(105,107,164)

<i>Drosophila</i> gene	Tissues affected in <i>Drosophila</i>	Molecular features	Vertebrate homologues involved in PCP (see also Table 2)	Selected associated PCP-specific references
		putative PDZ domain that requires Fz/PCP for localization to the proximal side of wing cells where Stbm and Pk are also localized		
<i>fuzzy (fy)</i>	Wing	A putative four-pass transmembrane protein that genetically interacts with <i>inturned</i>	<i>fuzzy (Xfy; Xenopus)</i>	(22,105)
<i>fritz (frtz)</i>	Wing	Coiled coil WD40 Protein	N.D.	(23)
<i>multiple wing hair (mwh)</i>	Wing	Molecular data is unavailable, but genetically <i>mwh</i> is downstream of <i>fz</i> ; and may work in parallel to <i>fy</i>	N.D.	(2,25,156)
<i>nemo (nmo)</i>	Eye	S/T protein kinase (MAPK superfamily; Nlk subfamily)	<i>Nlk</i> members	(19,137)
Vertebrate-specific PCP factors				
		Member of Wnt family of secreted glycoproteins	<i>Wnt5/pipetail (ppt; zebrafish)</i>	(52,68)
		Member of Wnt family of secreted glycoproteins	<i>Wnt11/silberblick (slb; zebrafish)</i>	(52)
		Member of Wnt family of secreted glycoproteins	<i>Wnt7a (mouse)</i>	(28)
		Glypican family member, required for Wnt signaling	<i>Glypican 4/6/knypek (kny; zebrafish)</i>	(138)
		Receptor Tyrosine kinase family member	<i>PTK7 (protein tyrosine kinase 7; mouse)</i>	(81)
			<i>Xpkt7 (Xenopus)</i>	
		S/T protein kinase of PKC superfamily	<i>PKCδ (protein kinase Cδ Xenopus)</i>	(69)

* Other tissues were not tested.

N.D.: not determined.

Table 2

Vertebrate PCP phenotypes

Tissues affected (defects)	Genes	References
CNS (neural tube closure defect)	Fz3/6, Dvl1/2, Vangl1/2, Celsr1, Fy, Int, BBS4/6, PTK7	(27,50,66,67,81,95,105,111, 115, 150,151)
Cochlea (stereocilia patterning)	Fz3/6, Dvl1/2, Vangl2, Wnt5a, BBS4/6, PTK7	(81,95,115,150,151)
Skin (hair patterning)	Fz6, Inv/NPHP2	(47,123)
Cardiac (outflow tract abnormalities)	Dvl2, Vangl2	(50,111)
Renal (polycystic kidneys)	Fat4, BBS genes, NPHP genes	(55,92,116)
CNS (axon guidance)	Fz3, Celsr2/3,	(119,153)
Anterior-posterior body plan (shortened body axis)/convergent extension	Virtually all PCP genes analyzed in this context display this phenotypic feature	See throughout the text and above in this Table