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Planar Cell Polarity Signaling: Coordination of cellular orientation across tissues

Jaskirat Singh and **Marek Mlodzik***
Department of Developmental & Regenerative Biology Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1020, New York, New York 10029

Abstract

Establishment of Planar Cell Polarity (PCP) in epithelia, in the plane of an epithelium, is an important feature of the development and homeostasis of most organs. Studies in different model organisms have contributed a wealth of information regarding the mechanisms that govern PCP regulation. Genetic studies in *Drosophila* have identified two signaling systems, the Fz/PCP and Fat/Dachsous system, which are both required for PCP establishment in many different tissues in a largely non-redundant manner. Recent advances in vertebrate PCP studies have added novel factors of PCP regulation and also new cellular features requiring PCP signaling input, including the positioning and orientation of the primary cilium of many epithelial cells. This review focuses mostly on several recent advances made in the *Drosophila* and vertebrate PCP field and integrates these within the existing PCP signaling framework.

Keywords

PCP; Frizzled; Dishevelled; Cilia; Convergent extension; Organ patterning

Polarization of epithelia is an important feature for the development, patterning, maintenance and homeostasis of individual organs and whole organisms. All epithelia are defined by their apical-basal polarization, which is critical for its function in vectorial secretion and uptake and also as barrier between a fluid filled space and the organism internal tissues. In addition, many (if not all) epithelia are also polarized within the plane of the epithelium. Polarization within the plane is referred to as Planar Cell Polarity (PCP).

The study of PCP originates from an observation in insects some 40 years ago, then referred to as "tissue polarity"[1–3]. Emerging from its obscurity, a lot has been uncovered since these early PCP studies and this type of polarity has become a highly studied topic of mainstream research[4–8] and links to human disease states[9]. *Drosophila* has been a highly valuable organism for the study of PCP, as all of its adult cuticular structures display PCP features and are thus easy to study (Figure 1)[4–6]. *Drosophila* PCP establishment has contributed a wealth of information regarding the mechanisms that govern PCP establishment[4–6, 10, 11]. Studies in *Drosophila* have uncovered two groups of PCP factors/systems: (1) the Frizzled (Fz)/PCP core group, which includes Fz, Van Gogh/Strabismus (Vang/Stbm), Flamingo (Fmi; a.k.a. Starry Night/Stan), Dishevelled (Dsh), Prickle (Pk) and Diego (Dgo) (see Table 1 for details), and (2) the Fat/Dachsous (Ds) group containing Fat, Ds, Four-jointed (Fj), Dachs, and Approximated[5, 12] (Table 1).

*Corresponding Author 1-212-241 4272 <Marek.Mlodzik@mssm.edu>.

PCP studies in vertebrates revealed that the Fz/PCP core factors are functionally conserved[4, 7, 8] (Table 1). Such vertebrates studies have identified several processes that now serve as model systems for PCP analyses (Fig. 2). These include, for example, the polarization of rows of sensory cells in the mammalian inner ear/cochlea[13, 14], mouse skin hair orientation[15], mucus secreting and ciliated cells in the *Xenopus* skin[16], somitic patterning in the chick[17], cell orientation of the lateral line in fish development[18], left-right asymmetry generated by ciliary function in the node[19–24], and other cilia associated functions throughout development[8, 9, 25]. In addition to these largely epithelia-associated PCP features, Fz/PCP-signaling is required during the convergent extension (CE) process in gastrulation and neurulation, a cellular process involving mesenchymal cells that require polarization to allow cells to converge and intercalate leading to body axis elongation[26–29].

Apart from the core PCP factors, regulatory proteins have been identified that specifically modulate core Fz/PCP group members. These include among others Casein kinase 1ε[30] and Abelson kinases [31] with a documented PCP function in several organisms or more specifically in vertebrates, Ror2[32–34], Ryk[35, 36], RACK1[37, 38], and Smurf1/2[39]. Additionally, other factors have been proposed to act in PCP like $G\alpha_o$ and Widerborst (a regulatory subunit of PP2A) in *Drosophila*[40, 41], or PAR 1 in *Xenopus*[42] just to mention a few (see also Table 1). These factors are thought to modulate the core components of the Fz/Dsh-PCP signaling pathway.

In this review we highlight the latest developments in the PCP field in *Drosophila* and integrate these findings with the previous data. Likewise we compare these studies to recent advances in vertebrate PCP research. We will focus primarily on Fz/PCP signaling, but will also briefly discuss its relationship to the Fat/Ds-system.

HOW MANY PCP-SIGNALING SYSTEMS REGULATE PCP ESTABLISHMENT?

The Fz/PCP signaling cassette regulates PCP establishment in all adult external *Drosophila* tissues and in many if not all vertebrate contexts. The general features are conserved, with the vertebrate systems having a larger set of regulatory components as compared to *Drosophila* (see below and Table 1). The Fat/Ds-system is also required in all PCP contexts in *Drosophila* and likely also in many PCP models in vertebrates[5, 43].

The relationship between local Fz/PCP-signaling and the long-range regulation of PCP across a field of cells remains a topic of great interest. In the past it was proposed that both Fz/PCP and the Ft/Ds-systems function in a single pathway to establish PCP, with the Fat/Ds-group asymmetrically regulating the activity of Fz/PCP-signaling[44]. This hypothesis was based on observations that components of the Fat/Ds system (notably Ds itself and Four-jointed) are expressed in a gradient, whereas the core factors of the Fz/PCP pathway are expressed uniformly across all tissues analyzed[45, 46]. As such, they would lend themselves as an asymmetric input to Fz/PCP signaling, as to date an upstream regulatory input to the Fz/PCP pathway remains unknown in *Drosophila* (see below). However, the single-pathway hypothesis has been questioned and refuted by a comprehensive set of experiments in the *Drosophila* abdomen model of PCP[47]. This study elegantly demonstrated that the Fz/PCP and Fat/Ds-systems act independently of one another and thus are two parallel pathways. Both *fz* and *fat*/*ds* display non-autonomous effects (in both gain and loss-of-function scenarios) on neighboring wild-type cells in the absence of the other system. For example, *fz* and/or *fmi* mutant backgrounds do not affect the non-autonomous effects of the clonal expression of Ft or Ds, and similarly the inverse holds true as well[47]. The proper interpretation of these data must be that the Ft/Ds system does not require the presence of Fz/PCP signaling for its polarity information and vice versa[5]. The global mechanism(s) by which PCP is regulated across a field of cells still remain unclear (see below).

PCP ESTABLISHMENT IN *DROSOPHILA*

In *Drosophila*, PCP features are the most evident and thus preferentially studied in the eye, wing, thorax and abdomen[4–6] (also Fig. 1). Much of the present day understanding of PCP establishment comes from numerous studies in these *Drosophila* tissues. Strikingly, several of the *Drosophila* tissues, while relying on a conserved signaling cassette, show variations in PCP establishment: in the eye Fz/PCP signaling sets up cell fate determination through gene expression; in the thorax/notum, PCP mediates spindle orientation in the sensory organ precursor cells; and PCP in the abdomen and wing largely results from localized asymmetric actin polymerization giving rise to asymmetrically positioned cellular hairs. Each of the *Drosophila* tissues shares unique advantages and features and thus studying PCP in multiple tissues is very helpful to understand the underlying conserved general features and also the differences between tissues.

In the following sub-chapters, we will discuss the specifics of PCP establishment in these *Drosophila* tissues.

PCP in the Drosophila *wing*

Historically this is one of the most studied “model organs” in animal development, serving as a paradigm for many patterning events including the action of morphogens. One of the last steps in wing development is the precise orientation of wing cells in the proximal-distal axis mediated by PCP signaling.

In adult wings, cells are uniformly packed in a hexagonal manner with each cell producing a single actin-rich hair that originates from the distal vertex and points distally (Fig. 1c–d and 3a). PCP generation in the wing follows earlier patterning processes that define the wing regions and cell fates. PCP in the wing is initiated during late 3rd instar larval and early pupal stages[48, 49]. Although it was thought until recently that the first apparent signs of polarity become evident in mid-pupal stages[50–53], recent work has firmly established that PCP in the wing is already visible in the prepupa and early pupal stages[48, 49]. Strikingly at these early stages, PCP orientation is aligned in a radial manner perpendicular to the wing margin, rather than in the proximal-distal axis evident in the adult[48]. The late proximal-distal arrangement is generated from the early radial pattern through a series of cellular rearrangements, including cell flow and rotation induced by anisotropic mechanical stress, originating from the contraction of the hinge region during wing development in pupal stages[48]. Hinge contraction causes wing cells (besides their proximal streaming) to rotate in opposing directions in anterior and posterior compartments and these cell movements eventually reorient PCP to the proximal-distal axis[48, 54].

The first sign of PCP-type polarization is evident in the asymmetric localization of the proteins of the Fz/PCP core group (Fig. 3). How is this established? Initially and prior to the stage when PCP is visible, all core PCP factors are uniformly localized in a subapical ring, partially overlapping with adherens junctions[55]. This is best understood and studied in the *Drosophila* wing, but largely applies to all *Drosophila* tissues and probably also to vertebrate PCP establishment. First, the subapical localization of Fz/PCP components is a prerequisite for the interactions that will define polarization in the plane[55]. Through subsequent interactions among the core Fz/PCP factors, two stable complexes form on opposing sides of each cell: a Vang/Stbm-Pk complex and a Fz-Dsh-Dgo complex (Fig. 3; asymmetric localization of the core PCP factors is the first visible sign of planar polarization/PCP). Fmi becomes enriched at both ends of the apical membrane, helping to stabilize both complexes (see below). The two complexes are formed through a series of molecular interactions: (1) negative (inhibitory) intracellular interactions mostly between Pk and Dsh and modulated by Dgo[52, 56], (2) clustering of “like” complexes (e.g. Pk clusters Vang/Stbm intracellularly and Dsh causes Fz clustering

through their multimerization features[56, 57]), (3) intercellular stabilization across cell membranes mediated by Fz-Fmi complexes binding to Vang-Fmi complexes[53, 58–61], likely through a direct physical intertaction between Fz and Vang[60, 61], and (4) differential trafficking and stability of such complexes[49, 62, 63]. Within this molecular network Fz recruits Dsh to the membrane, while Vang/Stbm recruits Pk to the membrane. Dgo binds to Dsh and protects it from antagonistic binding by Pk and thus Dgo competes with Pk for Dsh binding (see earlier reviews[4, 6, 10] and also Fig. 3d). Of note, apical membrane localization of the core PCP proteins depends on Fmi, as well as on Fz and Vang/Stbm, as it is lost or strongly reduced in mutant clones of either *fz*, *Vang/stbm* and *fmi*[64, 65]. Besides these molecular interactions and interdependence of the core PCP factors, non-centrosomal microtubules (MT), which are aligned in the proximal-distal axis of wing epithelia[66, 67], contribute to the asymmetric localization. MTs appear to be polarized and direct the movement of Fz-Fmi complexes along them[62, 63]. Intriguingly, Ds and Ft have been shown to control both proximal-distal alignment and asymmetric polarization of MT, possibly through involving the Ser/Thr kinase PAR-1, the subcellular localization of which was altered in *ft* mutant and over expression clones[63].

Although these events are best understood in the *Drosophila* wing due to its relatively simple structure, many of these mechanisms are also key in establishing PCP in other *Drosophila* tissues and also likely in vertebrate PCP contexts (see below).

Once the PCP factor asymmetry is set, downstream effectors then set-up the initiation point for the formation of the actin hair, the so-called trichome. Mutations in core PCP genes not only disrupt cellular and trichome orientation, but can also result in cells with multiple wing hairs/trichomes. These downstream effectors which include inturned (in), fritz (frtz), multiple wing hair (mwh) and *fuzzy (fy)* are also proposed to localize asymmetrically and act downstream of core PCP genes[68–72]. *mwh* among these downstream effectors seems to be different in a way that it is genetically downstream of both core PCP members as well as the other downstream effectors like *in, frtz* and *fy*. Further, *mwh* is not required for the asymmetric localization of core PCP factors or the other downstream effectors, though proximal localization of Mwh itself depends on the other downstream effectors [73].

PCP in the fly eye

In the *Drosophila* eye, PCP is evident in the regular arrangement of ommatidia in the retina with respect to both the dorsal-ventral and anterior-posterior axes[10, 74, 75]. The *Drosophila* eye is a compound eye made up of ~800 ommatidia, each consisting of eight photoreceptor cells (R1–R8) and twelve non-neuronal accessory cells. Fz/PCP signaling sets up the asymmetric specification of the photoreceptor pair, R3 and R4, via nuclear signaling within each ommatidial precluster, giving rise to the two chiral forms of ommatidia across the dorso-ventral midline, the equator (Fig. 1a). This is then followed by a 90° rotation of ommatidial preclusters in opposing directions around the equator, resulting in a mirror-symmetric arrangement of ommatidia in the adult eye across the equator. Mutations in the core PCP genes disrupt R3/R4 specification, resulting in stochastic cell fate specification and random ommatidial chirality and rotation (Fig. 1b).

PCP in the eye is established in the third instar larval eye imaginal disc, where the R3/R4 precursor pair is part of the 5-cell precluster. In the 5-cell precluster (emerging from the morphogenetic furrow via an “arc”-configuration;[76]), the R3 precursor within the R3/R4 pair is closer to the equator than R4 and hence is thought to receive higher levels of Fz/PCP-signaling and adopts an R3 fate[77–79]. Fz activity in R3 then upregulates *Delta* (*Dl*) and *neuralized* (*neur*) transcription[77, 80, 81], which in turn activates Notch-signaling in the adjacent cell and specifies it as R4[77, 78, 80]. This two-tiered mechanism allows the robust amplification of small signaling differences at the Fz/PCP level to large and robust difference in Notch

signaling. Once Notch is active, the R4 fate is determined and, as such, indiscriminate activation of Notch in both cells of the R3/R4 pair results in symmetrical R4/R4-type ommatidia[77, 78, 80]. The initial Fz/PCP factor interactions in the R3/R4 cells are mediated by a very similar molecular circuitry among the Fz/PCP core set as in the wing, leading to their asymmetric localization (and activity) with the R3/R4 pair (Fig. 3b).

Following the cell fate specification of Fz/PCP signaling, ommatidial preclusters rotate 90° towards the equator in opposing direction in each half of the eye. Mutations in the core PCP factors usually not only result in random R3/R4 specification and associated chirality, but also in random ommatidial rotation. Generally, the rotation process is much less understood than the R3/R4-cell fate specification. As such rotation could be considered to be at a comparable effector level as trichome/wing hair formation. Accordingly, mutations in some of the Fz-Dsh effectors like Rho-associated kinase (dRok) display rotation defects when mutated in addition to a "multiple wing hair"-phenotype[82]. Besides the general downstream effectors of Fz/PCP-signaling such as dROK, Myosin Regulatory Light Chain (MRLC, Sqh in *Drosophila*) and Myosin II (Zipper) have been proposed to control ommatidial rotation[82, 83]. In addition, the cell adhesion factors E-cadherin/Shotgun (*shg*) and Drosophila N-cadherins (*cadN1* and *cadN2*) and their associated β-catenin (*arm* in Drosophila) protein have been implicated in rotation[84]. Few rotation specific genes are known, and of those *Nemo* (Nmo, the founding member of the Nlk subfamily of MAPKs), is the best characterized. Originally it was shown that mutations in *nmo* caused ommatidia to rotate only partially[85]. It was later shown that *nmo* is required for the entire rotation process[86]. Recent work has demonstrated that *nmo* serves as a link between the core PCP factors and the cell adhesion E-cad/β-catenin machinery, providing input to promote rotation and thus Nmo regulates the rate of rotation by affecting the activity of E-cad/β-catenin complexes[87]. Strikingly though, it is the Vang-Pk complex that interacts physically and genetically with Nmo (not the Fz-Dsh complex) and regulates Nmo activity by affecting its localization to the adherens junctions where it can then phosphorylate components of the E-cad/β-catenin complex[87]. Although the core PCP factors clearly feed into the rotation process, its regulation is more complex as it is also affected by Notch-signaling and EGF-receptor signaling input[88–90]. Thus although the specification of the R3/R4 pair is quite well understood, the integration of different signaling pathways[91] and the downstream events of ommatidial rotation remains less defined.

PCP on the Drosophila *thorax*

Similar to the wing, most of the fly cuticle is covered by cellular hairs (trichomes) aligned in the antero-posterior axis. Thus, common mechanistic interactions have been proposed to direct cellular orientation in other *Drosophila* tissues, including the abdomen and thorax (notum)[5, 47, 92, 93]. In addition, many cuticular structures like the notum display polarized orientation of a large number of sensory bristles (Fig. 1e and f). The development of these sensory bristles involves a primary cell (sensory organ precursor/SOP), which divides asymmetrically giving rise to two daughter cells (pIIa and pIIb). The asymmetric division *per se* is not affected in PCP mutants, but the orientation of the division axis/mitotic spindle is randomized in *fz*- and other core PCP mutant backgrounds[94]. The molecular interactions among the core Fz/PCP factors are largely the same, but in the case of the SOPs they result in an alignment of the spindle with the body axis. Although the mechanisms by which the PCP pathway regulates spindle orientation are not clear (and some redundancy might exist between the Fz/Dsh and Vang-Pk complexes[94, 95]), it has been shown recently that the DEP domain of Dsh is sufficient to orient spindle polarity in *Drosophila* S2 cells[96]. The Dsh DEP binds to C-terminal domain of the protein Mud (*mushroom body defective*, the *Drosophila* nuclear mitotic apparatus [NuMA] orthologue), and Mud is required for Dsh mediated spindle orientation. Mud is localized to the posterior cortex of the SOP, requiring Dsh for this localization, which itself is localized to the posterior cortex of SOP cells as part of the Fz/Dsh complex. Similarly,

during zebrafish gastrulation, reducing levels of NuMA disrupts spindle orientation suggesting a conserved mechanism by which the spindle is orientated in a proper axis[96]. Thus, although all three tissues/contexts use the same molecular system or cassette to establish PCP, the downstream effectors and interactions are context specific, ranging from actin polymerization in wing and body wall cells, nuclear signaling in photoreceptors, to spindle orientation in asymmetric cell divisions.

Intriguingly, the notum recently added a new cell behavior to the PCP puzzle: mechanical stress and cell flexibility can also affect PCP orientation[97]. Most of the cuticle/body wall cells on the notum are actually tendon cells where the muscles are attached (although externally they do not look different from other trichome bearing body wall cells). As such the tendon cells need to buffer the mechanical stress of muscle contraction as they establish PCP orientation. Filamin (*jitterbug* in flies) or the associated factor *chascon* (*chas*), expressed in tendon cells, are important for the maintenance of cellular PCP orientation on the notum by balancing mechanical stress generated by the attachment of the indirect flight muscles (IFMs) to the exoskeleton/cuticle. This mechanism is independent of and acts in parallel to Fz/PCP signaling[97]. It is likely that in other tissues, including vertebrate examples, a similar balance between mechanical pull and Fz/PCP signaling is required for proper cellular orientation.

REGULATION OF FZ/PCP CORE FACTOR SIGNALING

Upstream input to Fz/PCP signaling

Most studies of Fz/PCP signaling have addressed intracellular interactions and how these lead to the asymmetric PCP core complex localizations (Fig. 3). However, a big remaining question is how the initial directional bias is established in the first place. Although it was suggested that the Fat/Ds-system could be acting upstream of Fz/PCP signaling in *Drosophila* (see above), it has been quite convincingly demonstrated that two systems act in parallel[5, 47]. Fz/PCP and canonical Wnt/Fz-signaling share several membrane associated components, most notably Fz itself and Dsh. Canonical Wnt/Fz-signaling is activated by Wnt family members in vertebrates and *Drosophila*. In vertebrates, Fz/PCP signaling is linked to regulatory input from Wnts[98–102], but the precise mechanistic function of Wnts in vertebrate PCP regulation remains unclear. Do they activate Fz/PCP signaling or do they regulate other core PCP factors, e.g. as suggested for Ror and Vangl[99]. Alternatively they might regulate the asymmetric localization of any of the core Fz/PCP factors without directly regulating Fz/PCP signaling “activity” as asymmetric localization is more important in this context than cellular activation (see also below). Moreover, in *Drosophila* the involvement of Wnts (equivalent to mammalian non-canonical Wnts) and/or other “global” upstream regulatory input to Fz/PCP signaling remains a big question mark[53].

In vertebrates, Wnt5 and Wnt11 appear dedicated to Fz/PCP signaling. In particular, in zebrafish Wnt5/*pipetail* and Wnt11/*silberblick* have been shown genetically to regulate CE during gastrulation[100, 103]. Similarly, these Wnts act in PCP signaling in other vertebrate contexts as mainly shown through mammalian cell culture and mouse genetics (reviewed in[6, 29]). Interestingly, the non-canonical (PCP) Wnts do not appear to bind to the LRP5/6-Fz co-receptor complex, but bind only to Fz family members[104, 105]. The identification of Wnt-binding domains in the Ror2 and Ryk receptor tyrosine kinases (RTKs) and the fact these RTKs are also involved in PCP signaling[31, 99, 106–108] has suggested a complex co-receptor scenario for Wnt-Fz/PCP signaling. In particular, it has been demonstrated that Wnt5 can bind to a Ror2-Fz co-receptor complex[32, 34, 109, 110]. Interestingly, Wnt5a mediated activation of Ror2 also requires Dsh (and Fz) causing Ror2 phosphorylation of Ser864 (by GSK3), suggesting an analogous mechanism to Fz/Dsh-dependent canonical Wnt3a induced phosphorylation of LRP6[110]. Whether the equivalent Ror2 and Ryk homologues play any role in *Drosophila* PCP remains to be explored.

Are these PCP Wnts providing instructive information to orient PCP? The genetic data from zebrafish would suggest that Wnt5 and Wnt11 act in a permissive manner as the respective mutants can be rescued by RNA injections into the one or two-cell stage embryos[100, 101]. In contrast, recent papers suggest that non-canonical Wnts provide directional information to PCP establishment. Both Wnt11 (during chicken somite patterning) and Wnt5a (in mouse limb patterning) have been shown to provide directional cues to PCP signaling and cellular orientation[17, 99]. It is thus likely that the non-canonical Wnts do indeed serve an instructive PCP function and provide global orientation cues. However, the mechanism(s) by which non-canonical Wnts activate PCP signaling in vertebrates and whether Wnt5a or Wnt11 act through similar or different mechanisms remain unclear. It will be very interesting to dissect the mechanism(s) of their regulatory inputs; for example, it is not clear whether Wnt5a and Wnt11 act through the same or different Fz (and/or co-receptor) members. Moreover, the issue needs to be resolved also in *Drosophila* as well, where in tissues such as the wing (see above), dissection of a precise mechanism should be possible.

Dsh regulation and Fz/PCP pathway selection

At the level of the membrane, the core Fz/PCP factors interact among each other to resolve their initial homogeneous localization into two polarized complexes. These interactions are discussed in some detail above (see subchapter “PCP in the Drosophila wing” and Fig. 3d) and thus not repeated here. However, one member of the Fz core group Dsh (Dvl in mammals) deserves special attention. Dsh/Dvl proteins are quite central to the intracellular aspects of Fz/PCP establishment. Moreover, Dsh/Dvl also act in canonical Wnt-Fz signaling, required for beta-catenin stabilization and thus are at the branch point of canonical Wnt-Fz and PCP signaling pathways. As such, Dsh is central to signaling specificity regulation[111–113]. Second, it is both an integral component of the intracellular interactions between the core PCP complexes (see above; Fig. 3) and a critical link of the core factors to the downstream Fz/PCP-effector pathways, as it is thought to bind and localize downstream effectors (see for example reviews[4, 7, 114] for more detail on downstream Fz-Dsh signaling events). All Dsh/Dvl proteins contain three highly conserved domains, the DIX, PDZ and DEP domains, but have no catalytic activity[111–113]. There is also a conserved proline-rich region with a SH3 protein-binding motif downstream of the PDZ domain, which might act as binding substrate for SH3-domain containing proteins.

Whereas, there is a single Dsh in *Drosophila*, there are three Dvls (Dvl1, Dvl2 and Dvl3) in mammals. Genetic studies in mice have defined functional redundancy among all three Dvls as a result of their conserved structure and overlapping expression patterns during development[115]. Individual *dvl* knock out mice display very weak PCP defects or no defects[115]. Single homozygous mutants combined with trans-heterozygotes for another *dvl* display stronger phenotypes[116–118]. $dvl1^{-/-}$; $dvl2^{-/-}$ double knock out mice display neural tube closure defects, cochlear defects, and cardiovascular outflow tract defects[116]. These $dvl1^{-/-}$; $dvl2^{-/-}$ double knock phenotypes can be rescued by exogenous expression of Dvl3, consistent with functional redundancy among all Dvls[118].

Due to the above mentioned complexities of Dvl redundancy, functional studies have been more informative in *Drosophila*. However, it is still largely unclear how Dsh becomes “activated” and how it is differentially regulated between canonical Wnt-Fz and Fz/PCP signaling. One possible mechanism for specific Dsh regulation could be differential binding, where binding partners may interact with distinct domains of Dsh. Accordingly, distinct domains of Dsh are required in the different signaling pathways. Whereas the DIX domain functions exclusively in canonical Wnt-Fz signaling, the PDZ domain is required for both pathways, and the DEP domain acts in Fz/PCP signaling[111, 112, 119, 120]. Each of these domains has a defined set of binding partners. The PDZ domain, in particular, is quite promiscuous and

can be bound by many factors acting in either pathway. Moreover, the PDZ domain binds the C-tail of Fz receptors in either pathway context. For example, CK1 family members, GSK3, GBP/FRAT, Frodo, Dapper, Naked cuticle (Nkd), PP2A, IDAX (Inhibitor of Dsh and Axin) and Daple among others have been shown to associate with the PDZ domain and function in canonical signaling. DAAM1, Vang/Stbm, Pk, Dgo, and PAR1 can bind the PDZ domain in the context of PCP signaling[112]. The DEP domain acting specifically in PCP signaling also binds to a host of factors including potential downstream effectors and, importantly, it also plays a key role in the stable PCP specific membrane association of Dsh[112, 113, 121, 122] (see below). Although the mechanistic differences of Dsh membrane association for either canonical or Fz/PCP pathway signaling still remain largely elusive, it is a likely mechanism for differential activation of Dsh. The PCP specific membrane recruitment requires the DEP domain, while the DEP domain is dispensable for canonical signaling. In particular, a PCP-specific mode of regulation at the level of Dsh membrane recruitment has recently been documented[122]. It involves a basic surface within the DEP domain and its binding to an acidified intracellular plasma-membrane, making the Fz/PCP-specific Dsh-membrane recruitment pH dependent. This is generated by *dNhe2*, a Na^+/H^+ exchange pump, which co-localizes with Fz at the plasma membrane[122]. Intriguingly, other studies have documented that Prorenin receptor (PRR) and vacuolar H^+-ATPase mediated acidification are important in both the canonical and Fz/PCP pathways. PRR, as the name suggests binds to Renin, is a single pass membrane protein consisting of a large extracellular domain. PRR forms a complex with Fz and LRP6 thus acting as an adaptor between the Wnt receptors and vacuolar H^+-ATPase (V-ATPase)[123]. This was independently confirmed by two reports, demonstrating that *Drosophila* PRR binds Fz to regulate both canonical and Fz/PCP signaling pathways[124, 125].

Subcellular membrane localization is likely to provide signaling specificity cues even at the level of the Fz receptors. In *Drosophila*, distinct localization of Fz and Fz2 (dedicated to canonical signaling) is important for signaling. Fz is mainly localized subapically at adherens junctions, whereas Fz2 is distributed throughout the entire plasma membrane including the baso-lateral side[55]. The difference in subcellular localization is critical for Fz/PCP signaling and thus contributes to the signaling outcome: apical localization of Fz favors Fz/PCP signaling and is less effective for canonical signaling. Thus a (over)recruitment of Dsh to the subapical Fz site, depletes it from the canonical signaling pool[55]. The role of membrane association and/or subcellular localization of various Dvls in vertebrates remain poorly understood. For example, In *Xenopus* animal cap explants and in mammalian cells canonical Wnt signaling activation results in the membrane localization of Dsh/Dvls, while Wnt stimulation in embryonic mouse kidney cells results in the accumulation of Dsh/Dvl in and around the nucleus[126, 127].

A third potential regulatory input to Dsh is phosphorylation, which has been thought to provide pathway specificity. Dsh is hyperphosphorylated upon activation of either pathway, but the phosphorylation pattern is thought to vary between pathways. Due to the presence of many Ser/Thr residues (over 100 out of ~600 residues in Dsh/Dvls are Ser and Thr) identification of physiological pathway specific phosphorylation events remains challenging. A host of serine/threonine kinases has been identified which can phosphorylate Dsh, including many members of the Casein Kinase 1 superfamily, as well as Casein Kinase 2 family members, Par-1 and PKC family members[30, 42, 128–132]. The physiological relevance of these phosphorylation events remains unclear. Recently, Tyrosine (Tyr) phosphorylation has emerged as a likely contributor to Dsh/Dvl activity and signaling pathway selection. Dsh/Dvls are phosphorylated by Abelson family kinases on Tyr residues within the DEP domain and C-term[31]. Abl phosphorylation of Dsh on Tyr473 appears essential for its function in Fz/PCP signaling, while it is dispensable for canonical signaling. This appears to be conserved, as *Abl1*−/−, *Abl2*−/− double-knockout MEFs (mouse embryonic fibroblasts; removing all Abl function) display changes in Dvl2/3 phosphorylation patterns and subcellular localization, but display no change

in nuclear β-catenin levels and signaling[31]. The mechanistic insight of how Dsh/Dvl phosphorylation could provide pathway specificity however still remains obscure. One possibility is that different phosphorylation events result in changes in Dsh conformation, which results in differential protein-protein interactions and activation of a specific pathway.

Downstream effectors of Fz/PCP signaling

The downstream effectors of the Fz/PCP pathway differ depending on the tissue in which the pathway is being activated. This can range from activation of nuclear signaling, asymmetric organization of the cytoskeleton, or orientation of the mitotic spindle in epithelial cells. In the eye, Fz/Dsh signaling leads to transcriptional activation of for example the Notch ligand Delta, while in the wing epithelium actin cytoskeletal rearrangements lead to proper hair orientation.

Genetic and biochemical studies have shown that Fz/PCP signaling downstream of Dsh consists of small GTPases of the Rho subfamily (Rho, Rac and cdc42), the STE20 like kinase Misshapen (Msn), the Rho associated kinase (dROK), and the JNK MAPK cascades[66, 82, 120, 133]. Downstream of dROK, the role of Sqh (Myosin Regulatory Light Chain, MRLC) and Myosin II (Zipper) has been proposed to control ommatidial rotation in the eye and to restrict the formation of a single actin rich hair in developing wing cells[82]. Further studies in *Xenopus* have shown a similar requirement for RhoA during CE, suggesting a conserved mechanism of regulation downstream of Dsh[134]. This study has also identified a Formin homology domain protein, Daam1, which binds to both Dsh and Rho GTPase[134]. The N-terminus fragment of Daam1 has been shown to bind RhoA, while its C-terminal binds PDZ and DEP domains of Dsh thus linking Dsh and its downstream effector RhoA[134]. More recently in Xenopus, the role of Septins have been postulated downstream of the PCP effector Frtz to control collective cell migration and ciliogenesis, thus highlighting the diversity of effector proteins that are involved downstream of Fz/PCP signaling pathway[135].

The effectors of the Fz/PCP pathway downstream of Dsh have distinct functions and their requirement depends on the context in which they are activated. Although cytoskeletal organization is the main response in wing PCP and probably in CE during gastrulation, a transcriptional response is also important in the *Drosophila* eye. In the eye, genetic interactions suggest that JNK/p38 signaling acts downstream of Dsh. In biochemical assays, *Drosophila* Dsh acts as potent activators of JNK suggesting JNK downstream of Dsh[120]. Intriguingly, loss of JNK in the eye does not show a phenotype, possibly because of genetic redundancy in the JNK/p38 kinases in Fz/PCP signaling. Nevertheless JNK signaling has also been implicated in the context of CE in vertebrates, suggesting a general requirement of JNK in PCP establishment[136]. Downstream of JNK, the AP-1 transcription factor (consisting of Jun and Fos) has been proposed as one of the necessary nuclear factors for R3/R4 cell fate specification during eye development[137].

Recent work has also identified effectors of the Vang/Stbm-Pk complex[71, 72, 87], suggesting that this complex has signaling roles independent of its function to restrict the Fz/Dsh complex to one side of the cell. As such the regulator of ommatidial rotation, Nemo, is linked to its function in cell adhesion regulation by binding to the Vang/Stbm-Pk complex[87]. Similarly, the asymmetric localization of several of the factors that inhibit the formation of too many actin hairs (trichomes) being formed in individual cuticle/wing cells, is mediated by the Vang-Pk complex[71, 72]. These observations suggest that there is more effector signaling to be expected from the Vang/Stbm-Pk side of PCP signaling.

PCP, CILIA AND DISEASE

The cilium, a microtubule-based organelle present on the surface of many cells plays a critical role in many aspects of developmental patterning, signaling, and disease. The role of cilia in

vertebrate Hh-signaling has been studied extensively[138], while its role in other signaling pathways including canonical Wnt and PCP signaling remains unclear. The first study highlighting a connection between Wnt-signaling and ciliary function showed that Inversin (Inv, one of the two mammalian homologues of the core Fz/PCP factor Dgo), mutated in Nephronophthisis (NPHP, an autosomal recessive cystic kidney disease), was localized to cilia[139]. Inversin was originally identified due to its left-right polarity defect in mouse (hence its name), which provided a further link to PCP signaling (PCP signaling is thought to regulate at least some aspects of left-right specification[8, 140, 141]). Inversin was later shown to co-localize with Dvl1 in MDCK cells and to inhibit canonical Wnt-signaling by targeting Dvl for degradation, while also being required for CE in *Xenopus* embryos[142].

The primary cilium is anchored to the cell surface by a microtubule-based structure, the basal body, which serves as a nucleation site for the growth of the axoneme as well as plays a role in cell division. Directional beating of motile cilia has been shown to require PCP signaling in several tissues, primarily by regulating the orientation of the basal body[143–145]. Mutations in components of the basal body such as *bbs1*, *bbs4*, *bbs6*, *mkks*, *ift88* and *kif3a* not only show PCP associated defects (disorganized stereocilia) in the cochlea and CE but these mutants also interact with core PCP pathway components (e.g.[146–149]). Conversely, components of ciliary and centrosomal machinery such as the ciliary kinesin Kif3A, the Bardet-Biedl (BBS) proteins, the nephronophthisis protein 3 (NPHP3), and the oro-facial-digital syndrome protein (OFD1), have been implicated in Wnt signaling pathways[147, 148, 150]. Mutations in these ciliary proteins have been linked to rare diseases referred to as ciliopathies, including Bardet-Biedl syndrome (BBS), Autosomal-dominant polycystic kidney disease (ADPKD), Oro-facio-digital syndrome (OFD), Meckel-Gruber syndrome (MKS), and Nephronophthisis (NPHP) and are caused by defects in cilia formation and function[151, 152]. As such, defects in primary cilia underlie the pathogenesis of Bardet-Biedl syndrome (BBS), a genetic disorder whose symptoms include among others obesity, retinal degeneration, and nephropathy[153]. The depletion of BBS proteins also impair CE movements in zebrafish and genetically interacts with the mouse *Vangl2* allele *looptail* in the context of neural tube closure and stereociliary bundle orientation in the cochlea[146, 147]. Furthermore PCP proteins have also been implicated in neural tube closure defect (NTD). This was first shown in patients with familial and sporadic NTDs, where mutations in Vangl1 were reported[154, 155].

In kidney, defective PCP signaling has been linked to polycystic kidney disease (PKD), probably via proper orientation of the cilia/basal body apparatus. There is strong genetic co-relation showing that the defect in cilia is one of the contributing factors to the PKD pathogenesis thus providing an indirect link between PCP and PKD[156, 157]. ADPKD is caused by mutations in *Pkd1*, which encodes a large transmembrane protein polycystin-1 (PC1) or by mutations in *Pkd2* encoding a TRP cation channel polycystin-2 (PC2) that regulates calcium entry inside a cell. These proteins localize to the ciliary axoneme of kidney tubule epithelial cells[158]. Direct evidence of PCP protein involvement in cystic kidney disease comes from studies of mouse *fat4* loss-of-function, which resulted in disruption of tubule formation during kidney development[43]. *fat4* mutant kidneys showed randomization in spindle orientation, resulting in cysts containing dilated tubules[43]. Recently, Wnt9b was also shown to play a role in kidney morphogenesis by disrupting the planar polarization of oriented cell division during development[159]. This lead to tubules with significantly increased diameter, affecting normal kidney development and leading to cyst formation. These studies highlight the importance of oriented cell division for convergent extension processes, which regulate kidney tubule diameter in vertebrates. For additional discussion of PCP associated diseases see respective review[9].

Earlier studies postulated that PCP is important for cilia formation as well as for planar polarization of basal bodies[144, 160–162]. Loss of Dsh in bronchial epithelial cells disrupts cilia

formation as a result of defective apical docking of basal bodies[144]. In *Xenopus* embryos, the PCP effector genes *inturned* and *fuzzy* control the assembly of an apical actin network that is essential for the normal orientation of ciliary microtubules and thus regulate ciliogenesis[160]. However, recent studies showed that zebrafish embryos, which were devoid of *trilobite*/*vangl2*, surprisingly showed no defects in cilia formation. Instead, these cells showed abnormal localization of the cilia[19]. This was further confirmed in mouse, where in the absence of *Vangl1* and *Vangl2*, cilia are positioned randomly around the centre of the posterior notochord (PNC) cells, leading to turbulent nodal flow that results in disrupted left-right asymmetry[24]. This would suggest that the relationship between PCP proteins and cilia formation/localization is not that simple and may depend upon the specific protein and the context in which it is studied. Thus the molecular mechanism of interaction between cellular polarization, PCP signaling, and cilia still remains elusive.

CONCLUSIONS

PCP studies in *Drosophila* have provided a wealth of information and have laid a framework for the better understanding of PCP in vertebrates. Still there are many open areas in the field that lack genetic and molecular understanding. Moreover, there are also additional molecular pathways that can regulate polarity within the epithelial plane that appear (at least for now) unrelated to either the Fz/PCP or Fat/Ds systems. For example, in *Drosophila* embryos planar polarity is established by the enrichment of Bazooka/Par3 and Myosin II at the borders between dorsal and ventral cellular interfaces leading to the formation of polarized structures, consisting of actin-myosin cables along adherens junctions[11, 163–165].

A critical issue that is not yet resolved among the Fz/PCP and Fat/Ds systems is how they are linked (if at all) and how they might converge on cellular effector pathways. Moreover, the long-range global regulation of PCP orientation via the Fz/PCP core genes remains unresolved, as it is certainly lacking some players in *Drosophila*[53] and mechanistic insight in vertebrates. Thus, the coordination of cellular polarization across whole tissues and organs remains mysterious.

In vertebrates, PCP regulation is more complex than in *Drosophila* as it plays very diverse roles during development (including in mesenchymal cells during CE) and disease in different tissues and thus it is likely that some unexpected turns will be made before we have a more complete picture. This includes the molecular relationship between cilia and PCP proteins/signaling. Genetic studies in *Drosophila* and other model organisms will be needed to continue to provide new insights and enhance our understanding the molecular mechanisms associated with PCP establishment in development and disease.

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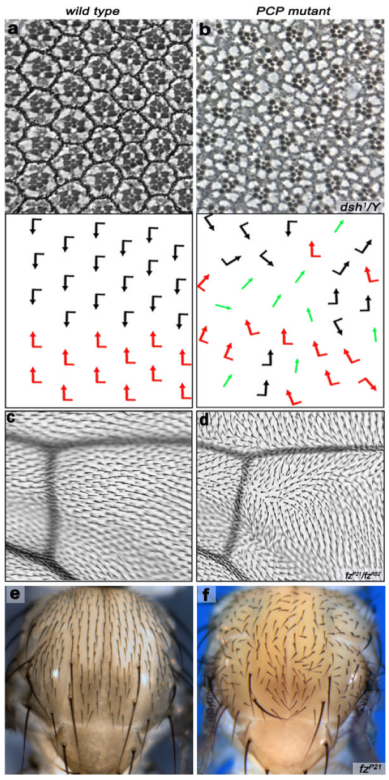

Figure 1. Examples of PCP in adult *Drosophila* tissues

(a–b) PCP features in the eye. Anterior is left and dorsal is up. Tangential eye sections showing *wild-type* adult eye **(a)** and a *dsh*1 eye **(b)** centered on the equator; *bottom* panels show schematic representations reflecting ommatidial orientation and polarity. Black and red arrows represent the dorsal and ventral chiral forms respectively while green arrows represent R3-R3 symmetrical clusters. In the PCP mutant (dsh^1 in **b**) the arrangement of ommatidia is disorganized. **(c–d)** PCP aspects of wing patterning. Anterior is up and distal right. Each wing cell gives rise to an actin based hair (trichome) that is pointing distally in wild-type (**c**). Mutations in PCP genes (a *fz* example is shown in **d**) disrupt this near perfect orientation of wing hairs/trichomes, creating swirls and waves.

(e–f) Aspects of PCP establishment on the thorax/notum. Anterior is up. Wild type adult thorax (**e**) showing mechano-sensory bristles, which are patterned uniformly across the notum and oriented in the anterior-posterior axis of the *Drosophila* body. In *fz* mutant (**f**) this regular pattern is randomized. In addition to the sensory bristles, all body wall cells form actin-rich trichomes (like in the wing), which are also oriented in the Anterior-posterior axis (not visible at this magnification).

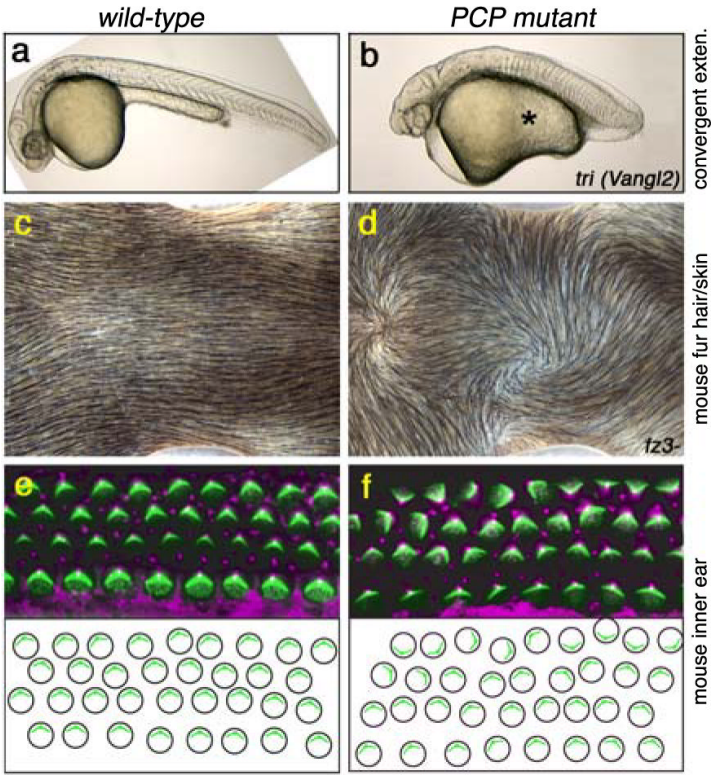

Figure 2. Examples of PCP features in vertebrates

PCP features of convergent extension gastrulation movements in the zebrafish (**a–b**), the mouse skin (**c–d**) and the mouse inner ear (**e–f**). Anterior is right in all panels. Wild-type is on the left and PCP mutants in the right column.

(**a–b**) Zebrafish embryos: the mutant PCP genotype is a maternal-zygotic mutant of *trilobite/Vangl2*. Note short and wide (fat) body axis in PCP mutant. The original pictures were provided by Brian Ciruna.

(**c–d**) Dorsal view of mouse neck displaying the orientation of fur hair (and underlying skin) in wild-type (**c**) and m*fz3* mutants (**d**). Note random waves and whorls in the *fz3*- genotype, compare to the normal anterior-posterior orientation in wild-type (**c**).

(**e–f**) Orientation of sensory hair cells of the mouse choclea (inner ear). Each cell contains polarized bundles of actin-based stereocilia (green; labeled with phalloidin) and a tubulin based kinocilium (labeled with anti-acetylated tubulin; magenta). In PCP mutants these bundles still form but their orientation becomes randomized (**f**; *Looptail/Vangl2* mutant). The lower panels show schematic representation of the cellular (actin bundle) orientation.. The original pictures of **c–f** were kindly provided by Jeremy Nathans.

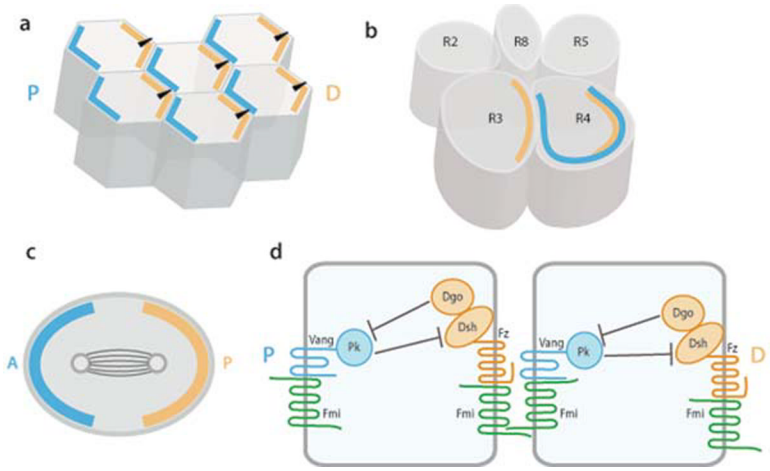

Figure 3. Schematic Presentation of Asymmetric Core Fz/PCP Protein Localization

(a) Schematic of wing cells highlighting the epithelial nature of these cells. These hexagonal cells display PCP orientation in the proximal-distal axis). Single actin rich hairs (black arrowheads in each cell) project from the distal vertex of each cell, where the Fz-Dsh complex (orange) gets localized. The asymmetric localization of the core protein complexes at the end of PCP establishment (shown in blue and orange) serves as molecular markers for cell orientation. The blue complex contains Vang/Stbm, Pk and Fmi proteins, while the orange complex contains Fz, Dsh, Dgo, and Fmi (see panel d for molecular interactions). **(b)** Asymmetric distribution of core PCP proteins is also observed during eye patterning in the precursors to the R3 and R4 photoreceptors, which is a prerequisite for proper fate specification of R3 and R4, at the time of the 5-cell precluster posterior to the furrow (individual R-cells are numbered according to their final fate) **(c)** Example of a dividing sensory organ precursor (SOP) cell, showing polarized orientation of the mitotic spindle. The orientation of the spindle depends on the asymmetric localization of the core PCP proteins (shown in blue and orange as above).

(d) Schematic presentation of asymmetric localization and molecular interactions of core PCP proteins across two wing epithelial cells. Fz–Dsh–Dgo–Fmi is enriched in a form of complex at the distal edges of cells, while the Vang–Pk–Fmi complex is concentrated to proximal edges of cells. Fz (orange) binds to Vang (blue) primarily via its CRD and this interaction is stabilized by homophilic interactions mediated by the atypical cadherin Fmi (green). Fz forms an intracellular complex with Dsh and Dgo, while Vang interacts intracellularly with Pk. Dsh and Dgo physically interact with each to promote Fz-Dsh signaling and can antagonize Pk. Diego competes with Prickle for binding to Dsh and thus antagonizes the inhibitory effect of Pk on Dsh.

Table 1

Core PCP genes and selected associated regulators in *Drosophila* and vertebrates

***Drosophila* genes**	**Vertebrate genes**	**Molecular features**	**Tissues/processes affected**		**Refs**
			Drosophila	**vertebrates**[#]	
Core Fz/PCP components					
frizzled (fz)	*Fz1* (mouse)	Seven-pass transmembrane receptor; can bind Wnt ligands; binds Dsh; recruits Dsh and Dgo to membrane.	All adult tissues	Inner ear, epidermis,neu ral tube closure, CE	[3, 15, 79,166–170]
	Fz2 (mouse)				
	Fz3 (mouse)				
	Fz6 (mouse)				
	Fz7 (Xenopus)				
	and others				
dishevelled (dsh)	*mDvll/2/3 (mouse)* *XDsh (Xenopus)*	Cytoplasmic protein containing DIX, PDZ, DEP domains; recruited to membrane by Fz; binds Fz, Pk, Stbm and Dgo; undergoes extensive phosphorylation.	All adult tissues	CE, inner ear,	[21, 103, 115, 119, 120, 144, 171–176]
strabismus (stbm)/Van Gogh (Vang)	*Vangl2 (looptail*; mouse), *Vangl1* (mouse), *trilobite (tri;* zebrafish), *xStbm* (Xenopus)	Novel 4-pass transmembrane protein; binds Pk, Dsh and Dgo; recruits Pk to membrane.	All adult tissues	CE, inner ear,limb elongation, growth cone guidance	[24, 98, 99,177–182]
flamingo (fmi)/starry night (stan)	*Celsr1/3 (mouse)*	Cadherin with seven-pass transmembrane receptor features; capable of homophillic cell adhesion.	All adult tissues	CE, epidermis, inner ear, growth cone guidance	[50, 181, 183–189]
prickle (pk) (a.k.a. *prickle-spiny legs)*	*Pk1/2* (mouse, zebrafish)	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.	All adult tissues	CE	[52, 190–194]
diego (dgo)	*Diversin (ankyrin repeat domain 6)) Inversin (invs)*	Cytoplasmic ankyrin repeat protein; recruited to membrane by Fz; binds Dsh, Stbm and Pk; competes with Pk for Dsh binding.	Eye, wing, notum (GOF)*	CE	[56, 64, 142, 195–197]

Drosophila genes	Vertebrate genes	Molecular features	Tissues/processes affected		Refs
			Drosophila	vertebrates[#]	
Regulators of Fz/PCP signaling					
Casein Kinase Iε/ CK1ε (discs overgrown,dco)	*CK1 ε*	Serine/Threonine protein kinase; acts positively on Fz/ PCP signaling; regulates Dsh localization in the wing.	Eye and wing*	only analyzed in cell culture	[30], [132], [198]
G protein o-α47A (Goα47A; brokenheart, bkh)	N.D.	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.	Wing*	N.D.	[40], [199]
Abelson kinase (dAbl)	*Abl1, Abl2*	Member of non receptor tyrosine kinases; binds and phosphorylate Dsh on tyrosine residues	Eye and Wing	only analyzed in cell culture	[31]
N.D.	*Glypican 4/6/knypek (kny;* zebrafish)	Heparan sulfate proteoglycan with a GPI-anchor; binds Wnt11, Wnt5 and Fz7; enhances Wnt-fz/ PCP signaling.	N.D.	CE	[200], [201]
N.D.	*Protein tyrosine kinase 7 (PTK7; mouse) Xpkt7 (Xenopus)*	A single pass transmembrane protein with tyrosine kinase homology. Binds to dsh via its PDZ domain and is required for Fz7 mediated Dsh localization.	N.D.	Inner ear CE	[106], [107], [202]
N.D.	*Wnt5/pipetail (ppt;* zebrafish)	Secreted cysteine-rich glycoprotein; act as ligands for Fz receptors.	N.D.	CE, limb elongation, growth cone guidance	[98–102], [159], [181]
	Wnt11/silberbl ick (slb; zebrafish)			CE	
	Wnt9b			Kidney	
N.D	*mRor2(mouse), XRor2 (Xenopus)*	Transmembrane protein tyrosine kinase contains extracellular Frizzled-like cysteine-rich domain (CRs) and kringle domain acts as a coreceptor for Wnt5a to mediate non canonical Wnt signaling	N.D.	CE, Inner ear, Limb elongation	[32–34], [99]
N.D	*Ryk*	Atypical receptor related tyrosine kinase (contains	N.D.	CE	[35], [36]

***Drosophila* genes**	**Vertebrate genes**	**Molecular features**	**Tissues/processes affected**		**Refs**
			Drosophila	**vertebrates**[#]	
		dead tyrosine kinase domain), Binds to Wnt5a			
N.D.	*Smurf1* and *Sm (mouse)*	Smurf1 (Smad ubiquitination regulatory factor-1) and Smurf2 are related E3 ubiquitin ligases; targets Prickle1 for ubiquitin-mediated degradation	N.D.	Inner ear CE	[39]
N.D	RACK1	Receptor for activated C kinase 1; physically interacts with Vangl2 and required for its membrane localization. Also inhibits canonical Wnt signaling.	N.D.	CE, Inner ear	[37], [38]
***Fat/Dachsous* PCP factors**					
fat (ft)	Fat4	Divergent member of the Cadherin super-family; heterophillic interaction with Ds; binds Atro.	All adult tissues	Kidney	[43], [44], [93], [203–205]
dachsous (ds)	N.D.	Divergent member of the Cadherin super-family; heterophillic interaction with Fat.	All adult tissues	N.D.	[44], [93]
four-jointed (fj)	N.D.	Golgi resident kinase that phosphorylate in extracellular cadherin domains of ft and ds.	All adult tissues	N.D.	[206 – 209]
atrophin (atro)	N.D.	Transcriptional co-repressor; binds to Fat.	Eye and wing	N.D.	[210], [211]
dachs (d)	N.D.	Atypical myosin; negatively regulates *ft* signaling.	Wing	N.D.	[212], [213]
approximated (app)	N.D.	Member of DHHC family, control subcellular localization of Dachs.	Wing	N.D.	[12]

CE convergent extension

N.D. not determined

[#]only tested tissues mentioned, combination of analysis in *Xenopus*, zebrafish and mouse

* other tissues were not tested