Published in final edited form as:

Curr Top Dev Biol. 2012 ; 101: 1–31. doi:10.1016/B978-0-12-394592-1.00001-6.

The *frizzled/stan* Pathway and Planar Cell Polarity in the *Drosophila* Wing

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Abstract

Drosophila has been the key model system for studies on Planar Cell Polarity (PCP). The rich morphology of the insect exoskeleton contains many structures that display PCP. Among these are the trichomes (cuticular hairs) that cover much of the exoskeleton, sensory bristles and ommatidia. Many genes have been identified that must function for the development of normal PCP. Among these are the genes that comprise the *frizzled/starry night* (*fz/stan*) and *dachsous/fat* pathways. The mechanisms that underlie the function of the *fz/stan* pathway are best understood. All of the protein products of these genes accumulate asymmetrically in wing cells and there is good evidence that this involves local intercellular signaling between protein complexes on the distal edge of one cell and the juxtaposed proximal edge of its neighbor. It is thought that a feedback system, directed transport and stabilizing protein-protein interactions mediate the formation of distal and proximal protein complexes. These complexes appear to recruit downstream proteins that function to spatially restrict the activation of the cytoskeleton in wing cells. This leads to the formation of the array of distally pointing hairs found on wings.

Keywords

Drosophila; Planar Cell Polarity; *frizzled* pathway; wing

1. Introduction to *Drosophila* Planar Cell Polarity

The cuticular surface of insects has a rich morphology that led them to be the first systems where the development of planar cell polarity (PCP) was studied in depth (see for example (Lawrence, 1966). For the last 30 years genetic studies using *Drosophila* have provided many of the most important insights that resulted in the blossoming of the field (Gubb and Garcia-Bellido, 1982; Held et al., 1986; Wong and Adler, 1993). These included the identification of many of the genes that play key roles in PCP (Adler et al., 1998; Chae et al., 1999; Collier and Gubb, 1997; Collier et al., 2005; Feiguin et al., 2001; Gubb and Garcia-Bellido, 1982; Klingensmith et al., 1994; Strutt and Warrington, 2008; Taylor et al., 1998; Theisen et al., 1994; Usui et al., 1999; Vinson et al., 1989; Wolff and Rubin, 1998; Yan et al., 2008; Yang et al., 2002; Zeidler et al., 1999), that the protein products of these genes accumulate asymmetrically in cells (Adler et al., 2004; Axelrod, 2001; Bastock et al., 2003; Feiguin et al., 2001; Shimada et al., 2001; Strutt, 2001; Strutt and Warrington, 2008; Tree et al., 2002; Usui et al., 1999; Yan et al., 2008), that many of the proteins interact physically (Bastock et al., 2003; Das et al., 2004; Jenny et al., 2003; Jenny et al., 2005; Wong et al., 2003) (Lu et al., 2010) and the evidence for feedback systems (Tree et al., 2002) that are a key for the functioning of the system. As has proved to be true for so much in Biology the genes that function in PCP in flies have similar functions in a wide range of animals (see (Goodrich and Strutt, 2011; Wang and Nathans, 2007) and other articles in this volume).

2. The cellular basis for PCP

Three types of adult structures have been the primary focus of experiments on PCP in *Drosophila* (Adler, 2002). The most important are the cuticular hairs found over much of the fly's body. The wing, which is flat and where each cell elaborates a relatively long distally pointing hair has been the principal tissue for studies on hairs (Fig 1) (Gubb and Garcia-Bellido, 1982; Vinson and Adler, 1987; Wong and Adler, 1993), although they have also been studied in depth on the abdomen (Casal et al., 2006).

2.1 Epidermal hairs and the fly wing

The *frizzled* (*fz*) pathway (also called the *starry night* (*stan*) pathway (Casal et al., 2006) controls PCP by restricting the site of hair initiation to the distal most part of wing cells (Wong and Adler, 1993) (Fig 2). The hairs grow out away from the distal cell periphery resulting in a distally pointing hair (Wong and Adler, 1993). Mutations in *fz/stan* pathway genes lead to hairs forming at abnormal subcellular locations and having abnormal polarity (Figs 1, 2). In this review I will focus on the wing with an emphasis on the *fz/stan* pathway. The simple cell biology and flat shape of the wing make it an ideal tissue for studies on Planar Cell Polarity and the principles deduced from studying it have for the most part proved to be conserved in other tissues in the fly and in other organisms.

2.2 Sensory Bristles

The cuticular surface of the fly is also decorated with many bristle sense organs. On the dorsal thorax and abdomen the bristle shaft points posteriorly and on appendages they point distally (Adler, 2002) (Fig 3AC). In other body regions (e.g. the head) bristles are locally aligned and show a reproducible polarity. The *fz* pathway regulates bristle polarity by controlling the orientation of the spindle during the determinative cell divisions that give rise to the cells of the sense organ (Gho and Schweisguth, 1998; Lu et al., 1999) (Fig 3B). On the leg some bristle sense organs signal to a neighboring epidermal cell to form a bract (Fig 3C). This involves the EGFR pathway and this system displays planar polarity as the bract is routinely proximal to the bristle (Held, 2002) (Fig 3). Most leg bristles do not show strongly abnormal polarity in *fz/stan* pathway mutants but in those that do the bract is coordinately positioned "upstream" (Fig 3D).

2.3 The eye

The third developmental unit that has been extensively studied with respect to PCP are the ommatidia of the compound eye (Zheng et al., 1995). Each ommatidium is comprised of about 20 cells including 8 photoreceptor cells. The arrangement of the photoreceptor cells is asymmetric and chiral giving each ommatidium and the eye as a whole a polarity (Fig 4A). As each ommatidium develops there is a stepwise recruitment of photoreceptor cells (for a recent review of this see (Kumar). The R3 and R4 cells are recruited at the same time. The cell located closer to the equator becomes R3 and the other R4 (Fig 4A). The ommatidium undergoes a subsequent rotation and this is guided by the position of the R3 and R4 cells (Fig 4B). The *fz* pathway controls PCP by regulating the R3/R4 cell fate decision (Zheng et al., 1995). This is based on the R3 cell having higher Fz activity and R4 higher Vang (Strutt et al., 2002b). This leads to the Delta dependent activation of the Notch (N) receptor in R4, which controls cell fate (Cooper and Bray, 1999; Fanto and Mlodzik, 1999; Tomlinson and Struhl, 1999). There is an argument in the literature with regard to the mechanism involved in N activation and how this regulates cell fate (del Alamo and Mlodzik, 2006; Fanto and Mlodzik, 1999; Strutt et al., 2002b; Weber et al., 2000). Recent data argues that the Ral GTPase also plays a role in R3/R4 cell fate (Cho and Fischer, 2011).

2.4 Other manifestations of PCP

There are several other cell types/structures/tissues where *fz/stan* based PCP has been studied. Collier and colleagues discovered that the fly wing has parallel cuticular ridges that and that their orientation is under the control of the *fz/stan* and *ds/ft* pathways (Fig 5EFG) (Valentine and Collier, 2011). Interestingly, the ridges are oriented differently in the anterior and posterior parts of the wing and this appears to be related to differences between two phases of *fz* signaling that utilize different *pk* isoforms (Doyle et al., 2008; Hogan et al., 2011; Valentine and Collier, 2011). Their data also argues that the early phase is dependent on *ds/ft* while the latter is not. The lateral side branches of the arista are another body part where the *fz* pathway has been found to regulate PCP (He and Adler, 2002). The laterals are produced by polyploid cells and share features of both epidermal hairs and bristles. As is the case for epidermal hairs the *fz* pathway controls the subcellular location for lateral outgrowth although in this cell type the outgrowth is not juxtaposed to the distal most edge of the cell in wild type (He and Adler, 2002).

The denticles that are part of the larval cuticle also display PCP and they have been intensively used as markers of pattern formation in embryonic segments. In recent years they have also been used to study PCP (Donoughe and DiNardo, 2011; Price et al., 2006; Repiso et al., 2010). Here as in the adult abdomen the *fz/stan* and *ds/ft* systems appears to function in parallel.

The *fz/stan* pathway, which plays such a key role in PCP has also been found to regulate a number of processes that are not always thought of as being related to PCP. The first of these to be identified was the formation of the leg joints (Held et al., 1986). Mutations in genes such as *fz* give rise to defective leg joints that often show mirror image symmetry typical of duplications (Fig 3EF). One often also sees "blebs". The cellular basis for this has not been established.

Mutations in genes such as *fz* also lead to occasional defects in wing evagination so that the resulting wing points anteriorly in the pupal case (Fig 5AB) (Lee and Adler, 2002). Such wings end up shorter and deformed, perhaps due to defects in cell rearrangements. This could be related to the effects of the *fz* pathway on the movement of sheets of cells in vertebrates (Goodrich and Strutt, 2011). Mutations in genes such as *fz* also inhibit the repacking of pupal wing cells so that the fraction of hexagonal cells is decreased compared to wild type (Classen et al., 2005). The connection between the altered hair polarity and the effect on the repacking is unclear (Classen et al., 2005; Ma et al., 2008). An interesting and related observation is that cell rearrangements in the pupal wing lead to changes in the anatomical orientation of *fz/stan* signaling (Aigouy et al., 2011).

Mutations in *fz/stan* pathway genes have also been found to alter the pattern of dendrites and axons in some *Drosophila* neurons (Matsubara et al., 2011; Mrkusich et al., 2011). In both cases it remains to be established as to how much of the pathway is conserved in different tissues. A similar very wide range of cell types have been found to utilize *fz* pathway homologs in vertebrates (Goodrich and Strutt, 2011; Wang and Nathans, 2007).

2.5 Planar Cell Polarity that is not *fz/stan* pathway dependent

There are also several interesting cases of Planar Cell Polarity in *Drosophila* that are not dependent on the *fz/stan* pathway. The most notable being the polarized cell rearrangements that mediate germ band elongation (Bertet et al., 2004; Zallen, 2007; Zallen and Wieschaus, 2004) and the polarized actin cytoskeleton seen in the follicle cells of developing egg chambers (Bateman et al., 2001; Frydman and Spradling, 2001). Interestingly the *fat2* gene is required for actin polarization in follicle cells (Viktorinova et al., 2009).

3. PCP Genes

3.1 Early studies on the *fz/stan* pathway

Several of the genes of the *fz/stan* pathway were discovered long ago and were used as makers in classical genetic experiments (see Table 1). These include *fz*, *prickle* (*pk*), *dishevelled* (*dsh*), *inturned* (*in*) and *multiple wing hairs* (*mwh*). Other *fz/stan* pathway genes were discovered in screens designed to identify new PCP genes. These include *stan* (also known as *flamingo*) (Chae et al., 1999; Usui et al., 1999), *Van Gogh* (*Vang*) (also known as *strabismus*) (Taylor et al., 1998; Wolff and Rubin, 1998) and *fritz* (*fritz*) (Collier et al., 2005). (Note in this review we will use the primary FlyBase name for all Drosophila genes). The first detailed study on the function of these genes in PCP was published about 30 years ago by Gubb and Garcia-Bellido (Gubb and Garcia-Bellido, 1982). Several important conclusions came from this work. One was that the mutant hair polarity patterns seen on wings were not random. Rather, the mutant pattern was stereotypic. Thus, cells in the anterior region of a *fz* mutant wing routinely point more anteriorly than do wild type (Fig 1C). A second important insight was that altering wing shape (by mutation) did not make substantial differences to the stereotypic *fz* mutant polarity pattern. Similarly, the loss of part of the wing margin due to mutation did not affect the mutant polarity pattern.

The insight that a set of genes comprised a regulatory pathway that controlled PCP came from Wong and Adler (Wong and Adler, 1993). They made several key findings. They realized that mutations in all of the *fz/stan* pathway genes gave rise to similar stereotypic polarity patterns (Fig 1ABC) but that genes could be placed into phenotypic groups by the frequency of extra hairs produced (Fig 2A). The 3 phenotypic groups were also epistasis groups and it is now clear that they represent different levels in the regulatory hierarchy. The upstream genes (often called core genes) consist of *fz*, *dsh*, *pk*, *stan*, *Vang* and *dgo* (note *stan* (Chae et al., 1999; Usui et al., 1999), *Vang* (Taylor et al., 1998; Wolff and Rubin, 1998) and *dgo* (Feiguin et al., 2001) had not been discovered at the time of the paper). Below the core group are *in*, *fy* and *fritz*, which are often referred to as the Planar Polarity Effector (PPE) genes (note *fritz* had not been discovered at the time of the paper (Collier et al., 2005)). The *mwh* gene was the only member of the third group. They also found that in wild type pupal wing cells the cytoskeleton was activated in the vicinity of the distal most vertex to promote hair outgrowth and this resulted in a hair that grew distally. Further, mutations in all of the *fz* pathway genes resulted in hairs forming at an alternative subcellular location. An important insight from the analysis of the pupal phenotype was that the *fz/stan* pathway regulated hair initiation.

The observation that *fz* pathway proteins accumulated asymmetrically in wing cells was first observed by Uemura and colleagues studying the *stan/flamingo* gene (Usui et al., 1999) and this breakthrough opened up a new stage in PCP research (Fig 2AB). Over the next few years similar results were obtained for all of the *fz/stan* pathway proteins (Adler et al., 2004; Axelrod, 2001; Bastock et al., 2003; Feiguin et al., 2001; Shimada et al., 2001; Strutt, 2001; Strutt and Warrington, 2008; Tree et al., 2002; Usui et al., 1999; Yan et al., 2008). Further biochemical experiments established that several pairs of these proteins could interact directly with one another (Bastock et al., 2003; Das et al., 2004; Jenny et al., 2003; Jenny et al., 2005; Wong et al., 2003) (Lu et al., 2010). A more detailed discussion of the function of these genes and how the asymmetric accumulation of the proteins is achieved is presented later.

The *fz/stan* pathway functions to limit the region of the cell where the cytoskeleton is activated to form a hair. Not all wing cells are the same size, nor are all epithelial cells in other body regions the same size or shape as wing cells. Further, nutrition and the temperature during development can alter cell size without altering planar polarity. Hence

the pathway has the ability to scale and function in a variety of cell geometries. It is clear however that this ability is not infinite. Cells that are much larger than normal can arise from the cells being polyploidy or stretched due to wound healing. Both of these conditions result in the cells often forming multiple hairs that can be of abnormal polarity (Adler et al., 2000b). The *fz/stan* pathway is still functioning in these large cells but it is unable to regulate the cytoskeleton well enough so that a single distally pointing hair is produced.

3.2 *ds/ft* pathway

Mutations in several other groups of genes also give rise to PCP phenotypes. The atypical cadherins *dachsous* and *fat* and the golgi kinase *four jointed* were first discovered to result in PCP phenotypes due to their leg joint phenotypes (Held et al., 1986). Later it was established that they were also required for wing and eye PCP (Adler et al., 1998; Matakatsu and Blair, 2004; Simon, 2004; Zeidler et al., 1999). A variety of evidence indicates that Ft and Ds act as a receptor ligand pair and that Fj modulates their activity by phosphorylation (Brittle et al., 2011; Matakatsu and Blair, 2004; Simon, 2004; Simon et al., 2010; Sopko et al., 2009). One observation that does not fit this model is the observation that transgene supplied Ft that lacks the extracellular domain provides rescue of the *ft* PCP phenotype over most of the wing (Matakatsu and Blair, 2006). How to reconcile these observations is not clear. The Ft and Ds proteins do not appear to accumulate asymmetrically as do *fz/stan* pathway proteins however they are able to polarize cells. This is seen both by their effect on hair polarity and by their activity leading to the asymmetric accumulation of the atypical myosin Dachs (Mao et al., 2006; Mao et al., 2011). Early studies found that the *fz/stan* pathway was functional in *ds* and *ft* mutants but that it signaled in an anatomically abnormal way (Adler et al., 1998) and subsequently it was proposed that the *ds/ft* pathway functioned as a global signal that oriented the activity of the *fz/stan* pathway with respect to the body as a whole in the wing and eye (Ma et al., 2003; Simon, 2004; Yang et al., 2002). However, studies by Casal, Lawrence and Struhl provided compelling data that in the abdomen that the *ds/ft* and *fz/stan* pathways functioned in parallel (Casal et al., 2006). For example, double mutants of one *ds/ft* and one *fz/stan* pathway gene had a more severe phenotype than any single mutant or double mutant where only one of the pathways was affected. They also showed that *ds/ft* could repolarize cells that were mutant for the *fz/stan* pathway. One interpretation of these observations is that the relationship between the two pathways is different in different tissues. This is not a satisfying explanation, however it may be correct. More recent experiments suggest that *ds/ft* may alter *fz/stan* signaling in indirect ways by affecting the axis of cell division, cell rearrangements and the polarization of microtubules that are involved in the transport of Fz containing vesicles (Harumoto et al., 2010; Mao et al., 2011). There is increasing evidence that *ds/ft* also function in vertebrate PCP (Goodrich and Strutt, 2011).

3.3 Septate Junction proteins

A third set of genes essential for the morphogenesis of normal wing PCP are genes such as *Gliotactin*, *Neuroglian*, *Coracle* and *varicose* (Moyer and Jacobs, 2008; Venema et al., 2004). These genes encode proteins that are associated with the septate junction and they are required for the alignment of neighboring hairs (Fig 5HI). The septate junction is the invertebrate equivalent of the vertebrate tight junction. These genes appear to act after hair outgrowth and unlike the *fz/stan* pathway mutations in these genes do not result in cells forming multiple hairs. The asymmetric localization of Dsh is not altered in a Gli mutant and the localization of Coracle is not affected by mutations in *fz/stan* genes Venema, 2004 #71}. Further, double mutants of septate junction and *fz/stan* genes show an additive phenotype consistent with their functioning in parallel. How the septate junction genes function in PCP has not been extensively studied. It is also not clear if this set of genes is needed for PCP in other contexts in *Drosophila* or in other organisms.

3.4 Other genes that impact PCP

In recent years many additional genes have been identified that are required for PCP in the fly. The literature is somewhat inconsistent as to the properties of a gene required to consider it a PCP gene. Some authors require a hair/bristle orientation phenotype (or ommatidia of the incorrect chiral type), while others have simply required cells form multiple hairs (of normal orientation) or result in misrotated ommatidia of the correct chiral type. As is discussed in more detail below many aspects of general cell biology are likely involved in polarizing cells hence it is not surprising that genes that encode a wide variety of protein types and functions have been found to produce PCP phenotypes. These include some that might be thought of as having rather general functions. Not surprisingly, these genes differ from those of the *fz/stan* pathway components in being much less specific with regard to their mutant phenotypes. The collection of genes include ones that encode proteins that function in intracellular trafficking such as *Rab23* (Pataki et al., 2010), *Rab5* (Purvanov et al., 2010) and the Rab5 effector *Rabenosyn-5* (Mottola et al., 2010). Mutations in genes that encode proteins that function to promote actin filament disassembly (*twinstar* (*cofilin*) (Blair et al., 2006) and *flare* (*AIPI*) (Ren et al., 2007) have been found to result in PCP phenotypes and disruptions in the normal asymmetric accumulation of *fz/stan* pathway proteins. Also implicated in PCP are genes that encode transcription regulators such as *grainy head* (*grh*) (Lee and Adler, 2004) and *atrophin* (Fanto et al., 2003), kinases such as *misshapened* (Paricio et al., 1999), *Rho Kinase* (Winter et al., 2001), the Abelson tyrosine kinase (Singh et al.), *aPKC* (Djiane et al., 2005), *casein kinase I* (Strutt et al., 2006), and the *gilgamesh* kinase (Gault et al., 2012), the *Widerborst* phosphatase (Hannus et al., 2002), the *approximated* Palmitoyltransferase (Matakatsu and Blair, 2008) and small GTPases such as *Rho1* (Strutt et al., 1997; Yan et al., 2009) and *Go* (Purvanov et al., 2010). An interesting and unexpected group of genes that are required for normal PCP function in ion transport including the Na⁺/H⁺ exchanger *Nhe2* (Simons et al., 2009), a component of the vesicle ATPase (Buechling et al., 2010; Hermle et al., 2010) and an organic anion transporter, *oat30B* (Mummery-Widmer et al., 2009). The effect of *Nhe2* was suggested to be mediated through an effect on the interaction of Dsh and plasma membrane lipids. Many of the genes noted above produce mutant phenotypes that suggest they could function in concert with or affect the function of either the *fz/stan* or *ds/ft* pathways. For example, the PCP phenotype that results from a loss of *grh* function in wing cells was shown to be associated with a loss of *stan* expression in the mutant cells (Lee and Adler, 2004). A notable and interesting exception was the identification of *chascon* and *jitterbug*, which affect notum PCP by impacting the tendons that attach the indirect flight muscles to the notum (Olguin et al., 2011). In this case a loss of the ability of the tissue to respond to the mechanical tension produced by the IFMs appears to be the mechanism responsible for the PCP mutant phenotype.

3.5 Genome wide screen for PCP genes

A genome wide screen based on transgene mediated RNAi that was designed to identify genes that played a role in Notch signaling also identified many genes required for PCP (Mummery-Widmer et al., 2009). In this screen *pannier-Gal4* was used to drive transgene expression. *pannier* is expressed in the central region of the notum, hence it is an ideal driver to use to look for effects on bristle sense organ determination and differentiation. Effects on PCP in this screen were manifested by the misalignment of notum bristles. Satisfyingly this screen identified in order of the strength of phenotype *fz*, *Vang*, *fritz*, *pk*, *stan*, *fy*, *in*, *ft*, and *ds*. Thus most of the *fz/stan* and *ds/ft* pathway genes were identified confirming that the screen was very effective. The screen failed to identify *dgo*, *fj* and *mwh*. The failure to identify *dgo* and *mwh* is not surprising as null alleles of *dgo* and *mwh* do not show a bristle polarity phenotype (Feiguin et al., 2001; Strutt and Warrington, 2008; Yan et al., 2008). This is not the case for *fj* and the failure to identify *fj* may simply reflect the transgene not

knocking down the expression enough to produce a mutant phenotype. It is unlikely that this screen identified all of the genes that play a role in PCP. Some genes would likely be missed due to the knock down not being effective (as is presumably the case for *fz*). Other genes would likely be missed due to the knock downs resulting in lethality or a loss of bristles due to effects on the determinative cell divisions. This seems likely to be the case for genes involved in essential basic cellular functions, and indeed genes that are important for bristle morphogenesis such as *Rab11* and exocyst components were missed in the genome wide screen for this reason (Nagaraj and Adler, 2012). This screen has already served as a valuable source of candidate PCP genes. For example, *VhaM8.9* (Buechling et al., 2010) and *jitterbug* (Olguin, 2011) were both identified in this screen and subsequently shown in other studies to produce PCP phenotypes. It is interesting to consider that many of the genes that produced the strongest phenotypes in the screen have not yet been the focus of PCP papers. A knockdown of the *Organic anion transporting polypeptide 30B* produced the strongest PCP phenotype (along with *fz*). In the wing a knockdown of this gene can reverse hair polarity much as the over expression of the *spiny leg* isoform of the *pk* gene can. It will be interesting to see if these two proteins function in an antagonistic way. Among the other genes where knock downs produced very strong phenotypes were *d-Cup* (a Ca⁺⁺ binding protein), *CG17290* (which contains a gyrase motif), Protein tyrosine phosphatase 69D, *CG15649* (a novel protein) and *CG18005* (which contains RED domains suggesting a role in RNA splicing). The roles that these genes and their encoded proteins play in PCP can currently only be guessed at. It is notable that even this small set of candidate genes and proteins suggests a wide range of biochemical functions. It seems likely that much remains to be learned about PCP.

4. What is the basis for the asymmetric localization of *fz/stan* pathway proteins?

All of the *fz/stan* pathway proteins accumulate asymmetrically in wing cells, with all except Stan accumulating on either the proximal or distal cell membrane (Stan is found on both) (Adler et al., 2004; Axelrod, 2001; Bastock et al., 2003; Feiguin et al., 2001; Shimada et al., 2001; Strutt, 2001; Strutt and Warrington, 2008; Tree et al., 2002; Usui et al., 1999; Yan et al., 2008) (Fig 2A). The accumulation is uneven across these membranes. That is, some locations along these membranes show a higher level of protein than others and all of the *fz/stan* pathway proteins appear to be enriched at the same foci on the membrane (Fig 2B). This suggests that the proteins accumulate in a synergistic way. Further, all of the core group proteins must be functional for the normal asymmetric accumulation to occur (Fig 2A).

4.1 Interactions of transmembrane proteins

The distal edge of one cell is juxtaposed to the proximal edge of the neighboring cell distal to it (Fig 6). This provides an interface for asymmetric signaling that is likely to be part of a positive feedback mechanism that helps establish the distinct proximal and distal membrane domains. Several groups have proposed that interactions between the three *fz/stan* pathway proteins that are transmembrane proteins, Fz, Vang and Stan are a key to this process (Chen et al., 2008; Strutt and Strutt, 2008; Wu and Mlodzik, 2008). A variety of data supports these models. These include biochemical evidence for an interaction and in situ protein localization studies. There are however, differences between experimental results and the interpretations reported by these groups so at the current time there is not a consensus for how these proteins interact and provide for polarized signaling. It will be important for these differences to be resolved; however the general conclusion that heterotypic protein interactions provide the basis for the intercellular signaling between cells appears to be on solid ground.

4.2 Intracellular proteins

It is likely that in addition to intercellular signaling an intracellular feedback system plays an important role in the formation of the proximal and distal protein domains (Amonlirdviman et al., 2005; Tree et al., 2002). Several interactions have been detected between proximal and distal proteins. For example, Dsh and Vang, Dsh and Pk, Dgo and Pk, and Dgo and Vang have been found to interact (Bastock et al., 2003; Das et al., 2004; Jenny et al., 2003; Tree et al., 2002). The interactions between proximal and distal proteins appear to be negative ones. Hence, a negative interaction between Pk and Dsh could prevent Dsh from accumulating on the proximal side and Pk from accumulating on the distal side (Fig 6). Such models suggest the interactions be dependent on cellular location. For example, when Pk and Dsh interact on the proximal side of the cell, Dsh would be lost. A hint as to how this may work comes from experiments on mice where it was found that a Smurf ubiquitin ligase targets Pk for proteosome mediated degradation (Narimatsu et al., 2009). As of yet no equivalent experimental evidence has been published that a similar mechanism works in the fly (e.g. Pk interacting with Dsh results in Dsh being degraded in a proteosomal dependent mechanism), but it is certainly an attractive hypothesis to explain the negative protein interactions.

4.3 Wnts in fly PCP?

The *fz* gene family gets its name from the PCP phenotype of its founding member, but Fz proteins are very well known as a family of receptors for Wnt ligands (Bhanot et al., 1996). However, in *Drosophila* studies have failed to detect PCP phenotypes in genotypes where one or multiple Wnts are lost due to mutation (Chen et al., 2008; Lawrence et al., 2002). In vertebrate tissues there is substantial evidence for Wnt ligands functioning in PCP (see (Goodrich and Strutt, 2011; Wang and Nathans, 2007) and other articles in this volume).

4.4 Mechanisms for the formation of PCP protein complexes

There are several possible mechanisms that could be responsible for the asymmetric accumulation of PCP proteins on the proximal or distal membranes. One would be for the proteins to be preferentially synthesized at those locations (Berleth et al., 1988; Davis and Ish-Horowicz, 1991; Macdonald and Struhl, 1988). A second would be the directed trafficking of the proteins to the correct side of the cell (Shimada et al., 2006; Strutt et al., 2011). A third would be trapping of proteins to a domain by binding to a target (Strutt et al., 2011). A fourth possibility would be for the rate of diffusion of the protein to be regulated spatially across the cell (Griffin et al., 2011).

4.5 mRNA localization?

The data do not support the hypothesis for localized synthesis as in situ hybridization experiments have failed to show evidence for mRNA localization. Further, in other systems the localization of a mRNA is usually mediated by sequences outside of the coding region (see for example (Ferrandon et al., 1994; Macdonald and Struhl, 1988)). However, in fly PCP fully functional transgenes encode mRNAs that lack most of the 5' and 3' untranslated regions (see for example (Krasnow and Adler, 1994)).

4.6 Directional trafficking and trapping

There is evidence supporting the involvement of both directed transport and trapping in the asymmetric accumulation of PCP proteins. Uemura and colleagues have used in vivo confocal imaging to determine that Fz and Stan preferentially traffic along the proximal distal axis of wing cells as opposed to along the anterior-posterior axis (Shimada et al., 2006). They also provided evidence that the trafficking is along the web of apical microtubules that show a proximal/distal bias (Turner and Adler, 1998). This bias in the

orientation of microtubules appears to be at least partially mediated by the action of the *ds/ft* pathway. This may provide an explanation for the ability of the *ds/ft* pathway to bias *fz/stan* activity (Harumoto et al., 2010). It is not clear however if the bias for movement along the proximal distal axis is great enough to explain everything. Further, the in vivo observations showed that Fz containing puncta could fuse with accumulations on the membrane and that this appeared to be reversible (Shimada et al., 2006; Strutt et al., 2011). Recent results of Strutt and colleagues (Strutt et al., 2011) obtained by FRAP experiments established that the 3 transmembrane proteins Fz, Stan and Vang are all required for the stable asymmetric accumulation of PCP protein complexes and that the cytoplasmic proteins Dsh, Pk and Dgo are needed for the formation of large puncta. The cytoplasmic proteins could be recruited to the proximal and distal domains by interacting with the complexes of transmembrane domains leading to further stabilization and an increase in the size of the complexes. Consistent with that possibility Dsh has been shown to bind to Fz (Wong et al., 2003) and Pk has been shown to bind to Vang (Bastock et al., 2003; Jenny et al., 2003). The negative protein interactions between cytoplasmic proteins noted above could also serve to remove mislocalized proteins and hence to increase the asymmetry.

Taken together with earlier observations one is lead to a model where directed transport leads to a modest bias in the localization of the 3 transmembrane proteins. Direct protein interactions across the juxtaposed distal and proximal membrane domains would stabilize proximally localized Vang and distally localized Fz and hence increase the bias in protein localization. The binding of the cytoplasmic proteins would further stabilize and increase the size of the protein complexes. Thus, the formation of the asymmetric protein complexes would involve several layers of mechanisms.

5. Directional cell non-autonomy

One striking property of *fz* and *Vang* mutant cells is the directional domineering nonautonomy displayed by clones (Taylor et al., 1998; Vinson and Adler, 1987)(Fig 1DF). This differs from the essentially cell autonomous activity of other *fz* pathway genes (Fig 1E) (these other genes show very limited cell nonautonomy (rare or limited to neighboring cells) (Chae et al., 1999; Collier and Gubb, 1997; Collier et al., 2005; Gubb and Garcia-Bellido, 1982; Lee and Adler, 2002; Park et al., 1996). The polarity of wild type cells distal to *fz* clones and proximal to *Vang* clones are affected. This is due to hairs pointing toward cells of lower Fz activity and toward higher Vang activity (Adler et al., 2000a; Adler et al., 1997; Casal et al., 2006; Strutt and Strutt, 2007). Complementary effects are seen when cells are manipulated to express higher Fz or Vang levels (Adler et al., 2000a; Adler et al., 1997).

5.1 The basis for directional cell non-autonomy

Early evidence suggested that *fz* had both cell autonomous and cell nonautonomous functions (Vinson and Adler, 1987). Several *fz* alleles behaved cell autonomously (Vinson and Adler, 1987) and that the cell nonautonomous function of *fz* was independent of *dsh* and preceded and was temporally separate from the cell autonomous function (Lee and Adler, 2002; Strutt and Strutt, 2002). It is worth noting that the PCP system does not require patterned expression of any of the *fz* pathways genes as even expression of these genes provides complete rescue of null alleles (Axelrod, 2001; Bastock et al., 2003; Collier and Gubb, 1997; Collier et al., 2005; Feiguin et al., 2001; Krasnow and Adler, 1994; Park et al., 1996; Strutt, 2001; Strutt and Warrington, 2008; Usui et al., 1999; Yan et al., 2008). The basis for the domineering nonautonomy has been studied at length. Early studies established that it was a property of abnormal local signaling between cells (Adler et al., 2000a). The current consensus model is that the intercellular signaling between neighboring cells due to the asymmetric accumulation of PCP proteins is propagated on a cell by cell basis and this is the basis for the domineering nonautonomy (Amonlirdviman et al., 2005; Goodrich and

Strutt, 2011; Maung and Jenny, 2011; Tree et al., 2002; Wu and Mlodzik, 2008). Thus a cell with no Fz cannot recruit Vang to the juxtaposed membrane (Wu and Mlodzik, 2008). This leads to a high level of Vang on the side of the cell distal to the mutant membrane. This would be propagated for a number of cells and such a system could be at the heart of the intercellular signaling required for PCP. One drawback to such a model is that the function of a gene such as *dsh* that acts cell autonomously is required for the antisymmetric accumulation of other PCP proteins (Axelrod, 2001; Klingensmith et al., 1994; Strutt, 2001; Theisen et al., 1994; Tree et al., 2002; Usui et al., 1999). At first glance this result would seem to contradict the asymmetry propagation model. However, computer simulations indicate that the model can explain the observations (Amonlirdviman et al., 2005; Schamberg et al., 2010) as only modest levels of asymmetry may be required for signaling and this may be difficult to detect in immunostaining experiments. There remains however, a need for an explanation for the results that indicate the cell nonautonomous function precedes the cell autonomous function (Strutt and Strutt, 2002).

It is worth noting that this mechanism works well to explain both normal PCP development as well as domineering non-autonomy in a tissue where all cells express the *fz/stan* pathway proteins and show the asymmetric accumulation. In the eye only the R3 and R4 cells need to express *fz* pathway genes for the development of normal PCP (Zheng et al., 1995). In these cells *fz/stan* pathway proteins accumulate asymmetrically with proteins that accumulate on the distal side of wing cells accumulating in the R3 cell membrane that is juxtaposed to the R4 cell (Strutt et al., 2002a). Similarly, proteins that accumulate on the proximal side of wing cells accumulate on the R4 cell membrane that is juxtaposed to R3 (Strutt et al., 2002a). Thus, heterotypic interactions across cell membranes seems likely to be a mechanism used in the generation of the two domains (for example see (Wu and Mlodzik, 2008).

6. Downstream Effectors

6.1 Planar Polarity Effector (PPE) Genes

The 3 planar polarity effector proteins, In, Fy and Frtz are recruited to the proximal side of wing cells in a core group dependent manner (Fig 2A) (Adler et al., 2004; Strutt and Warrington, 2008). For example, in a *fz* mutant the asymmetric accumulation of In and Frtz is lost and indeed these proteins are found at much lower levels in such a mutant. It seems likely that at least one of these proteins is recruited by binding (either directly or indirectly) to either Pk or Vang, the two proximal specific proteins. As is the case for the upstream genes, each of the PPE genes need to be functional for the proteins to preferentially accumulate on the proximal side (Adler et al., 2004; Strutt and Warrington, 2008). In contrast to the situation with the upstream genes the over expression of PPE genes has not been reported to produce a gain of function PCP phenotype (Park et al., 1996). This seems somewhat surprising as over expression often leads to a loss in the spatially restricted accumulation of a protein, which results in altered function. One possibility is that the over expression does not saturate the system that localizes the proteins to the proximal side. This seems unlikely. A more attractive possibility is that protein that is not properly localized is not active due to a lack of one or more binding partners.

6.2 *mwh*

The *mwh* gene, which by epistasis tests is the most downstream member of the *fz/stan* pathway also accumulates on the proximal side of wing cells and this is dependent on both the core and PPE proteins and genes (Fig 2A) (Strutt and Warrington, 2008; Yan et al., 2008). Two papers have suggested possible mechanisms. In one, Lu and colleagues found that Mwh and In directly interacted and they suggested that In on the proximal side of wing

cells recruited Mwh (Lu et al., 2010). In the other, Strutt and colleagues found that Mwh was phosphorylated in a PPE dependent manner and suggested this was important in the action of Mwh in ensuring a single distally pointing hair is formed (Strutt and Warrington, 2008). These two mechanisms are of course, not mutually exclusive. A variety of results argue that Mwh serves as an inhibitor of the actin cytoskeleton (Fig 6). How this is accomplished is unclear but it is worth noting that the amino terminal half of the large Mwh protein contains a G protein binding domain (GBD) and has sequence similarity to diaphanous family formins. These formins, are known to function as dimers, be activated by Rho:GTP and to promote the formation of long actin filaments (Campellone and Welch, 2011; Chesarone et al., 2011; Goode and Eck, 2007). Consistent with the sequence similarity between Mwh and Dia both genetic interactions and co-immunoprecipitation experiments argue that Rho1 activates Mwh (Yan et al., 2009). This raises the possibility that Mwh might inhibit the actin cytoskeleton by acting as a dominant negative formin.

6.3 A distal target of Dsh?

The cytoskeleton is activated to form a hair in the vicinity of the distal most vertex of pupal wing cells (Wong and Adler, 1993). The level of activity is important for insuring a single hair is formed and that it is the proper size and shape. For example, if the actin cytoskeleton is inhibited by drug treatment or by mutations in actin cytoskeleton components such as myosin II, multiple shorter than normal hairs are formed (Franke et al., 2010; Turner and Adler, 1998). Inhibition at the proximal side of wing cells from the recruitment of Mwh seems insufficient to specify the distal vertex. Several lines of data indicate that distal edge proteins can stimulate the cytoskeleton. Although mutations in *in*, *fy*, *ftz* and *mwh* are epistatic to loss of function mutations in distal proteins such as *dsh* and *fz* that is not the case for all gain of functions in those genes. The late over expression of *dsh* leads to the formation of multiple hair cells and an increase is seen even when cells also lack *in* or *mwh* function (Lee and Adler, 2002). Indeed, the effects of these two genetic changes are additive. Thus, at least when over expressed Dsh is able to affect cytoskeleton function and it must be doing so by interacting with an unidentified cellular constituent and not known *fz*/*stan* downstream components such as *in* or *mwh*. Independent evidence supporting the distal edge proteins stimulating the cytoskeleton came from Strutt and colleagues who found that Fz acted to promote hair formation (Strutt and Warrington, 2008). Several experimental results supported this idea including a delay in hair initiation in *fz* mutant cells compared to wild type neighbors. This was seen even in when comparing *fz*- and *fz*+ cells in a *Vang* mutant background where Fz was not properly localized.

The identity of the putative distal target(s) is currently unknown. In principle the target could be a cytoskeletal activator that is activated by the distal proteins or alternatively a cytoskeletal inhibitor that is inactivated by the distal proteins (Fig 6). If the distal target is an activator than we can predict that a loss of function mutation would result in delayed hair initiation and perhaps small or short hairs. Several such genes have been reported including *shavenoid* which has a strong hair delay/loss phenotype (Ren et al., 2006). However, the phenotype of null alleles of *sha* is strongly enhanced by cells simultaneously being mutant for *fz*/*stan* pathway genes. Thus, if Sha is a target it cannot be the only one. Other possible activator targets are proteins that modulate the activity of the actin cytoskeleton such as formins (Campellone and Welch, 2011; Chesarone et al., 2011; Goode and Eck, 2007) or the Arp23 complex (Campellone and Welch, 2011; Zigmond, 2004). No evidence suggesting this is the case has been published. It is also possible that the target is an inhibitor, and if so we can predict that loss of function mutations would result in premature hair initiation. No possible targets with this property have been reported.

Acknowledgments

The author is supported by a grant from the NIGMS (GM-37136). I thank Simon Collier for generously providing the images of wing ridges.

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NOTE ADDED IN PROOF

Several quite important papers on fly PCP were published recently and interested readers should take a look at them (see below).

- Ambegaonkar A, Pan G, Mani M, Feng Y, Irvine KD. Propagation of Dachsous-fat Planar Cell Polarity. *Current Biology*. 2012; 22:1302–1308. [PubMed: 22727698]
- Brittle A, Thomas C, Strutt D. Planar Polarity Specification through Asymmetric Localization of Fat and Dachsous. *Current Biology*. 2012; 22:907–914. [PubMed: 22503504]
- Peng Y, Han C, Axelrod JD. Planar Polarized Protrusions Break the Symmetry of EGFR Signaling during *Drosophila* Bract Cell Fate Induction. *Developmental Cell*. 2012; 23:1–12. [PubMed: 22814594]
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Figure 1.

Hair Polarity on the fly wing. Panel A shows the polarity of hairs on the dorsal surface of a wild type wing. Panel B shows the stereotypic pattern seen on the dorsal surface of an *intumed* wing. The blackened area is where the polarity was too variable to draw a consensus vector. Panel C shows images of wings from two regions (noted in panel A) of Oregon R, *fz*, *in* and *mwh* mutant wings. Note the relative similarity of the polarity patterns. The downstream genes often show a slightly stronger polarity disruption, but with similar directionality. Panel D shows a *fz* clone marked by the cell marker *strb* (causes short deformed and multiplied hairs). Panel E a *pk* clone marked by *sha* (causes a loss of hairs) and Panel F a *Vang* clone marked by *sha*. Arrows show local hair polarity.

Figure 2.

Polarized protein accumulation and mutant phenotypes. Panel A shows cartoons of wild type and mutant cells. In the wild type cell all of the *fz/stan* pathway proteins accumulate asymmetrically and hairs are formed at the distal vertex. In cells mutant for *fz* or other core genes hairs form at a relatively central location and no proteins accumulate asymmetrically. In cells mutant for *in* or any of the other PPE genes multiple hairs form at an abnormal location on the cell periphery. The core proteins accumulate asymmetrically but the PPE proteins and Mwh do not. In cells mutant for *mwh* genes multiple hairs form at an abnormal location on the cell periphery. The core and PPE proteins accumulate asymmetrically but Mwh does not. Panel B shows the accumulation of Fz-GFP by direct imaging of GFP (green) (no immunostaining) and actin in red (hairs). Panel C shows the coordinate asymmetric accumulation of Fz (green) and In (red).

Figure 3. Bristles and PCP. Panel A is an SEM of a wild type thorax and panel B a *fz* thorax. Panel C is a wild type femur and panel D a *fz* femur. Arrows point to bracts. Panel E is a wild type tarsus and panel F a *fz* tarsus. The arrow points to a segment with a mirror image duplication and the arrowhead to a bulge.

Figure 4.

The eye and PCP. Panel A is a cartoon of the adult retina with Northern (blue) and Southern (red) hemisphere ommatidia in mirror image across the equator. Panel B shows how the pattern in the adult retina is derived by rotation of the developing retina. The crucial R3 (blue) and R4 (green) cells are marked.

Figure 5.

Less well known PCP related phenotypes. Panels A and B show wild type and *fz* pupae respectively. In a modest fraction of *fz* pupae the wing everts forward instead of posteriorly (as shown in B). Arrowheads point to the eye and arrows to the wing hinge region. Panel C is a wild type wing and Panel D is a distorted wing that results from the abnormal eversion as shown in B. Panel EFG are wings imaged by Cuticle Reflection microscopy (E) and normal bright field microscopy (G) and a merged image (F). These panels were generously provided by S. Collier. Panel H is a wild type wing and panel I the same region of a wing from a fly homozygous for a mutation in *Glottactin*. Note the lack of parallel alignment of neighboring hairs in I.

Figure 6.

A possible model for PCP protein action in wing cells. Two neighboring cells are diagrammed. Proteins on the distal membrane of one cell (Fz and Stan) interact with proteins on the proximal membrane of the neighboring cell (Vang and Stan). The core transmembrane proteins recruit the cytoplasmic core proteins (Dsh, Dgo and Pk). The PPE proteins are recruited to the proximal side where In recruits Mwh. Mwh inhibits the actin cytoskeleton in the distal part of the cell. Dsh activates an activator of the actin cytoskeleton distally. For simplicity only one of the feedback interactions between cytoplasmic proteins is drawn (Pk inhibiting Dsh on the distal side).

Table 1**Key Drosophila Planar Cell Polarity Genes**

Drosophila gene	synonyms	Vertebrate	Comments	Key Drosophila References
<i>fz</i>		<i>fz</i> (1,2,3,6)	7 transmembrane domains	(Strutt, 2001; Vinson and Adler, 1987; Vinson et al., 1989)*
<i>dsh</i>		<i>Dvl</i> (1,2,3)	PDZ, Dix domains	(Axelrod, 2001; Klingensmith et al., 1994; Theisen et al., 1994)
<i>dgo</i>		Inversin diversin	Ankyrin repeat	(Feiguin et al., 2001)
<i>stan</i>	<i>fmi</i>	Celsr	Cadherin domains, 7 transmembrane domains	(Chae et al., 1999; Usui et al., 1999)
<i>pk</i>		<i>pk</i> (1,2)	Lim domain, PET domain	(Gubb et al., 1999; Tree et al., 2002)
<i>Vang</i>	<i>stbm</i>	<i>Vangl</i> (1,2)	4 transmembrane domains	(Taylor et al., 1998; Wolff and Rubin, 1998)
<i>in</i>		<i>into</i>	PDZ domain	(Adler et al., 2004; Park et al., 1996)
<i>fy</i>		<i>fuz</i>		(Collier and Gubb, 1997; Strutt and Warrington, 2008)
<i>frtz</i>		<i>firtz</i>	WD40 domain	(Collier et al., 2005)
<i>mwh</i>		none	GBD-FH3	(Strutt and Warrington, 2008; Yan et al., 2008)
<i>ds</i>		<i>Dchs1</i>	Cadherin domains	(Adler et al., 1998; Casal et al., 2006; Clark et al., 1995; Ma et al., 2003; Matakatsu and Blair, 2006; Simon, 2004)
<i>ft</i>		<i>Fat</i>	Cadherin domains	(Adler et al., 1998; Casal et al., 2006; Ma et al., 2003; Mahoney et al., 1991; Matakatsu and Blair, 2006; Simon, 2004)
<i>fj</i>		<i>Fj</i>	Golgi kinase	(Simon et al., 2010; Villano and Katz, 1995; Zeidler et al., 1999)
<i>Rho1</i>		<i>RhoA</i>	GTPase	(Strutt et al., 1997; Yan et al., 2009)