Planar polarity from flies to vertebrates

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Summary

Planar cell polarity (PCP) has been demonstrated in the epithelium of organisms from flies to humans. Recent research has revealed that the planar organization of cells requires a conserved set of genes, known as the PCP genes. Tbe PCP proteins Frizzled (Fz) and Dishevelled (Dsh) function as key players in PCP signalling. Although Fz and Dsh are also involved in Wingless (Wg)/Wnt signalling, these proteins have independent functions in a non-canonical pathway dedicated to PCP. Reorganization of the cell surface and cytoskeleton is required, and recent work has focused on how cell adhesion molecules (such as Fat, Dachsous and Flamingo) function in this process.

Key words: PCP, Planar cell polarity, Frizzled, Dishevelled

Introduction

Polarity is a fundamental property of many cells. Yeast cells can become polarized along the mother-daughter axis, epithelial cells are characterized by apical-basal polarity and neuronal cells are marked by a clear axonal-dendritic polarity. These forms of cellular polarity have been well studied in various cell culture models. However, there is an additional, higher-order, form of polarity only seen in vivo in complex tissues. This tissue polarity, or planar cell polarity (PCP), is a property shown by some epithelia to become polarized within the plane of the epithelium, along an axis perpendicular to the apical-basal axis of the cell. PCP can be found throughout the animal kingdom. The coordinate organization of scales in fish, feathers in birds and hair in mammals are easily visualized examples of PCP. However, PCP is also found in internal tissues, such as stereocilia in the inner ear, and this planar organization of stereocilia is essential for normal hearing and balance. Recent work has suggested that genes involved in PCP also play a key role in polarized tissue movements during vertebrate gastrulation, in a process known as convergent extension. *Drosophila melanogaster* provides many striking examples of PCP: studies focusing on PCP in wing hairs, body bristles and eye ommatidial clusters have uncovered a conserved genetic network that may underlie all forms of PCP. Some genes play only a tissue-specific role in PCP, but a group of genes, known as the core PCP genes, function in all known instances. Although mutations in PCP genes result in loss of the coordinate, planar organization, cells maintain their normal apical-basal polarity and overall structure (Fig. 1). Below, we discuss recent progress in understanding how PCP is controlled, and exciting findings that suggest that core mechanisms controlling PCP are conserved from flies to humans.

Core PCP genes

Molecular and genetic studies have implicated *frizzled (fz)* as a key player in establishing PCP. *fz* mutations affect planar polarity in all tissues, and it is thought that two signalling pathways – a cell-autonomous one and a non-cell-autonomous one – are independently mediated by Fz (Adler et al., 2000; Adler et al., 1990; Park et al., 1994a; Park et al., 1994b). Fz is the founding member of a family of serpentine transmembrane receptors that bind the Wingless (Wg)/Wnt family of ligands. However, the role of Fz in PCP is distinct from its activity as a Wg receptor because Wg itself does not appear to be directly involved in this process (Wehrli and Tomlinson, 1998). Its activity in PCP is independent of canonical Wg signal transduction pathways [for canonical and non-canonical Wg pathways, see Hulsken and Behrens (Hulsken and Behrens, 2002)].

Dishevelled (Dsh), another molecule involved in Wg signalling, is also required for tissue polarity (Theisen et al., 1994). However, like Fz, Dsh seems to act in a non-canonical pathway. Systematic analysis of Dsh domain structure and function has revealed that certain domains are crucial for its role in PCP, but are dispensable for Wg signalling (Axelrod et al., 1998; Boutros et al., 1998).

There are other core PCP genes that do not seem to have any function in the canonical Wg pathway. Prickle (Pk) is a LIM-domain-containing protein thought to negatively regulate the Fz/Dsh PCP pathway (Gubb et al., 1999; Tree et al., 2002). Mutations in the atypical cadherin Flamingo (Fmi, also called Starry night) (Chae et al., 1999; Usui et al., 1999) and the putative transmembrane protein Strabismus (Stbm, also called Van Gogh) also disrupt polarity in many tissues, and hence belong to the core PCP pathway.

Wing hair polarity

The simplest and best-understood form of PCP is the organization of hairs in the fly wing. Each cell in the wing produces a single cellular extension called a trichome or hair. All hairs coherently align along the proximal-distal axis, pointing towards the distal end of the wing (Fig. 2A). PCP genes control both the orientation and the subcellular localization of the hair, as well as the number of hairs produced by each cell. Disruption of the PCP signal produces different

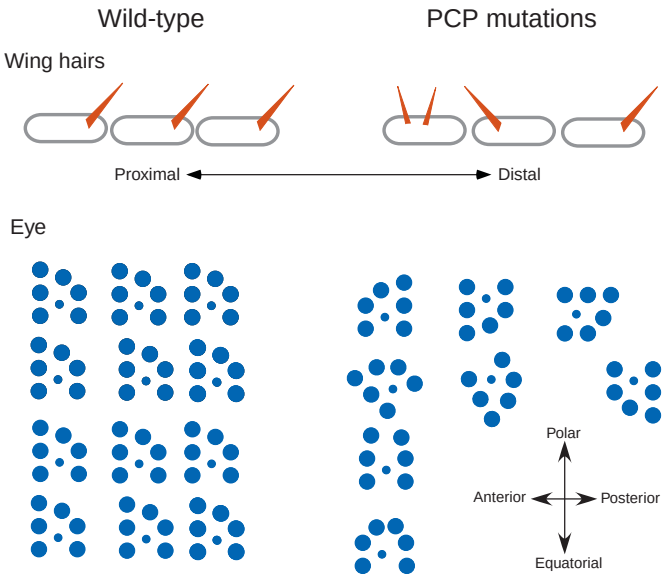

Fig. 1. PCP is evident in the coordinate organization of wing hairs and eye ommatidial clusters in the fly. Mutations in PCP genes cause cells to lose their planar organization, yet maintaining their individual cell polarity. Loss of PCP genes in the wing can cause misorientation of hairs, or multiple hairs to form in a single cell. Loss of PCP genes in the eye can cause alterations in degree of rotation, dorsal-ventral inversions, and loss of the chiral, asymmetric organization of the ommatidia. Cells appear to have lost their 'compass' yet maintain their identity.

classes of phenotype, which are used to classify PCP genes into different groups (Wong and Adler, 1993). Mutations in *fz*, *dsh*, *fmi* and several other PCP genes primarily affect the orientation of wing hairs but not their number. Mutations in the genes encoding novel proteins such as *fuzzy* (*fy*) and *inturned* (*in*), as well as in the uncharacterized mutant *multiple wing hair* (*mwh*), result in multiple hairs growing from a single cell (Gubb and Garcia-Bellido, 1982; Held et al., 1986). This phenotype is often associated with some mild orientation defects. Finally, mutations in genes that encode the small GTPases Rac and RhoA, and the Rho effector *Drok*, lead to multiple hair phenotypes but modest, if any, orientation defects (Eaton et al., 1996; Strutt et al., 1997; Winter et al., 2001). Thus, a molecular network emerging from studies in the wing links the Fz PCP pathway to cytoskeleton changes, which ultimately result in the growth of the actin bundle that constitutes the hair (Turner and Adler, 1995).

Ommatidial polarity

PCP in the eye is much more complex than in the wing and is consequently subject to much more extensive genetic controls. The unit of polarity in the eye is a distinct group of cells called an ommatidium. An ommatidium is composed of eight photoreceptors (R1-R8) and several accessory cells, and resembles an asymmetric arrowhead in sections. There are two fields of PCP in the eye: one comprises dorsal ommatidia, which 'point' dorsally; the other comprises ventral ommatidia, which point ventrally. These mirror image fields meet at the dorsal-ventral (D/V) midline, which is called the equator (Fig. 2B). Polarization of the ommatidia begins in the larval eye imaginal disc as photoreceptor preclusters emerge from the morphogenetic furrow. Dorsal clusters rotate 90° clockwise, whereas ventral clusters rotate counterclockwise, which produces ommatidia that have opposite orientations. These rotations occur in two genetically separable 45° steps.

PCP mutations can lead to very diverse alterations in the polarity of the ommatidia (Fig. 1). Ommatidia can be flipped along the D/V axis (e.g. for a dorsal ommatidium, the adoption of ventral polarity), or along the anterior-posterior (A/P) axis). They can lose their polarized, trapezoid form, resulting in symmetric ommatidia, and can display both under- and over-

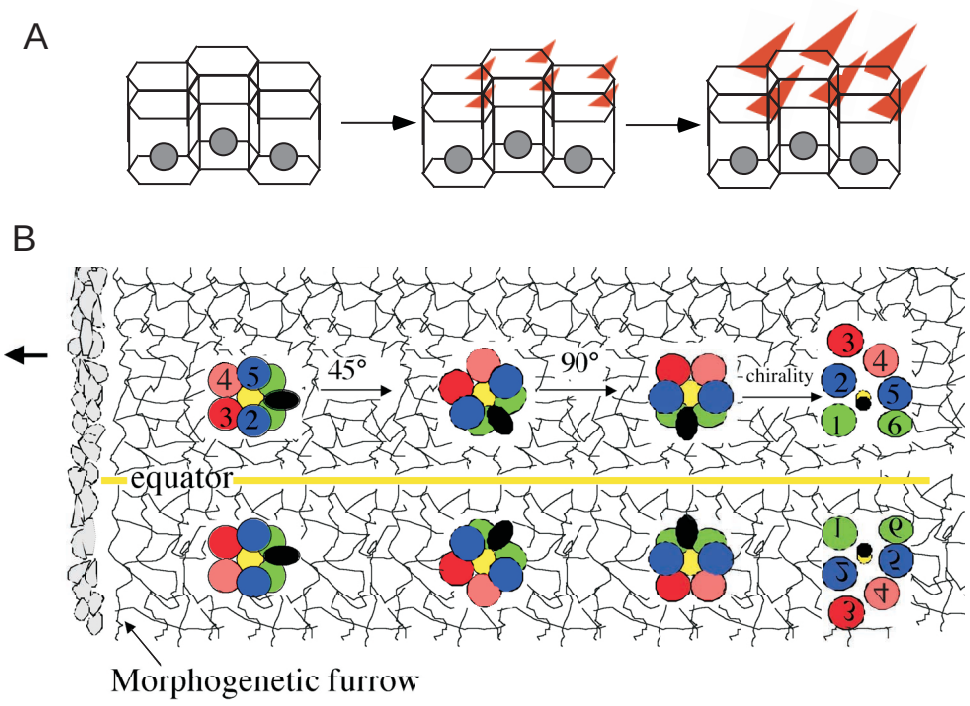

Fig. 2. Development of PCP in the wing and eye. (A) Wing cells display only apical-basal polarity until the pupal stage. Planar polarity is first evident by the production of a single, actin-rich structure at the distal edge of a cell. This develops into a hair. (B) Ommatidial preclusters emerge from a moving wave of differentiation, marked by an indentation called the morphogenetic furrow. As ommatidial preclusters begin to differentiate, they begin to rotate. Ommatidia in one half of the eye will rotate clockwise, and the ventral ommatidia will rotate counterclockwise. This rotation occurs in two steps of 45°, and results in dorsal ommatidia having opposite orientations from ventral ommatidia. A symmetry-breaking step occurs after rotation, resulting in ommatidia with different chiralities in the dorsal and ventral fields.

rotation defects. All these defects are visible in strong *fz* alleles. Other genes might affect only some of these aspects of PCP; for example, elements of the epidermal growth factor (EGF)/Ras pathway, such as Roulette (an allele of the EGF inhibitor Argos) and mitogen-activated protein (MAP) kinases such as Nemo can specifically effect rotation (Choi and Benzer, 1994; Yang et al., 1999; Strutt and Strutt, 2002; Brown and Freeman, 2003; Gaengel and Mlodzik, 2003). Mutations in the small GTPases RhoA and Rac and the secreted protein Scabrous also primarily affect rotation (Strutt et al., 1997; Chou and Chien, 2002), whereas loss of the atypical cadherins Fat (Ft) and Dachsous (Ds) lead to only D/V flips (Rawls et al., 2002; Yang et al., 2002).

An early step in establishing PCP in the eye is the definition of the equator. Iroquois transcription factors such as Mirror (Gomez-Skarmeta et al., 1996; McNeill et al., 1997; Yang et al., 1999) are expressed only in the dorsal half of the eye, and establish the position of the equator through regulation of cell adhesion and by restricting expression of Fringe to the ventral half of the eye. This leads to activation of Notch at the presumptive equator (reviewed by Axelrod and McNeill, 2002). Notch activation is thought to lead to the production at the equator of a diffusible factor, 'Factor X'. Genetic data suggest that Factor X diffuses from the equator and binds to and activates Fz, resulting in a gradient of Fz activity. It is thought that this gradient of Fz activity gives positional information to developing ommatidia.

A great deal of work has elucidated how Fz signalling establishes the polarity of a single ommatidium. The key players are the photoreceptor cells R3 and R4. When clusters emerge from the morphogenetic furrow, the presumptive R3 cell (preR3) is closer to the midline than the preR4. Fz signalling is activated on both cells, but there is a bias for stronger levels of activation in preR3 rather than in preR4. According to the Factor X model, this is because the preR3 is closer to the midline, which is proposed to be the region of production for this signal. The cell with higher Fz activity will become R3, and the other cell will become R4 (Tomlinson and Struhl, 1999; Zheng et al., 1995). It has also been shown that the cell with the higher Notch activity becomes the R4 cell. It is thought that regulation of Notch activity occurs by transcriptional regulation of a Notch ligand, Delta, by Fz signalling. *Delta* expression is higher in the preR3 cell, which is thought to activate Notch on the preR4 cell (Cooper and Bray, 1999; Fanto and Mlodzik, 1999). Recently, an alternative model has been proposed, suggesting that Notch activity in preR3 is downregulated by a direct interaction of Notch with Dsh (Strutt et al., 2002). However, Notch activity is regulated, it is clear that the establishment of R3 versus R4 cell fate after Notch activation directs the polarity of the entire ommatidium.

The JNK pathway has also been implicated in regulating PCP in the eye, primarily on the basis of overexpression experiments (reviewed by Axelrod and McNeill, 2002). However, loss of Jun or its activating kinase Bsk, does not significantly affect PCP. This could be because there are redundant pathways that act in PCP, masking the *jun* and *bsk* phenotypes. The p38 pathway has been suggested to be this redundant pathway. However, it is also possible that *jun* and *bsk* are essential for the PCP phenotype that is caused by Dsh or Fz overexpression but not for the normal establishment of PCP. There is no evidence for a JNK pathway in PCP in the fly wing. Several studies have linked activation of the JNK pathway in vertebrates with convergent extension and have suggested a common Fz→Rho→JNK pathway (see below). However, in mammalian systems, JNK is primarily activated by Cdc42 and Rac, and not by Rho (Noselli and Agnes, 1999). Although DN-Rac can induce polarity changes in the fly eye (Fanto et al., 2000), loss of all Racs (Hakeda-Suzuki et al., 2002) does not alter PCP, highlighting the caution needed in interpreting overexpression phenotypes.

Asymmetric localization

One of the most exciting developments in the PCP field over

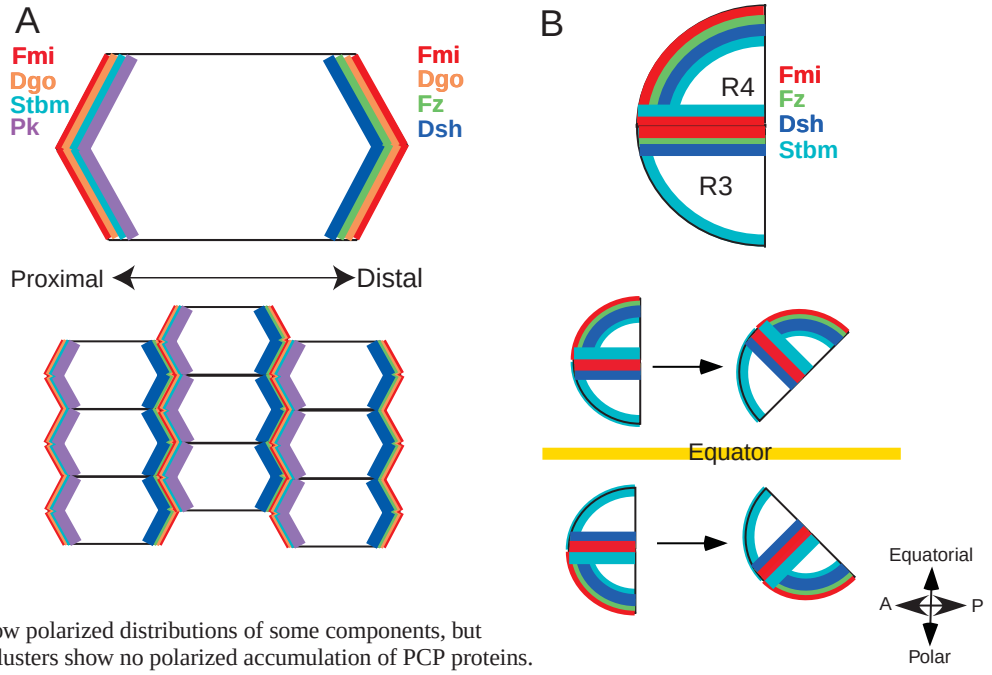

Fig. 3. Polarized subcellular distribution of PCP genes in wing and eye cells. (A) Pupal wing cells show a transient accumulation of PCP proteins on either the proximal or distal cell membranes. Fz and Dsh accumulate on the distal membranes, Stbm and Pk accumulate on proximal membranes, and Fmi and Diego appear to be enriched on both proximal and distal membranes. All are depleted from anterior and posterior membranes. (B) PCP proteins accumulate specifically on subsets of ommatidial precursor cells, most importantly at the R3/R4 interface, shown here. Fz and Dsh accumulate on the R3 cell at the R3/R4 interface, whereas Stbm is enriched in the R4 cell at the R3/R4 interface. Other photoreceptor cells (not shown) show polarized distributions of some components, but importantly cell in-between ommatidial clusters show no polarized accumulation of PCP proteins.

the past few years has been the observation that many tissue polarity molecules are asymmetrically distributed in the cells in which PCP is established. This has been particularly well studied in the wing, which has larger cells than the eye and provides a better system for cell biological observations.

Most PCP proteins are initially symmetrically distributed on the cell membranes. At 26-30 hours after pupation (APF), these proteins relocalize to specific membrane domains (Fig. 3A). The atypical cadherin Fmi becomes transiently localized on both the proximal and distal sides, and depleted from the anterior and posterior cell membranes (Usui et al., 1999). The ankyrin repeat protein Diego is also thought to accumulate on both proximal and distal membranes (Feiguin et al., 2001). Fz and Dsh become localized only to the distal membrane, whereas Stbm and Pk localize solely on the proximal side (Axelrod, 2001; Bastock et al., 2003; Shimada et al., 2001; Tree et al., 2002). Interactions along the proximal-distal axis between proteins on the distal membrane of one cell and the proximal membrane of the next cell are thought to stabilize the system. Interestingly, the regulatory subunit of the protein phosphatase PP2A, encoded by *widerborst* (*wdb*), becomes localized to the distal side of the cell before there is any obvious asymmetric localization of Fz, Dsh, Pk or Stbm. Remarkably, Wdb localization undergoes a dramatic shift: at 8 APF, it is localized proximally, and only later switches to the distal side, where it colocalizes with microtubules (Hannus et al., 2002). This suggests that some form of PCP is present well before the asymmetric localization of the core PCP proteins.

PCP proteins are also asymmetrically localized in the eye. However, in the eye, only a few cells in each ommatidial precluster show protein relocalization. Fz, Dsh, Fmi and Stbm are asymmetrically localized in the preR3 and preR4 cells as clusters begin their rotation (reviewed by McNeill, 2002) (Fig. 3B). Significantly, no such asymmetry is seen on the other photoreceptor cells, or in the cells surrounding the clusters. Fz and Dsh become localized at the preR3/preR4 boundary on the preR3 side, and on the anterior and polar side of the preR4 membrane. Fmi is localized on both the sides of the preR3/preR4 boundary, whereas Stbm is localized only on the preR4 side of the boundary. It is not known where Pk is localized in the eye but it is likely that a feedback loop similar to that proposed in the wing also functions in the eye. However, this can happen only at one cellular interface: that found between the preR3 and preR4 cells. This is very different from the wing, where all cells show asymmetric localization of these PCP proteins.

How is positional information sensed?

A large body of data suggests that Fz has a key role in sensing positional information. However, it does not address the question of what is upstream of Fz: that is, what provides positional information to the cell. A recent breakthrough in the field has come from the discovery that the atypical cadherin genes *ft* and *ds* control PCP upstream of the Fz/Dsh pathway. Loss of either *ft* or *ds* results in eyes in which dorsal and ventral forms of ommatidia are found throughout the eye rather than restricted to their appropriate D/V position, indicating that *ft* and *ds* are essential for PCP (Rawls et al., 2002; Yang et al., 2002). Importantly, *ft* and *ds* also appear to function in PCP in the wing and abdomen, suggesting that they are core elements

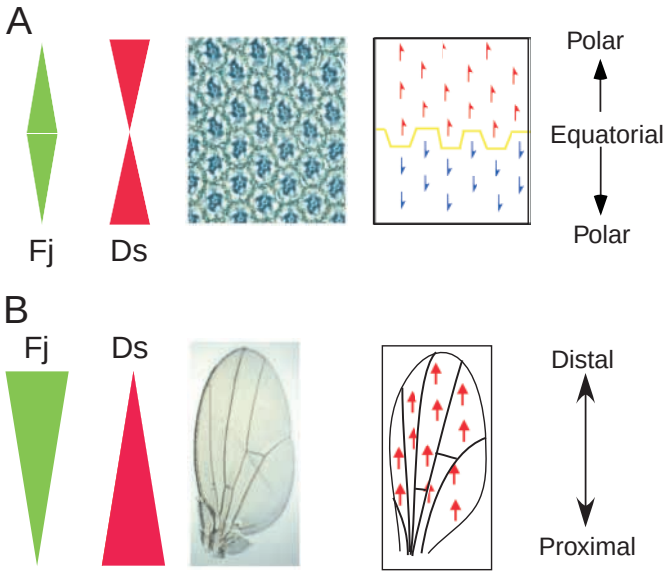

Fig. 4. Fj and Ds impart positional information in the eye and wing. Fj and Ds are transmembrane proteins that are expressed in opposing gradients in the eye (A) and the wing (B). The distribution of these proteins defines the equatorial-polar axis in the eye, and the distal-proximal axis in the wing. Disrupting the polarized distribution of Fj and Ds perturbs planar polarity in both the eye and wing.

of the PCP pathway (Adler et al., 1998; Casal et al., 2002; Ma et al., 2003).

Initial studies describing the role of *ft* and *ds* in the eye focused on their role in R3/R4 fate determination. Yang et al. reported that Ft biases the cells in the preR3/preR4 pair towards R3 cell fate, whereas Ds biases towards R4 identity (Yang et al., 2002). Ds is expressed in a gradient in the eye: there are low levels of Ds at the equatorial region, and high levels at the poles (Fig. 4). Therefore, the cell closest to the pole (the R4 cell) would have higher levels of Ds than would the cell closer to the equator (the R3 cell). The requirement for Ft in the R3 cell resembles that of Fz, and Yang and coworkers proposed that Ft cell-autonomously regulates Fz activity (Yang et al., 2002).

There are also particularly striking non-cell-autonomous polarity effects caused by loss of *ft* or *ds*. For example, although ommatidia inside a *ft* mutant clone tend to have randomized polarity, ommatidia on one side of a *ft* clone, the side closest to the equator, have their polarity rescued by wild-type tissue. Bu contrast, wild-type ommatidia on the side furthest from the equator have their polarity disrupted by the nearby mutant cells. This is very similar to the phenotype of loss of non-cell-autonomous *fz* function, and has led to the suggestion that Ft and Ds control the production of Factor X. The finding that the cytoplasmic domain of Ft binds directly to a transcriptional repressor, Atrophin (Atro), supports this hypothesis (Fanto et al., 2003). Ds binding to Ft is thought to alter Atro transcriptional activity and thereby the production of Factor X. Ft and Atro transcriptionally control the production of one known PCP morphogen, Four-Jointed (Fj). *fj* is expressed in a gradient in the eye disc with highest levels around the equator (Zeidler et al., 1999) (Fig. 4). Loss of *fj* in clones can reorient adjacent wild-type ommatidia, as can ectopic expression of *fj*. Intriguingly, eyes entirely lacking *fj*

display very weak PCP defects, indicating that there are redundant mechanisms that control PCP. Genetic epistasis studies indicate that Fj acts upstream of Ds, which is in turn upstream of Ft/Atro. However, *ds*, *ft* and *atro* also control *fj* transcription, which suggests that feedback loops operate in PCP establishment in the eye.

In the wing, these genes also play an important role in PCP. Ds and Fj are expressed in opposing gradients in the wing, as in the eye (Fig. 4). Careful analysis of their subcellular distributions showed that, unlike other core PCP proteins, Ds and Ft do not appear to localize asymmetrically along the proximal-distal axis within wing cells. They are located just above the zonula adherens, where Fz, Dsh and Pk localize, and their localization is not affected in *fz* clones. Together with epistasis experiments, the data suggest that Fj, Ft, Ds and Atro act upstream of Fz and the other tissue polarity genes, whose activity and localization is randomized but not blocked by mutations in these genes.

An eye for an eye, a wing for a wing

Ommatidial polarity in the fly eye clearly requires a very different system of PCP establishment compared with that found in the wing hairs. The wing provides an example of an epithelium in which all cells need to become polarized individually. By contrast, the eye is an example of a situation in which polarity is achieved by groups of cells (the ommatidial clusters) that must act as a single unit, and are clearly separated by other cells of the same epithelium that do not display any obvious polarity.

There appear to be significant differences in the functions of PCP genes in different tissues. For example, *ft* clones perturb hair polarity only in particular regions of the wing (Strutt and Strutt, 2002), but no such spatial restrictions have been reported in the eye. Furthermore, several reports agree that small *ft* or *ds* clones have little effect on wing hair polarity (Adler et al., 1998; Ma et al., 2003; Strutt and Strutt, 2002), whereas quite small clones can disrupt PCP in the eye. Similarly, in the eye, both *fj* and *fz* cause non-cell-autonomous polarity inversions on the same side of clones (Zeidler et al., 1999; Zheng et al., 1995) whereas, in the wing, *fj* and *fz* cause non-cell-autonomous polarity phenotypes on opposite sides of clones (Vinson and Adler, 1987; Zeidler et al., 2000). We believe that these differences between the two systems should always be kept in mind when proposing 'one-size-fits-all' mechanisms for PCP establishment. Although the cross comparison of data and interpretations between the two systems has been intense and proven to be extremely fruitful, the field has perhaps reached a point where differences need to be taken into greater account.

Dominos versus the mysterious Factor X

Several models for PCP establishment in the wing have been proposed on the basis of the asymmetric localization of Fz, Dsh, Stbm and Pk, the proposed feedback loop between these molecules, and the upstream influence of Ft, Ds and Fj. One model involves a domino effect, in which the asymmetric localization of complexes on one cell alters localization of these complexes on an adjacent cell through Fz-dependent feedback cycles (Tree et al., 2002; Adler et al., 1997). It has been suggested that a gradient of Ft activity controlled by Ds and Fj expression sets up an initial weak bias along the proximal-distal axis (Ma et al., 2003). This initiates a weak asymmetric localization of Fz, Dsh, Stbm and Pk, which becomes amplified and stabilized through Fz-dependent interactions between neighbouring cells. How Ft activity would alter the localization of the PCP proteins is unclear**.** Finally, the asymmetric localization of these proteins would cause hair outgrowth to take place on the distal tip of each cell**.**

Alternative models rely on the presence of a Factor X that activates Fz, and some have even proposed the existence of a Factor Z, which would be produced as a result of Fz activity and would relay the signal to Fz receptors on that cell and on neighbouring cells (Adler et al., 2000). Interestingly, views in the field about Factor X have changed. Initially, it was proposed to be a morphogen-like molecule produced in a few crucial cells (the most proximal cells in the wing or at the D/V midline in the eye) and able to diffuse in a gradient over long distances. More recent views propose that this activity may be a short-range diffusible factor produced throughout the epithelium but in different amounts according to the position of the different cells (Fanto et al., 2003).

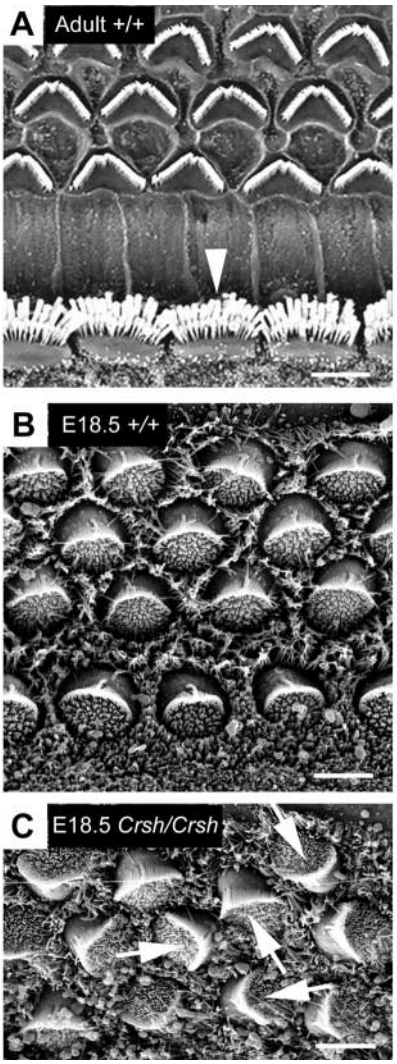

Fig. 5. Mutations in vertebrate PCP genes lead to a PCP defect in the inner ear. Scanning electron micrographs of the inner ear from wild-type mice (A and B) and mice homozygous for mutations in a vertebrate homologue of *flamingo* (C), called *crash* (*Crsh/Crsh*). At (A) 3-5 months, wild-type stereocilia form regularly organized arrays, with the apex of the stereocilia pointing in one direction. This organization is evident in wild-type at E18.5 (B). In *Crsh* homozygotes at E18.5, the outer hair cells (OHCs) are extensively misrotated, showing a clear defect in PCP. Arrows show new axis of polarity. [Figure reproduced, with permission, from Curtin et al. (Curtin et al., 2003)].

We think a model relying on Factor X is necessary to explain the establishment of PCP in the eye. Here, the domino model is less appealing, because only a few cells in the tissue appear to be internally polarized and asymmetrically localize Fz/Dsh/Stbm. The preR3 and preR4 cells are surrounded by non-polarized cells, which provide a formidable obstacle to the domino model. Moreover, such models leave unresolved the problem of how a cluster communicates and coordinates its polarity with other clusters. As previously mentioned, a candidate for controlling Factor X expression in the eye is the transcriptional repressor Atro. Understanding how Atro controls Factor X and PCP awaits the discovery of the mysterious Factor X.

Planar polarity in vertebrates

One visually striking example of PCP is the organization of the hair cells of the inner ear. The vertebrate inner ear has highly polarized sensory hair cells. Each hair cell has a single, microtubule-based structure called a kinocilium, which becomes localized to one side of the cell The kinocilium is flanked by actin-rich microvilli-like structures called stereocilium. All the hair cells become aligned, so that the kinocilium and stereocilia point in the same direction, giving the structure a planar polarized appearance (Fig. 5A) (reviewed by Axelrod and McNeill, 2002). Although this has long been thought to be analogous to *Drosophila* PCP (Eaton, 1997), there were no known mechanistic similarities. Several exciting papers have now shown that inner ear PCP depends on some of the vertebrate homologues of *Drosophila* PCP genes. Most strikingly, mutations in vertebrate homologues of Stbm (Montcouquiol et al., 2003) and Fmi (Curtin et al., 2003) cause the hair cells in the inner ear to form properly but to lose their planar polarity (Fig. 5C). It is not yet known if the proteins also localize asymmetrically during PCP development in vertebrates as they do in *Drosophila*.

Many of the PCP genes also function in vertebrate embryos during convergent extension, a process in which a tissue narrows in one axis and elongates in a perpendicular axis. Convergent extension is driven by the polarized rearrangement of cells within a tissue. In fish and mice, mutants in many PCP genes disrupt convergent extension. The first evidence that PCP genes might act in convergent extension was the finding that Dsh (acting through the DEP domain, which has been implicated in PCP signalling) is essential for polarized cell movements (Heisenberg et al., 2000; Wallingford et al., 2000). Subsequently, other PCP molecules, such as Stbm, were also found to be essential for convergent extension (reviewed by Mlodzik, 2002). Interestingly, these examples of cell migration are mediated by polarized protrusive activity of individual cells; however, the migrating unit is the whole tissue. This suggests that PCP signalling involves the establishment of signalling between cells that confers a collective identity upon them. The result would be a properly organized tissue able to act as a single entity, whether that tissue migrates or forms a planar organized structure.

Perspectives

Recent developments regarding asymmetric localization of PCP molecules and the involvement of atypical cadherins have generated enormous enthusiasm and a wave of new ideas and models. However, many basic questions remain unanswered. What is the real meaning of asymmetric localization – is it the polarity signal per se or could it be a memory mechanism that amplifies and stabilizes a weak biochemical signal? Does ‘Factor X’ exist, or is a gradient of expression of Ds and Fj enough to activate Ft differentially and reorganize the cell? If Factor X exists, what is it, and how does it signal positional information to the cell. The next few years should be exciting, as researchers get closer to filling the gaps left in our understanding of PCP in different model systems.

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