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Principles of planar polarity in animal development

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Summary

Planar polarity describes the coordinated polarisation of cells or structures in the plane of a tissue. The patterning mechanisms that underlie planar polarity are well characterised in *Drosophila*, where many events are regulated by two pathways: the 'core' planar polarity complex and the Fat/Dachsous system. Components of both pathways also function in vertebrates and are implicated in diverse morphogenetic processes, some of which self-evidently involve planar polarisation and some of which do not. Here, we review the molecular mechanisms and cellular consequences of planar polarisation in diverse contexts, seeking to identify the common principles across the animal kingdom.

Key words: *Drosophila*, Planar polarity, Vertebrate

Introduction

'Planar polarity' refers to any manifestation of polarity within a two-dimensional surface. Nübler-Jung (Nübler-Jung, 1987) introduced this term to describe the spatial organisation of polarised structures such as bristles on the insect cuticle. Planar polarity is a common property of animal tissues (Fig. 1) that is most obvious when cells are organised in epithelial sheets, where it is defined as polarity in a plane other than the apicobasal axis, but can also be seen in non-epithelial tissues. [For definitions of planar polarity, see Adler and others (Adler, 2002; Lewis and Davies, 2002; Lawrence et al., 2007; Wang and Nathans, 2007).]

Planar polarity is most frequently studied at the level of individual cells, for example in the *Drosophila* wing, or in the organisation of multicellular structures, such as ommatidia in the fly eye or hair follicles in mammalian skin (Fig. 1A,B,F). This level of organisation is often referred to as 'planar cell polarity' (PCP). However, planar polarity also exists at the subcellular level, for example in the common orientation of cilia on a multiciliated cell (Fig. 1C), as well as in whole tissues, as in the common distal polarisation of fly wing hairs and mouse limb hairs (Fig. 1A,F). For these reasons, we prefer the more general term 'planar polarity'.

This review aims to summarise our current knowledge of how planar polarity is established, emphasising the common mechanisms at work across the animal kingdom. We discuss how planar polarity arises in a range of contexts, in each case requiring polarised cell-cell interactions that align cells with their immediate neighbours and long-range patterning events that orient this polarisation with the axes of the tissue. For reasons of space, the only invertebrate considered is the well-studied dipteran *Drosophila melanogaster*. However, planar polarity has been studied in diverse insects (for a review, see Strutt, 2009), as well as in ascidians (e.g. Jiang et al., 2005), planarians (Almuedo-Castillo et al., 2011) and worms (for reviews, see Walston and Hardin, 2006; Segalen and Bellaïche, 2009). Using the example of the *Drosophila* wing, we define a framework for how planar polarity is established in epithelial tissues. To facilitate comparisons across species, we provide an operational definition for the term 'planar polarity', and in this light review a range of planar polarity processes identified in vertebrates. Finally, we consider the intriguing and recently discovered relationship between planar polarity and cilia function in vertebrates. As most planar polarised cells in *Drosophila* are non-ciliated, we discuss how these studies in vertebrates provide unique insights into planar polarity establishment.

The basics of planar polarity specification

Planar polarity studies began in the insect cuticle in the 1940s, and were followed by extensive genetic analysis in *Drosophila* (e.g. Gubb and García-Bellido), with the wing being particularly well characterised. A key advantage of the wing is its simplicity, with each cell in a monolayer epithelium adopting a polarity that is easily discerned by the presence of a single distally pointing trichome (a small hair, see Fig. 1A, Fig. 2B). To provide a framework for understanding planar polarity establishment, we first describe what has been learnt about this from the *Drosophila* wing, given the strong evidence that the principles seen in the wing are conserved across tissues and species.

Two main cellular systems govern the cell-cell interactions that underlie the local alignment of cell polarity in the wing: the so-called 'core' planar polarity pathway (often just referred to as the 'planar polarity pathway' or 'PCP pathway') and the Fat/Dachsous (Ft/Ds) system. Both act to generate asymmetric cell-cell contacts through heterophilic interactions between cell-surface proteins, which exhibit asymmetric subcellular activities and/or distributions.

The core pathway

Six proteins have been placed in the core pathway in flies, owing to their similar activities and colocalisation to the adherens junction (AJ) region of cells, where they form a putative intercellular complex (Fig. 2A). From early in wing development, the core proteins exhibit asymmetric subcellular localisations that are particularly prominent when trichomes form. At this stage, the seven-pass transmembrane protein Frizzled (Fz) is confined to distal cell junctions along with the cytosolic proteins Dishevelled (Dsh) and Diego (Dgo), whereas the four-pass transmembrane protein Strabismus (Stbm, also known as Van Gogh; Vang – FlyBase) and the cytosolic protein Prickle (Pk) are localised proximally; the seven-pass transmembrane cadherin Flamingo (Fmi, also known as Starry Night; Stan – FlyBase) is present both distally and proximally (Fig. 2A,B) (for a review, see Strutt and Strutt, 2009). Complete loss of activity of any of the core proteins leads to a loss of planar polarity, with trichomes initiating in the cell centre (Fig. 2B) (Wong and Adler, 1993).

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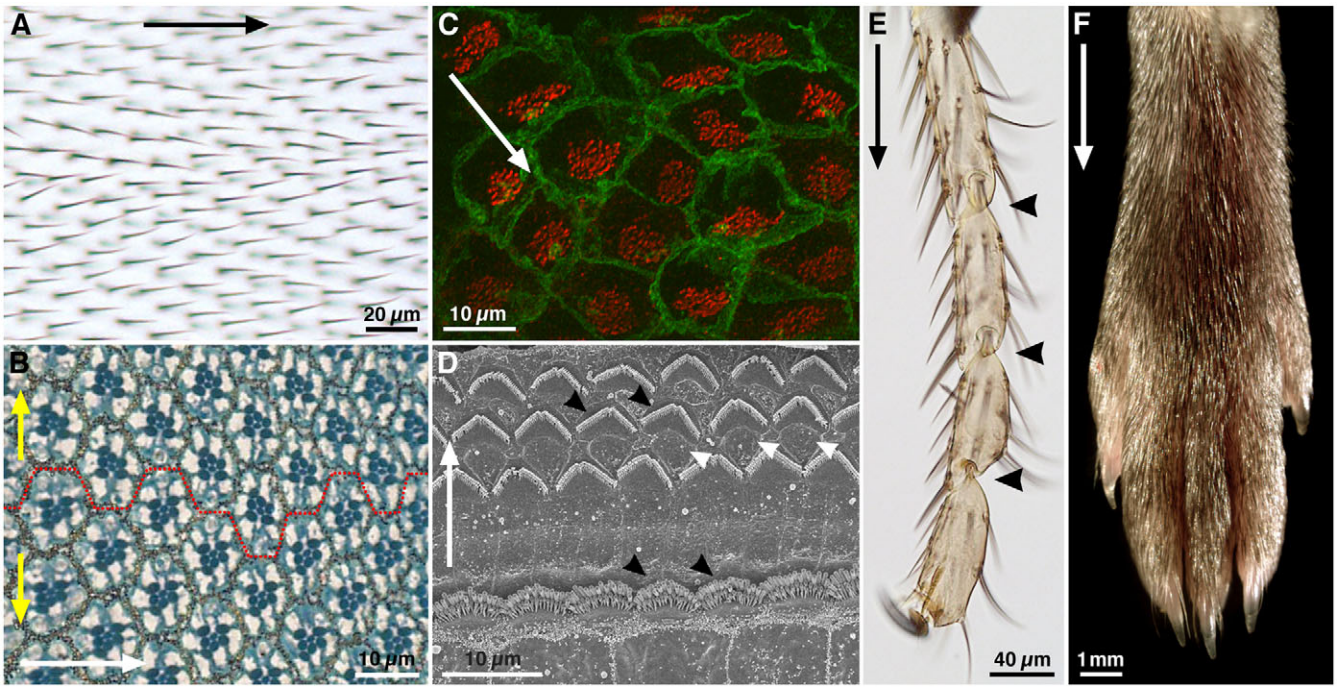

Fig. 1. Examples of planar polarity in flies and mice. (**A**) Adult *Drosophila* wing surface. Planar polarity is evident in the organization of trichomes on the proximodistal (PD) axis (black arrow). (**B**) Sub-apical section through an adult *Drosophila* eye at the dorsoventral (DV) midline. Each eye facet comprises a group of ~20 cells (an ommatidium). In this section plane, the pigmented rhabdomeres (dark blue) of seven photoreceptors are in the centre of each ommatidium. Ommatidia are hexagonally tesselated and show mirror-image symmetry around the DV midline (broken red line), revealing axes of planar polarity on the anteroposterior (AP, white arrow) and DV (yellow arrows) axes. (**C**) Confocal image of mouse brain ependymal cells, with cell membranes stained for β-catenin (green) and cilia basal bodies for γ-tubulin (red). In each cell, basal bodies are displaced towards one side (white arrow), creating 'translational' polarity. (**D**) Scanning electron micrograph of an adult mouse organ of Corti. Planar polarity is seen on the mediolateral axis (white arrow), in the arrangement of the hair cell stereocilia (black arrowheads). Support cells between the hair cells (white arrowheads) show no overt morphological polarisation. (**E**) Tarsal joints of an adult *Drosophila* leg. Planar polarity is evident on the PD axis (black arrow) through the polarisation of bristles and the joints (black arrowheads). (**F**) Distal end of an adult mouse leg, showing the PD polarised arrangement of the fur. Images courtesy of Dr Henry Ho (C), Dr XuDong Wu (D) and Dr Cindy Lu (F), unpublished. (A,B,E) D.S., unpublished.

The core protein asymmetric localisations are thought to result from intracellular feedback interactions between proximally and distally localising components (Tree et al., 2002), whereas the cell-cell coordination of this asymmetry involves the formation of asymmetric intercellular contacts (Chen et al., 2008; Strutt and Strutt, 2008; Wu and Mlodzik, 2008). At the local level, the emergence of coordinated core protein asymmetry is likely to be self-organising, as the activation of core protein expression shortly before trichome formation (when morphogen-based cues are most probably absent) leads to the short-range coordination of polarity (Strutt and Strutt, 2002; Strutt and Strutt, 2007). Evidence that the core pathway plays an instructive role in polarity establishment comes from its directional non-autonomous effects on hair polarity (Gubb and García-Bellido, 1982; Vinson and Adler, 1987; Taylor et al., 1998) (Fig. 2C,D). Groups of cells that lack Fz induce neighbouring cells to point their hairs towards the mutant cells, whereas loss of Stbm causes neighbouring cells to point their hairs away. In both cases, the phenotype suggests that mutant cells and their normal neighbours can only assemble asymmetric junctional complexes of a particular polarity, and this polarity is then propagated to neighbouring cells, an interpretation supported by several theoretical models (e.g. Amonlirdviman et al., 2005; Klein and Mlodzik, 2005; Le Garrec et al., 2006).

How polarised core protein localisation becomes aligned with the axes of the wing is poorly understood. Positional fates on the dorsoventral (DV) and anteroposterior (AP) axes of the wing are largely specified by gradients of the morphogens Wingless (Wg, a member of the Wnt family) and Decapentaplegic (Dpp), respectively (for a review, see Strigini and Cohen, 1999). As Fz also acts as a Wnt receptor, an early suggestion was that a Wnt gradient might provide a polarising cue (e.g. Adler et al., 1997). However, the absence of planar polarity phenotypes upon loss of activity of multiple Wnts (e.g. Lawrence et al., 2002; Chen et al., 2008) caused this idea to fall out of favour. Nevertheless, it is intriguing to note that early in wing development, Fz distribution in cells is oriented towards the source of Wg (Aigouy et al., 2010). An alternative suggestion that core protein localisation is aligned with the axes of the wing by Ft/Ds activity (Ma et al., 2003) is not consistent with the findings that in some genetic conditions in which Ft activity is absent or unlikely to be polarised, core protein-dependent polarisation is largely normal (Matakatsu and Blair, 2006; Feng and Irvine, 2007). However, Ft/Ds can influence core protein polarisation in some contexts, for example by affecting the axis of cell division, cell dynamics and cell packing (Ma et al., 2008; Aigouy et al., 2010), and by influencing the polarisation of microtubules that are involved in vesicle-based transport of Fz distally (Shimada et al., 2006; Harumoto et al., 2010).

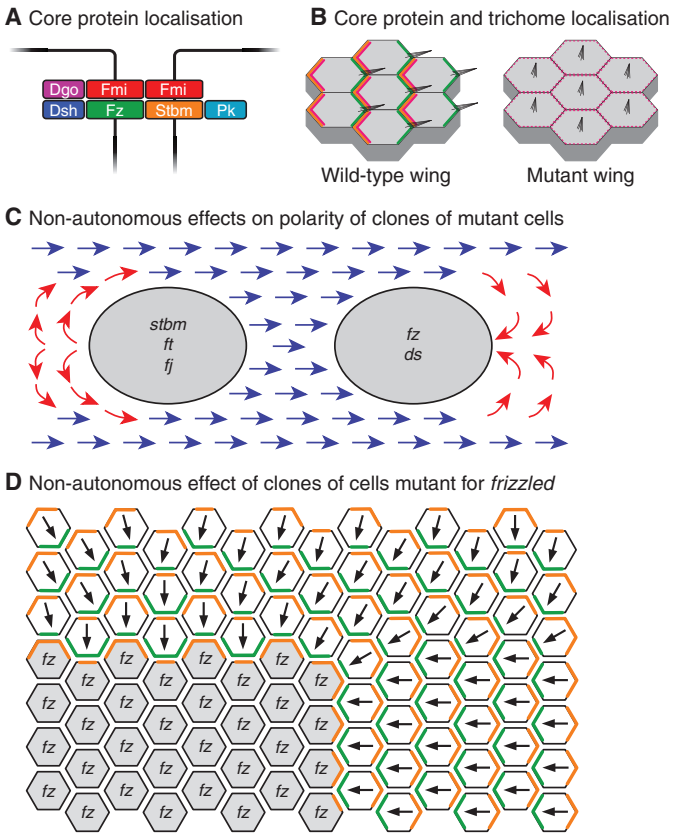

Fig. 2. Properties of the core planar polarity proteins in *Drosophila* wing development. (**A**) Core protein arrangement at the adherens junction zone of epithelial cells in the *Drosophila* wing. An intercellular asymmetric junctional complex forms, with the transmembrane proteins Fz (green) and Fmi (red), and the cytosolic proteins Dsh (dark blue) and Dgo (purple) in one cell, associating with the transmembrane proteins Stbm (orange) and Fmi, and the cytosolic protein Pk (pale blue) in the adjacent cell. (**B**) Subcellular distribution of the core proteins and effectors in the pupal wing. From ~28 hours of pupal life, the core proteins show strong asymmetric subcellular distributions, with Fz, Dsh, Dgo and Fmi (green) being localised at distal cell edges (right), and Stbm, Pk and Fmi (orange) at proximal cell edges (left). The effectors Inturned, Fuzzy, Fritz and Multiple Wing Hairs are recruited proximally (pink), and locally inhibit trichome formation, such that trichomes (black) only emerge distally. Cells that lack or have uniform core protein activity show unpolarised effector protein localisation (pink) and trichome production in the cell centre. (**C**) Non-autonomous effects on trichome polarity (normal polarity shown in blue) in the wing caused by clones of cells lacking planar polarity gene function. Groups of cells lacking *stbm*, *ft* or *fj* activity (grey, left) cause trichomes proximal to the clone to invert their polarity (red arrows), whereas groups of cells lacking *fz* or *ds* function (grey, right) cause trichomes distal to the clone to invert their polarity. (**D**) Model of how a *fz* clone might alter trichome polarity in neighbouring wild-type cells. Cells lacking Fz (grey) can only form complexes containing Stbm (orange) inside the clone, interacting with Fz (green) in the neighbouring wild-type cells. The abnormal polarity of these junctional complexes around the edge of the clone then propagates to neighbouring cells. Dgo, Diego; *ds*, *dachsous*; Dsh, Dishevelled; *fj*, *four-jointed*; Fmi, Flamingo; *ft*, *fat*; Fz, Frizzled; Pk, Prickle; Stbm, Strabismus.

The Ft/Ds pathway

Although once considered an ‘upstream’ pathway that provides long-range patterning information to the core pathway (Yang et al., 2002; Ma et al., 2003), current data suggest that the Ft/Ds pathway is a parallel system for locally aligning cell polarity. Ft and Ds both encode cadherins that preferentially bind to each other at the cell surface (Strutt and Strutt, 2002; Ma et al., 2003; Matakatsu and Blair, 2004), and this interaction is modulated by phosphorylation of both extracellular domains by the Golgi protein Four-jointed (Fj) (Strutt et al., 2004; Brittle et al., 2010; Simon et al., 2010) (Fig. 3A,B). As with the core proteins Fz and Stbm, groups of cells that lack Ft, Ds or Fj activity show directional non-autonomous effects on the polarity of neighbouring cells (Adler et al., 1998; Zeidler et al., 2000; Strutt et al., 2002; Ma et al., 2003) (Fig. 2C). As Ft and Ds interact heterophilically, such effects are best explained by models in which Ft/Ds mediate polarised cell-cell interactions (Casal et al., 2006) (for reviews, see Lawrence et al., 2008; Strutt, 2009).

Although the Ft/Ds system, like the core pathway, coordinates cell polarity through heterophilic interactions, neither Ft nor Ds exhibits strong asymmetric subcellular localisation (Strutt and Strutt, 2002; Ma et al., 2003). However, Ft and Ds activity does lead to the polarised subcellular distribution of Dachs (Fig. 4A), a downstream-acting atypical myosin (Mao et al., 2006; Rogulja et al., 2008). Hence, the uniform distribution of Ft and Ds may be accompanied by strongly polarised subcellular activity, perhaps mediated by the phosphorylation of the Ft intracellular domain induced by Ds binding (Feng and Irvine, 2009; Sopko et al., 2009). Alternatively, Ft/Ds asymmetries may be amplified by an unknown downstream mechanism.

The Ft/Ds pathway is aligned with the body axes via its coupling to the upstream morphogens that control the transcription of *ds* and *fj*. For example, in the *Drosophila* eye, a peripheral source of Wg activates *ds* and represses *fj* expression, creating opposing gradients of the two proteins (Zeidler et al., 1999; Yang et al., 2002; Simon, 2004) (Fig. 4B) and hence a gradient of Ft/Ds binding interactions across the tissue (Brittle et al., 2010; Simon et al., 2010) (Fig. 4C). In the wing, *fj* is expressed in a distal to proximal gradient (Zeidler et al., 2000; Strutt et al., 2004), most probably under the positive regulation of Wg and Dpp, whereas *ds* is largely confined to the wing hinge, with at best only locally graded expression (Strutt and Strutt, 2002; Ma et al., 2003; Matakatsu and Blair, 2004) (Fig. 4B). However, these gradients apparently play only a minor role in planar polarity patterning (Matakatsu and Blair, 2004; Simon, 2004), and a more potent cue is likely to be the boundaries between high and low *ds* and *fj* expression that occur between the wing pouch and the wing hinge, boundaries that also appear to be crucial for Ft/Ds-mediated control of growth (Zecca and Struhl, 2010).

Effectors and morphogenetic outputs of the core and Ft/Ds pathways

Factors that act downstream of the core and Ft/Ds pathways to mediate their effects on cell shape and behaviour are termed ‘effectors’. In general, effectors do not influence the asymmetric localisation or activity of the core proteins or of Ft and Ds, and they are often tissue- or cell-type specific, reflecting the diversity of potential readouts. The identification of effectors can be confounded if they have other cellular roles (such as being cytoskeletal modulators), and consequently their removal does not only affect planar polarity.

In the wing, the primary morphogenetic outcome of core pathway activity is the growth of the polarised trichome from the distal cell edge. This is mediated by a small group of proteins that apparently act exclusively as planar polarity effectors, influencing the polarity of both trichomes and bristles. These are Fuzzy (Fy), Inturned (In) and Fritz (Frtz) (Gubb and García-Bellido, 1982; Wong and Adler, 1993; Park et al., 1996; Collier and Gubb, 1997;

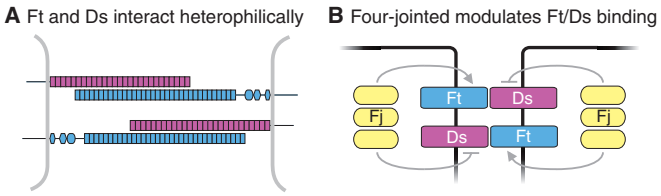

Fig. 3. Fat and Dachsous interactions in the *Drosophila* wing. (A,B) Schematics of the interactions between Fat (Ft) and Dachsous (Ds) at adherens junctions of epithelial cells in the *Drosophila* imaginal discs. (**A**) Ft (cyan) and Ds (magenta) are large atypical cadherin molecules that interact heterophilically. (**B**) Ft/Ds heterophilic interactions are modulated by Four-jointed (Fj, yellow) activity in the Golgi, which phosphorylates the extracellular cadherin repeats in Ft and Ds as they traffic to the cell surface. Fj-mediated phosphorylation of Ft increases its binding affinity for Ds, whereas phosphorylation of Ds decreases its affinity for Ft.

Collier et al., 2005). In the pupal wing, they colocalise with Fmi, Stbm and Pk at the proximal cell edge (Fig. 2B) (Adler et al., 2004; Strutt and Warrington, 2008) and regulate the subcellular localisation of another effector, Multiple Wing Hairs (Mwh), that antagonises actin polymerisation and helps limit trichome formation to the distal cell edge (Strutt and Warrington, 2008; Yan et al., 2008).

Other proteins often regarded as core pathway effectors in *Drosophila* are the p21 GTPase RhoA (Rho1 – FlyBase) and its effector Drok (Rok – FlyBase) (Strutt et al., 1997; Winter et al., 2001), both of which regulate actin dynamics. In the wing, such a role has proved hard to substantiate, as loss of RhoA blocks cell division, which itself can lead to hair polarity defects (Adler et al., 2000), and loss of Drok causes twinned hairs with no polarity defect (Winter et al., 2001), and indeed loss of RhoA activity can also affect core protein localisation, suggesting a possible upstream function (Yan et al., 2009). In the eye, neither RhoA nor Drok affects ommatidial DV polarity, but both are required for regulation of ommatidial rotation (Winter et al., 2001; Strutt et al., 2002), which is an additional function of the core pathway in eye patterning.

Defining effectors of the Ft/Ds system is challenging, as this pathway mediates intertwined effects on both planar polarity and tissue growth (for reviews, see Lawrence et al., 2008; Reddy and Irvine, 2008). In the wing, the Ft/Ds pathway alters hair polarity by influencing core protein localisation (Strutt and Strutt, 2002; Ma et al., 2003), showing that the core pathway can serve as an effector of the Ft/Ds pathway. However, in the abdomen and larval cuticle, the Ft/Ds pathway may instead couple directly to effectors such as In, Fy and Frtz, as it can influence hair, bristle and denticle polarity independently of the core pathway (Casal et al., 2006; Repiso et al., 2010). Ft/Ds signalling also regulates the orientation of cell divisions along the proximal-distal axis of the wing (Baena-López et al., 2005), and in this case, seems to act via asymmetric localisation of a different effector, the atypical myosin Dachs (Mao et al., 2011b). Notably, loss of Dachs has negligible effects on hair polarity (Mao et al., 2006), and the core proteins do not affect the orientation of cell division (Baena-López et al., 2005), indicating that these act as parallel pathways below Ft/Ds. Furthermore, Ft/Ds regulation of planar polarity apparently depends on recruitment of the transcriptional repressor atrophin (Fanto et al., 2003), although its relationship to Dachs and/or to growth control remains unclear (for a review, see Sopko and McNeill, 2009).

The simplest way of viewing the relationship between the core pathway and the Ft/Ds pathway is to regard them as parallel but overlapping local alignment systems, both of which can independently respond to upstream patterning cues, but in particular contexts can also influence each other and share common downstream outputs (Fig. 5).

Other planar polarity systems in *Drosophila*

There are manifestations of planar polarity in *Drosophila* that are not mediated by either the core or Ft/Ds pathways, indicating that other planar polarity systems also exist. The best-studied is polarised cell rearrangement during the embryonic gastrulation process of germband extension, which is controlled by the pattern of transcription factor expression present in embryonic segments and also relies on local cell-cell interactions (for reviews, see Zallen, 2007; Bertet and Lecuit, 2009). Another example is the initial AP polarisation of ommatidial clusters in the eye disc as they are born from the morphogenetic furrow (Heberlein et al., 1993). An additional local cell alignment system dependent on the activities of the septate junction proteins Gliotactin and Coracle has also been proposed to act in parallel to the core and Ft/Ds systems in the wing (Venema et al., 2004).

Another intriguing alternative pathway for establishing planar polarity is seen in the egg chamber, where each follicle cell has basal actin filaments that are oriented on the DV axis (Gutzeit, 1990). This planar polarity depends on the activity of a *ft* homologue, *fat2* (also known as *fat-like* and *kugelei*; *kug* – FlyBase) (Viktorinová et al., 2009), and of the receptor tyrosine phosphatase Dlar (Lar – FlyBase) (Bateman et al., 2001; Frydman and Spradling, 2001), and on components of the dystroglycan complex (Deng et al., 2003; Mirouse et al., 2009). These factors act non-autonomously, with clones that disrupt actin filament polarity also disrupting the polarity of neighbouring cells, suggesting roles in cell-cell communication. Furthermore, Dlar and Fat2 distributions are planar polarised, with Dlar found at both DV edges of each cell (Bateman et al., 2001) and Fat2 at only one end (Viktorinová et al., 2009). The involvement of novel factors, and the observation that this polarisation does not require the activity of the Ft/Ds or core pathways (Viktorinová et al., 2009), indicates that Fat homologues can coordinate planar polarity through novel mechanisms.

An operational definition for planar polarity

As we have seen, planar polarity is a well-defined phenomenon in *Drosophila*, which has permitted the characterisation of the underlying signalling events. However, as studies of these same pathways have expanded to tissues that do not show obvious planar organisation, ‘planar polarity’ events have become harder to recognise. Hence, processes are often labelled as involving planar polarity (or PCP) simply because one or more planar polarity proteins is reportedly involved. A particular source of confusion is that the core pathway was originally identified as a ‘non-canonical’ Wnt pathway, involving Frizzled family receptors and Dishevelled homologues in a β-catenin-independent signalling cascade (for reviews, see Strutt, 2003; Veeman et al., 2003a). Subsequently a plethora of non-canonical signalling processes have been designated as being ‘Wnt/PCP signalling’, even in the absence of evidence that they exhibit planar polarity at the cellular level. A related issue is that planar polarity may be indirectly affected by other defects in morphogenesis that are in fact due to signalling through the canonical Wnt pathway or some other uncharacterised pathway that involves known polarity proteins.

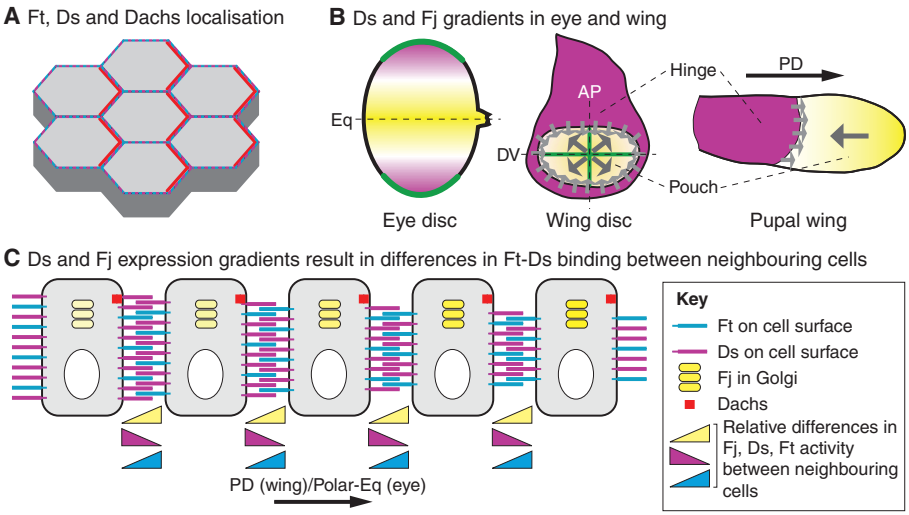

Fig. 4. Properties of the Fat and Dachsous system in *Drosophila*. (**A**) A schematic of the apical surface of epithelial cells in the *Drosophila* wing. Fat (Ft, blue) and Dachsous (Ds, magenta) are uniformly distributed, but promote planar polarised asymmetry of Dachs (red). (**B**) Ds and Four-jointed (Fj) gradients. In the eye disc (left), the secreted morphogen Wg (green) is highly expressed at the dorsal and ventral poles, and activates Ds (magenta) expression while suppressing Fj (yellow) expression. The dotted line indicates dorsoventral (DV) midline, also known as the equator (Eq). In the third instar wing disc (middle) and early pupal wing (right), high levels of Ds are present outside the wing pouch, including the hinge. Fj shows graded expression (large grey arrows) within the wing pouch that is highest distally, probably owing to morphogen signalling from the DV and anteroposterior (AP) midlines (green). The sharp boundary between high Ds hinge expression and low Fj pouch expression might serve as a polarising cue (small grey arrows). (**C**) Model of how opposing gradients of Ds and Fj expression could lead to different levels of Ft/Ds binding activity across cells on the proximodistal (PD) axis of the wing disc or the polar-equatorial (Polar-Eq) axis of the eye disc. Ds levels decline left to right, Fj levels decline right to left and Ft levels are uniform. Triangles at the bottom indicate relative differences between Ds, Ft and Fj activity between pairs of cells. Fj cell-autonomously inhibits Ds activity and simultaneously enhances Ft activity. Thus, considering any cell, its left neighbour has higher Ds expression and activity and lower Ft activity than its right neighbour, promoting formation of more and stronger heterophilic Ft-Ds interactions on the left-right axis and fewer and weaker interactions on the right-left axis. The resulting difference in the strengths of Ft-Ds interactions on opposing cell edges leads to asymmetric distribution of Dachs (red).

We suggest that when considering cellular organisation, a planar polarity process is defined as one in which cell-cell communication causes two or more cells to adopt coordinated polarity. Moreover, such a process should only be referred to as evidence of 'PCP signalling' or requiring the 'planar polarity pathway' when shown to be dependent upon planar polarity proteins that mediate these polarised cell-cell interactions. For some processes that involve the planar polarity proteins, further research will be required to establish whether they are true examples of planar polarity.

Planar polarity in diverse contexts

Although planar polarity is most obvious in two-dimensional epithelia such as the fly wing, it is prevalent throughout the animal kingdom, occurring in diverse contexts with many morphological outcomes. Multiple vertebrate orthologues of the major pathway components identified in flies have been found (see Table 1), and function via the same basic mechanisms, albeit with some modifications to accommodate the unique demands of each system. Here, we describe some of the best understood vertebrate planar polarised systems.

Arrays of polarised cells

The simplest manifestation of planar polarity is the alignment of a field of identical cells, as in the fly wing. A comparable vertebrate example is the node, where each epithelial cell extends a single primary cilium towards the posterior of the embryo (Fig. 6A). When all of the cells of the node are properly oriented, the cilia beat together and direct fluid flow to the left, thereby establishing the left-right (LR) axis of the embryo. Failure to uniformly align the cilia disrupts flow, and the embryos develop LR patterning defects (Antic et al., 2010; Borovina et al., 2010; Hashimoto et al., 2010; Song et al., 2010).

The emergence of planar polarity in the node involves both asymmetric positioning of the cilium within each cell and coordinated alignment of the polarised cells. Consistent with the parallels to the fly wing, this depends on expression of orthologues of the core pathway proteins Stbm, Pk and Dsh, which are asymmetrically distributed in the node prior to the posterior localisation of the basal body of the primary cilium (Fig. 6Aa). Moreover, as predicted from flies, Vang-like1 (Vangl1), Vang-like2 (Vangl2) and Prickle2 (Pk2) appear to be restricted to one side of the cell (Antic et al., 2010; Song et al., 2010), while Dishevelled2 (Dvl2) and Dishevelled3 (Dvl3) are on the other (Hashimoto et al., 2010). This localisation is probably instructive, as LR asymmetry defects occur when either Vangl or Dvl activity is severely reduced in multiple species, including mouse, frog and zebrafish (Zhang and Levin, 2009; Antic et al., 2010; Borovina et al., 2010; Hashimoto et al., 2010; May-Simera et al., 2010; Song et al., 2010). Moreover, in mouse, many cilia remain in the cell centre (Fig. 6Aa) (Antic et al., 2010; Hashimoto et al., 2010; Song et al., 2010), indicating that intrinsic planar polarity is lost, echoing the central position of hairs in mutant fly wing cells (Fig. 2B).

A related situation occurs in the ventricular lining of the brain, where multiciliated ependymal cells extend cilia that beat in a coordinated fashion to propel cerebrospinal fluid (Fig. 1C, Fig. 6Ab). These cells exhibit two forms of polarity (Mirzadeh et al.,

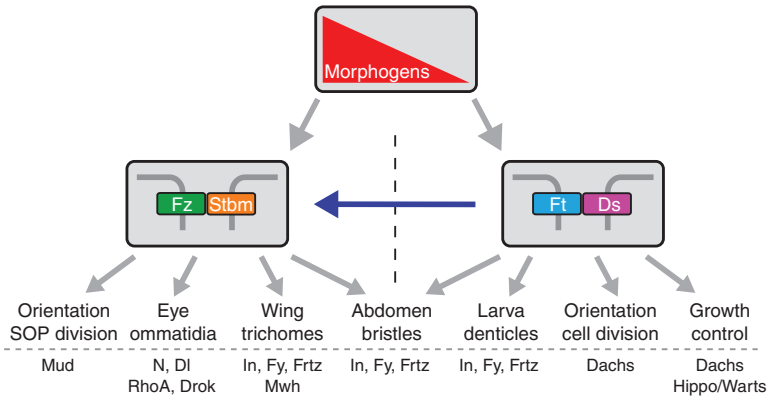

Fig. 5. Relationships between the core and Ft/Ds pathways in *Drosophila*. Both the core and Ft/Ds pathways can respond independently to upstream morphogenetic patterning information (gradient in red). The core pathway (represented by heterophilic Fz-Stbm binding) interacts directly with effectors to control polarity of trichomes in the wing, the orientation of sensory organ precursor (SOP) divisions, and the DV polarity and rotation of ommatidia in the eye. In these contexts the Ft/Ds pathway can alter polarity via the core pathway (blue arrow) by an unknown mechanism. The Ft/Ds pathway can act independently of the core pathway to mediate effects on growth control, cell division orientation in the wing and eye discs, and the polarity of larval denticles. The Ft/Ds pathway acts in parallel with the core pathway to control trichome and bristle orientation in the abdomen. Example effectors mediating these effects are shown at the bottom. Dl, Delta; Drok, Rho kinase; Ds, Dachsous; Frtz, Fritz; Ft, Fat; Fy, Fuzzy; Fz, Frizzled; In, Inturned; Mud, Mushroom Body Defective; Mwh, Multiple Wings Hairs; N, Notch; Stbm, Strabismus.

2010). First, the basal bodies and hence cilia are aligned relative to each other within the cell (rotational polarity). Second, the entire patch of cilia is displaced to the anterior side of each cell (translational polarity, Fig. 6Ab). Both forms of polarity emerge together and correlate with the onset of coordinated beating in a uniform direction (Hirota et al., 2010).

During establishment of translational polarity, the patch of cilia migrates to a peripheral position and the cells align uniformly according to this asymmetry. The polarisation event actually depends on the prior asymmetric positioning of the primary cilium in the radial glia precursors of the ependymal cells. When the primary cilium is not present – as occurs in the absence of the ciliogenic protein Kinesin family member 3a (Kif3a) – the patches remain central (Fig. 6Ab) (Mirzadeh et al., 2010). The mechanism is poorly characterised, but Vangl2 and Fz3 are localised to ependymal cell boundaries under the influence of the Fmi orthologues Celsr2 (Cadherin, EGF-like, LAG-like and seven-pass receptor 2) and Celsr3, consistent with the intracellular signalling functions of the core pathway (Tissir et al., 2010). Furthermore, Vangl2 distribution is asymmetric (Fig. 6Ab), suggesting that polarised cell-cell interactions occur (Guirao et al., 2010). Surprisingly, inhibition of Dvl2 does not affect the positioning of this cilia patch (Hirota et al., 2010); however, this could be due to redundancy or to the insufficient reduction of activity in the radial glial precursors.

Rotational polarity involves alignment not of cells but of organelles (Fig. 6Ab), raising the issue of how the core proteins might function in this context. The correct intracellular alignment of the cilia requires multiple core pathway proteins (Guirao et al., 2010; Hirota et al., 2010; Tissir et al., 2010) and both Dvl2 and Vangl2 localise to basal bodies (Fig. 6Ab) (Hirota et al., 2010; Park et al., 2008; Ross et al., 2005). Strikingly, basal bodies also fail to reach the apical surface of a number of ciliated cell types upon reduction of Vangl, Dvl or Celsr activity (Park et al., 2008; Mitchell et al., 2009; May-Simera et al., 2010; Tissir et al., 2010) (Fig. 6Bb). This suggests a model in which core proteins might polarise intracellular trafficking events that move basal bodies within the cell, influencing both basal body delivery to the apical surface and their alignment on the planar axis.

Mixed arrays of polarised and unpolarised cells

Polarised cells often reside in epithelia that house a diverse array of cell types, such as in the vertebrate inner ear, where morphologically asymmetric hair cells interdigitate with support cells (Fig. 1D, Fig. 6Ba). Each hair cell is topped by a bundle of actin-rich stereocilia linked to one true cilium, the kinocilium. The entire bundle is positioned along one edge, placing the kinocilium on the perimeter of the cell, and fields of polarised hair cells are further organized according to the axes of each sensory epithelium. For example, in the cochlea, all hair cells point their bundles laterally.

Abundant evidence shows that planar polarity in the inner ear is achieved by a conserved core protein pathway. Mutations in orthologues of Fmi (Celsr1), Stbm (Vangl1, Vangl2), Fz (Fz2, Fz3, Fz6) and Dsh (Dvl1, Dvl2, Dvl3) (see Table 1) all cause hair cell misorientation (Fig. 6Ba) (Curtin et al., 2003; Montcouquiol et al., 2003; Wang et al., 2005; Wang, J. et al., 2006; Wang, Y. et al., 2006b; Deans et al., 2007; Etheridge et al., 2008; Torban et al., 2008; Song et al., 2010; Yu et al., 2010), and core proteins are asymmetrically localised (Fig. 6Ba) (Wang et al., 2005; Montcouquiol et al., 2006; Wang, J. et al., 2006; Wang, Y. et al., 2006b; Deans et al., 2007; Qian et al., 2007; Etheridge et al., 2008; Jones et al., 2008; Song et al., 2010). Most exciting is the observation that core proteins are also polarised in the support cells, which may be active participants in the planar polarisation process (Wang, Y. et al., 2006b; Deans et al., 2007; Song et al., 2010; Warchol and Montcouquiol, 2010), despite the fact they do not themselves have any asymmetrically positioned appendages.

Whether the predicted relationships are also conserved is harder to demonstrate as it is difficult to distinguish whether a protein is localised on the medial side of the hair cell or on the lateral side of the closely apposed support cell. A further complexity is that the cells of the organ of Corti are moving as the cochlea extends, thereby obscuring when and where the relevant cell-cell interactions occur (Chen et al., 2002; Yamamoto et al., 2009a). However, mosaic studies conclusively demonstrated that Fz6 and Pk2 do indeed mark opposite sides of cells (Wang, Y. et al., 2006b; Deans et al., 2007), just as Fz and Pk do in flies. Moreover, Vangl2 is required for proper localisation of other core components (Wang

Table 1. Vertebrate homologues of planar polarity genes identified in *Drosophila*

Drosophila gene	Identified homologues known to function in planar polarity	Asymmetric localisation observed?	Key references
fz	*Fz1*, *Fz2*, *Fz3*, *Fz6* (mouse)	Fz3 (ependymal, inner ear); Fz6 (inner ear, hair follicles)	Wang, Y. et al., 2006b; Deans et al., 2007; Devenport and Fuchs, 2008; Jones et al., 2008; Tissir et al., 2010; Yu et al., 2010
stbm/Vang	*Vangl1*, *Vangl2* (mouse) *stbm/vangl2* (zebrafish, *Xenopus*)	Vangl1, Vangl2 (mouse node, ear, hair follicles); Vangl2 (ependymal); Vangl2 (chick node)	Montcouquiol et al., 2006; Qian et al., 2007; Devenport and Fuchs, 2008; Jones et al., 2008; Zhang and Levin, 2009; Antic et al., 2010; Guirao et al., 2010; Song et al., 2010; Tissir et al., 2010; Warchol and Montcouquiol, 2010
fmi/stan	*Celsr1*, *Celsr2*, *Celsr3* (mouse) *fmi/celsr* (zebrafish) *C-fmi-1* (chick)	Celsr1 (hair follicles); C-fmi-1 (chick ear)	Davies et al., 2005; Wada et al., 2006; Devenport and Fuchs, 2008; Carreira-Barbosa et al., 2009
dsh	*Dvl1*, *Dvl2*, *Dvl3* (mouse) *dsh* (zebrafish, *Xenopus*)	Dvl2, Dvl3 (mouse node, ear)	Heisenberg et al., 2000; Wallingford et al., 2000; Wang et al., 2005; Etheridge et al., 2008; Hashimoto et al., 2010
pk	*Pk1*, *Pk2* (mouse) *pk1* (zebrafish) *Pk* (*Xenopus*)	Pk2 (mouse ear, node); Pk (mesoderm, neural tube)*	Carreira-Barbosa et al., 2003; Takeuchi et al., 2003; Veeman et al., 2003b; Ciruna et al., 2006; Deans et al., 2007; Antic et al., 2010; Yin et al., 2008
dgo	Inversin (*Invs*), diversin (*Ankrd6*) (mouse)	Unknown	Watanabe et al., 2003
ft	*Fat4* (mouse)	Unknown	Saburi et al., 2008
ds	*Dchs1* (mouse)	Unknown	Mao et al., 2011a
fj	*Fjx1* (mouse)	Unknown	Saburi et al., 2008
dachs	None?	Unknown	
in	*Intu* (mouse) *Int* (*Xenopus*)	Unknown	Park et al., 2006; Zeng et al., 2010
fy	*Fuz* (mouse) *Fy* (*Xenopus*)	Unknown	Gray et al., 2009; Heydeck et al., 2009
frtz	*Fritz* (*Xenopus*)	Unknown	Kim et al., 2010

*Note that the asymmetric localisation of Pk observed in zebrafish and *Xenopus* (Ciruna et al., 2006; Yin et al., 2008) was seen using expression of a fusion of *Drosophila* Pk to GFP, not using native zebrafish and *Xenopus* proteins.
Celsr, Cadherin, EGF-like, LAG-like and seven-pass receptor; *ds*, *dachsous*; *dgo*, *diego*; *dsh*, *dishevelled*; *Dvl*, dishevelled; *fj*, *four-jointed*; *Fjx1*, four jointed box 1; *fmi/stan flamingo/starry night*; *frtz*, *fritz*; *ft*, *fat*; *Fuz*, fuzzy homologue; *fy*, *fuzzy*; *fz*, *frizzled*; *in*, *inturned*; *Int*, inturned; *Intu*, inturned; *pk*, *prickle*; *stbm/Vang*, *Van Gogh*; *Vangl*, Van Gogh like.

et al., 2005; Montcouquiol et al., 2006; Wang, J. et al., 2006; Wang, Y. et al., 2006b; Deans et al., 2007; Etheridge et al., 2008), indicating that the characteristic signalling events mediated by the core protein complex take place in this tissue. Indeed, ablation experiments in chick indicate that polarised Vangl2 in support cells may provide polarity information for newly regenerated hair cells, which consistently appear with the correct orientation (Warchol and Montcouquiol, 2010). The Ft/Ds pathway is also strongly implicated in inner ear patterning, as hair cell orientation is disrupted in mice with mutations in *Fat4* and *Dcsh1* mutations, which are the most conserved orthologues of *Drosophila ft* and *ds*, respectively (Saburi et al., 2008; Mao et al., 2011a). Although the effects on core protein distribution are unknown, *Fat4* interacts genetically with both *Vangl2* and *Fjx1* (Saburi et al., 2008), the sole mammalian *Fj* orthologue, indicating that a conserved relationship exists between the core and a putative vertebrate Ft/Ds pathway.

Additional evidence that polarity can be propagated by morphologically unpolarised cells comes from studies of the frog skin, where multiciliated epidermal cells are aligned along the AP axis of the animal (Fig. 6Bb). These ciliated cells are born in the inner epithelial layer and then migrate up to intercalate with unciliated cells in the outer layer (Drysdale and Elinson, 1992). Explant and transplant studies suggest that the outer epithelium is polarised first and passes this information to the ciliated cells as they arrive (Konig and Hausen, 1993; Mitchell et al., 2009). Planar polarity proteins seem to mediate this process: inhibition of a *dsh* orthologue or of *Vangl2* prevents alignment of both the basal bodies within the cell and of the cell relative to its neighbours (Fig. 6Bb) (Park et al., 2008; Mitchell et al., 2009). Similar effects occur upon overexpression of *Vangl2* or *Fz3* (Mitchell et al., 2009). Of particular interest is that wild-type ciliated cells become misoriented when they are forced to intercalate into an outer layer where core pathway signalling has been disrupted. Furthermore, at the boundaries of transplants, cells orient their cilia towards low levels of Vangl2 and high levels of Fz3 (Fig. 7) (Mitchell et al., 2009), an effect also seen upon overexpression of Vangl2 in the chick inner ear (Sienknecht et al., 2011). Thus, as in flies, Vangl and Fz provide directional information that allows cells to achieve a uniform polarisation, providing some of the best evidence for non-autonomous signalling in vertebrates, and highlighting the ability of multiple cell types to participate in polarised cell-cell interactions.

Polarisation of multicellular structures

Planar polarity mechanisms also align asymmetrically organised groups of cells. For example, in the *Drosophila* eye, planar polarity is manifest through the orientation of the ommatidia –

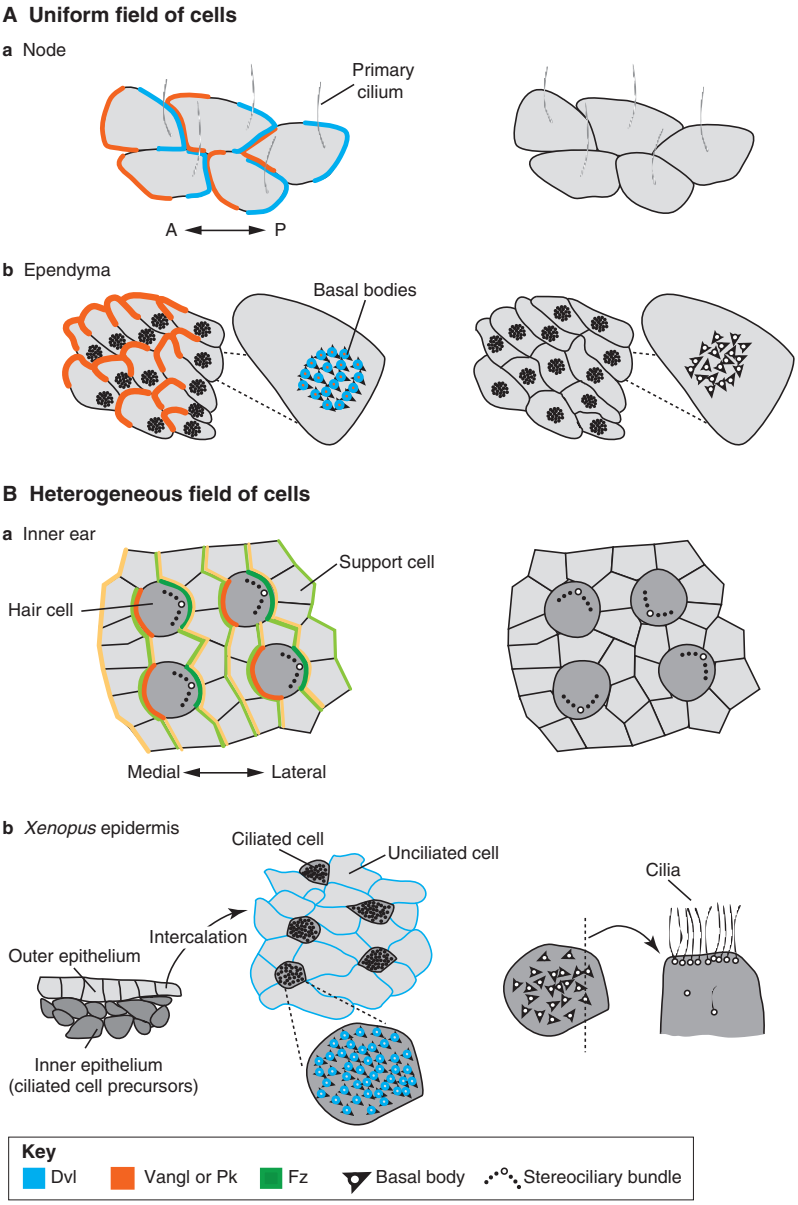

Fig. 6. Organisation of vertebrate planar polarity in uniform and heterogeneous fields of cells. (**A**) Planar polarity in uniform fields of cells. In all panels, protein distributions are schematised on the left where known: Dvl (Dishevelled; blue), Vangl (Vang-like) or Pk (Prickle; orange), Fz (Frizzled; green). Surface views shown except where noted. The arrangements of polarised cells as seen in planar polarity mutants are illustrated on the right. In (a) the vertebrate node and (b) the ependymal lining of the brain, identically polarised cells point in one direction, as revealed by the asymmetric position of primary cilia in the node and patches of cilia in the ependyma (translational polarity). Planar polarity also exists at the subcellular level – i.e. rotational polarity – as revealed by the alignment of basal bodies (arrowheads) in individual ependymal cells (b). Cilia remain in the centre and/or fail to align with each other when planar polarity is not properly established. (**B**) In heterogeneous fields of cells, such as (a) the mouse inner ear and (b) *Xenopus* epidermis, polarised cells interdigitate with cells that show no outward polarisation. In the inner ear, core proteins are asymmetrically distributed in both hair cells (dark grey) and support cells (light grey); protein distributions are represented in lighter shades in support cells. In polarity mutants, hair cells are not uniformly oriented. In the epidermis, ciliated cells are born in the inner epithelium and then intercalate with unciliated cells in the outer epithelium (shown in cross-section), creating a mosaic of polarised and unpolarised cells in the mature epithelium (shown in surface view). Dvl and Vangl proteins may localise to basal bodies, which normally all point in the same direction. In planar polarity mutants, ciliary orientation is disrupted; defects in ciliogenesis and the apical localisation of the basal bodies have also been reported, as illustrated for one cell shown in cross-section on the right. A, anterior; P, posterior.

groups of about 20 cells that give rise to the facets of the adult eye (for a review, see Wolff and Ready, 1993) (Fig. 1B, Fig. 8A). Ommatidia initially have AP polarity that is independent of the core or Ft/Ds pathways, which subsequently specify mirror-image planar polarity on the DV axis. Notably, the DV polarity of each ommatidium is determined by core pathway activity in just two cells, the R3/R4 photoreceptor pair, and is read out through a Notch/Delta-dependent feedback loop that causes one cell to take on R4 fate and the other R3 fate (Zheng et al., 1995; Cooper and Bray, 1999; Fanto and Mlodzik, 1999; Tomlinson and Struhl, 1999). Mosaic analysis established that R3/R4 fate determination requires higher Fz activity in the presumptive R3 cell and higher Stbm activity in the presumptive R4 cell (Zheng et al., 1995; Wolff and Rubin, 1998; Tomlinson and Struhl, 1999). Consistent with this, Fz is localised to the R3 side of the R3/R4 cell boundary and Stbm to the R4 side (Strutt et al., 2002). As Fz and Stbm expression levels do not seem to vary along the DV axis (Zheng et al., 1995; Rawls and Wolff, 2003), a plausible (but unproven) model is that the subcellular localisation of the core proteins is the key factor in modulating Notch/Delta activity and hence in defining cell fates (Strutt et al., 2002).

An absence of *fz* activity prior to photoreceptor differentiation leads to randomised DV polarity of ommatidia (Strutt and Strutt, 2002), indicating that long-range polarity coordination across the eye epithelium requires core protein activity in cells other than R3/R4. One hypothesis is that weak DV subcellular polarisation of the core proteins occurs throughout the epithelium, but only cells that take on the R3/R4 fate are primed to respond; the subcellular distribution of Fz/Stbm in cells other than the R3/R4 pair is unknown. Alternatively, asymmetry might only evolve in the R3/R4 pair. The Ft/Ds pathway also acts upstream of the core pathway in determining DV polarity of ommatidia (Zeidler et al., 1999; Rawls et al., 2002; Strutt and Strutt, 2002; Yang et al., 2002; Fanto et al., 2003), but how these pathways and long-range cues are integrated remains contentious (Fanto and McNeill, 2004).

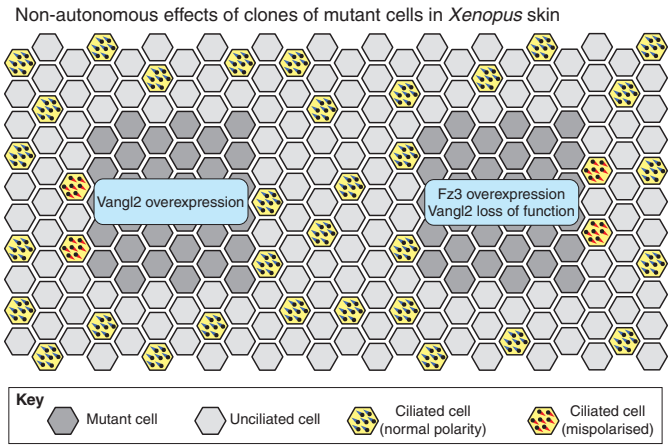

Fig. 7. Non-autonomous planar polarity phenotypes in the *Xenopus* epidermis. Grafting experiments in the *Xenopus* epidermis reveal that core proteins mediate non-autonomous cell-cell interactions that control the polarity of neighbouring tissue. Grafts of cells with altered core protein expression are indicated in dark grey. Surrounding cells are either multiciliated (yellow) or non-ciliated (light grey). Multiciliated cells are normally polarised to direct fluid flow posteriorly and ventrally (bottom left of the diagram, basal bodies shown in blue). However, in wild-type cells on the anterior edge of grafts that overexpress Vang-like2 (Vangl2), or on the posterior edge of grafts that overexpress Frizzled3 (Fz3) or that have reduced Vangl2 activity, cells produce cilia with inverted polarity (basal bodies shown in red). Anterior is towards the left.

Hair-follicle organisation in the mammalian skin is conceptually similar to that of ommatidia (Fig. 8B). Rodent skin is polarised, with body hairs directed towards the tail and limb hairs pointing distally (Fig. 1F). The polarised unit is the hair follicle, which consists of cells organised into an asymmetric structure, as revealed by differences in gene expression and morphology (Devenport and Fuchs, 2008). When the follicle is properly polarised, the hair emerges from the skin at an angle. Mutations in *Celsr1*, *Vangl2* and *Fz6* disrupt this orientation and create whorls and ridges in the fur (Guo et al., 2004; Devenport and Fuchs, 2008; Ravni et al., 2009). Moreover, these three proteins are asymmetrically distributed (Fig. 8B), and this distribution depends on cell-cell interactions mediated by them. Intercellular signalling events appear to propagate this polarity across the epithelium, as wild-type hair follicles can become misaligned when surrounded by mutant cells (Wang, Y. et al., 2006a; Devenport and Fuchs, 2008). How this uniform cell-to-cell planar polarity is translated into polarity of individual follicles is unknown.

An alternative process by which multicellular structures become polarised is seen in the notum and abdomen of *Drosophila*, where multicellular bristles become aligned on the same axis as surrounding trichome-bearing cells (Gubb and García-Bellido, 1982; Adler, 1992; Theisen et al., 1994). Trichome polarisation is probably analogous to wing planar polarisation, depending upon AP asymmetric localisation of core proteins. By contrast, bristle polarisation involves a different mechanism that acts through core pathway-dependent orientation of an initial asymmetric cell division (Gho and Schweisguth, 1998; Lu et al., 1999; Bellaïche et al., 2004). Consistent with the orientation of the trichomes in surrounding cells, the bristle cluster founder cell (the SOP) exhibits localisation of Fz posteriorly and Stbm anteriorly (Bellaïche et al., 2004), leading to the asymmetric distribution of factors that orient the spindle and specify different daughter cell fates (for a review, see Segalen and Bellaïche, 2009) (Fig. 8D).

Planar polarity-mediated changes in tissue shape

Planar polarity processes also shape three-dimensional tissues that do not exhibit obvious signs of planar polarity. In these cases, the orientation of cells reveals transient planar polarisation, as they move in a specific direction or divide with a specific orientation. When cell polarity is not coordinated along a specific axis, severe morphogenetic defects can arise, including failure of neural tube closure and polycystic kidney disease.

An important example of such a mechanism is convergent extension, during which cells within a tissue intercalate with each other to narrow and extend the tissue. For example, during neurulation of vertebrate embryos, cells in the neural plate migrate towards the midline and mediolaterally intercalate (Fig. 8C), permitting the neural plate to curl up and form the neural tube. When convergent extension fails, the neural plate remains short and broad, preventing the edges from meeting and closing. Convergent extension is also crucial for elongation of the body axis during gastrulation and of the cochlea during inner ear morphogenesis (for reviews, see Keller et al., 2000; Wallingford et al., 2002; Rida and Chen, 2009).

Convergent extension offers a prime example of a true planar polarity process that was revealed due to its dependence on planar polarity gene function. The manipulation of multiple core protein orthologues has resulted in the failure of body axis extension during gastrulation in both zebrafish and frogs (Heisenberg et al., 2000; Tada and Smith, 2000; Wallingford et al., 2000; Goto and Keller, 2002; Jessen et al., 2002; Park and Moon, 2002; Takeuchi et al., 2003; Veeman et al., 2003b). Mutation of these genes in mice results in craniorachischisis, where the neural tube remains open from hindbrain to tail (Kibar et al., 2001; Murdoch et al., 2001; Curtin et al., 2003; Wang, J. et al., 2006; Wang, Y. et al., 2006b).

Although there is ample evidence that planar polarity proteins are required for convergent extension, their effects at the cellular level remain unclear due to the wide variety of cell behaviours that contribute to this process. Imaging studies during zebrafish and frog gastrulation have revealed that core protein function is required for cells to elongate, align, directionally migrate and intercalate on the mediolateral and radial axes (Wallingford et al., 2000; Goto and Keller, 2002; Jessen et al., 2002; Veeman et al., 2003b; Goto et al., 2005; Ybot-Gonzalez et al., 2007; Yin et al., 2008). Importantly, these cell morphology changes probably involve direct cell-cell interactions, as transplantation experiments in zebrafish have shown that loss of core protein activity can non-autonomously affect neighbouring wild-type cells (Jessen et al., 2002; Veeman et al., 2003b).

Although intercalating cells behave as if they are planar polarised on the mediolateral axis, there are few reports that this polarity is accompanied by asymmetric distribution of planar polarity proteins. The use of fluorescently tagged proteins in some studies in zebrafish and frogs has failed to reveal such asymmetry (Wallingford et al., 2000; Carreira-Barbosa et al., 2003; Veeman et al., 2003b), possibly owing to non-physiological expression levels, whereas other studies have shown clear asymmetric localization of Pk and Dsh that is dependent on core pathway function (Ciruna et al., 2006; Yin et al., 2008) (Fig. 8C). However, during mouse neurulation, no asymmetry has been observed, even using a Dvl2-EGFP

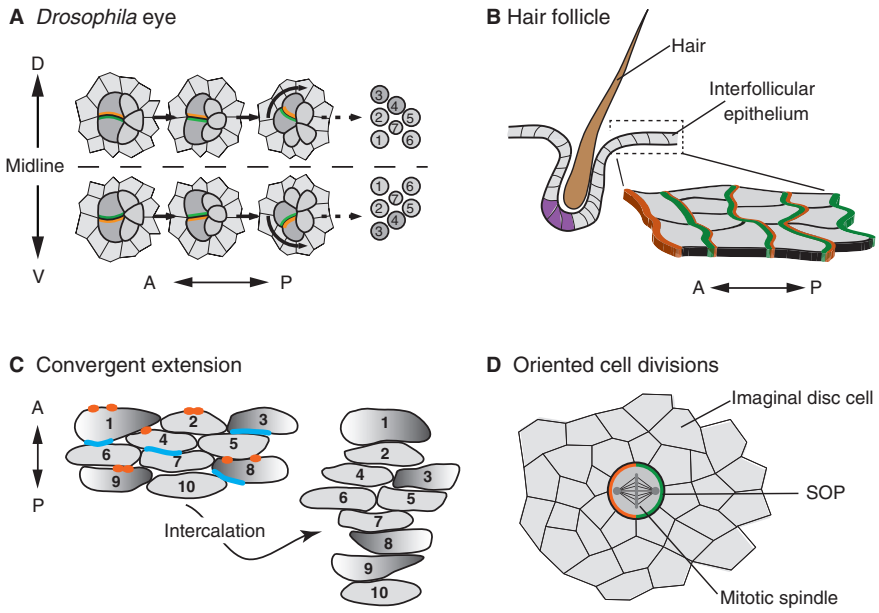

Fig. 8. Planar polarity organisation in multicellular structures and during morphogenesis. Planar polar organisation is also evident in multicellular structures, such as in (A) *Drosophila* ommatidia and (B) mammalian hair follicles. (**A**) In the developing fly eye, planar polarisation of core proteins (green and orange) determines which cells will be R3 and R4 photoreceptors (dark grey) and the direction of ommatidium rotation [which at this stage consists of the R3 and R4 photoreceptors, plus R7, R2 and R5 (light grey)]. (Right) The final adult orientation of R1-R7. (**B**) In mammalian skin, hair follicles comprise multiple cell types that differ in gene expression (purple) and morphology along the anteroposterior (AP) axis. Core proteins (green and orange) are asymmetrically localised across the epithelium, including in the interfollicular cells (as shown in the magnified view). Planar polarity also directs cell movements and oriented cell divisions that sculpt tissues during morphogenesis, as seen during (C) convergent extension in vertebrates and (D) sensory organ precursor (SOPs, dark grey) division in fly imaginal discs. (**C**) During convergent extension, cells extend along the mediolateral axis (illustrated by graded shading of a subset of cells) and intercalate with each other, causing elongation along the AP axis. Each cell is numbered before and after intercalation to highlight the changing cell-cell interactions. Dvl (Dishevelled) proteins (blue) are localised posteriorly, and Pk (Prickle; orange) anteriorly, although in some contexts, asymmetric localisation has been difficult to detect. (**D**) Asymmetric localisation of core proteins (green and orange) in SOPs determines the orientation of the mitotic spindle and hence cell division.

transgene that reveals Dvl2 asymmetry in the cochlea (Wang et al., 2005; Wang, J. et al., 2006). One explanation may be that convergent extension differs from other polarisation processes because the relevant cells are actively moving and shifting their cell-cell contacts. Thus, it may be difficult to capture transient asymmetric localisation of proteins. In support of this, Dsh protein localisation is variable in zebrafish mesodermal cells undergoing various cell shape changes (Yin et al., 2008).

Another important mechanism for altering tissue shape in a polarised manner is oriented cell division (for a review, see Lecuit and Le Goff, 2007). As already noted, in *Drosophila* the core proteins regulate bristle polarity by orienting an asymmetric division of the SOP cell (Fig. 8D). However, the oriented cell divisions that underlie changes in tissue shape are not mediated by core proteins in *Drosophila* (Baena-López et al., 2005). Instead, loss of either Ft or Ds results in truncated adult limbs, apparently owing to a failure to polarise Dachs distribution within the cell (Mao et al., 2011b), which causes a loss of oriented divisions in the growing tissue (Baena-López et al., 2005).

Vertebrate core proteins can also affect the orientation of cell divisions (Gong et al., 2004; Lake and Sokol, 2009; Segalen et al., 2010), and in contrast to *Drosophila*, this has been suggested to be a driving force in tissue elongation during gastrulation (Gong et al., 2004). However, recent results argue against this idea because blocking oriented cell division independently of core protein activity does not affect embryo length (Quesada-Hernández et al., 2010). In addition, a putative Ft/Ds pathway has been implicated in orienting cell divisions in the tubules of the mammalian kidney (Saburi et al., 2008), with mutations in *Fat4* causing misoriented mitoses and dilated tubules. Interestingly, this is enhanced by reduction in Vangl2 dose, suggesting that in vertebrates the core and Ft/Ds systems might cooperate to orient cell divisions.

Other possible examples of planar polarity

The loss of core protein activity results in additional morphogenetic defects, possibly reflecting other requirements for planar polarity. However, it is often unclear which defects are primary and which are secondary to other planar polarity-dependent events. For example, abnormal heart looping is a read-out of earlier LR patterning abnormalities (e.g. Song et al., 2010), whereas outflow tract defects more likely reflect a direct failure in polarised cell migration (Phillips et al., 2005). In addition, a subset of core planar polarity proteins may have been co-opted to mediate polarised changes in cell morphology that do not depend on heterophilic cell-cell interactions. This might include Fz- and Celsr-dependent axon guidance, as well as neuronal migration (for a review, see Wada and Okamoto, 2009), although it is also possible that planar polarity proteins mediate axon-axon or neuron-neuron interactions that have not yet been described. These issues highlight the need for caution in labelling an event as ‘planar polarity’ simply because a known planar polarity gene is involved: many of these genes participate in multiple, independent pathways that are not all used for planar polarity per se.

Novel features of planar polarity in vertebrates

So far we have emphasised the evidence that strongly supports conservation of planar polarity processes. However, some notable differences between flies and vertebrates also exist, reflecting novel ways that vertebrates mobilise and modulate an underlying polarising mechanism.

Upstream signals

One of the least understood aspects of planar polarity is how cells align along a specific tissue axis. At the local level, direct cell-cell interactions are involved, as illustrated by the presence of non-autonomous effects in flies and vertebrates. Where flies and vertebrates may diverge is at the level of global regulation, i.e. in the long-distance cues that ensure that wing trichomes point distally or that ear hair cells point laterally. The Ft/Ds system partly serves such a function in flies, where gradients of morphogens align cells with the body axis by inducing gradients of *ds* and *fj* expression. To date, little is known about the roles of Ft and Ds vertebrate orthologues. However, the presence of planar polarity phenotypes in *Fat4* and *Dchs1* mutant mice suggests that at least some functions are conserved (Saburi et al., 2008; Mao et al., 2011a).

Aside from the Ft/Ds system, cell orientations may be determined by an as yet unidentified secreted factor (sometimes referred to as 'Factor X'), which can bias the initial distributions or activity of core proteins. Given that Wnt family ligands bind to Fz family receptors, Wnts are obvious candidates for such factors. Although experimental data do not support such a role for Wnts in *Drosophila* (Lawrence et al., 2002; Chen et al., 2008), Wnts are strongly implicated in several planar polarity processes in vertebrates, including convergent extension and hair cell orientation (Heisenberg et al., 2000; Tada and Smith, 2000; Dabdoub et al., 2003; Qian et al., 2007).

Whether or not Wnts actually serve as orienting cues is unresolved. For example, the mild hair cell orientation defects in *Wnt5a* mutant mice (Qian et al., 2007) could instead reflect an effect on the expression of Fat4, Dchs1 or Fjx1, similar to the relationship between Wg and the Ft/Ds system in flies. Moreover, many studies that support a role for Wnts in planar polarity coordination rely on overexpression assays, in which a Wnt might inappropriately stimulate a Fz receptor. Nevertheless, it is widely thought that Wnts directly orient planar polarity in vertebrates, where the increased number of cells and greater distances may necessitate additional long-range cues.

Novel pathway components

Several molecules are required for planar polarity in vertebrates but not in flies, raising the issue of whether additional vertebrate-specific mechanisms exist. The best studied example is Protein Tyrosine Kinase 7 (Ptk7), the homologue of Off-track, which mediates axon guidance but not planar polarity in flies (Winberg et al., 2001). *Ptk7* mutant mice suffer typical planar polarity defects such as craniorachischisis and misoriented hair cells (Lu et al., 2004; Yen et al., 2009; Paudyal et al., 2010). Whereas Ptk7 function remains unclear, two other proteins implicated in the activation of vertebrate planar polarity signalling – Collagen Triple Helix Repeat Containing 1 (Cthrc1) and Receptor Tyrosine Kinase-like Orphan Receptor 2 (Ror2) (Hikasa et al., 2002; Yamamoto et al., 2008) – are proposed to promote Wnt signalling through effects on Fz receptor activity (Shnitsar and Borchers, 2008; Yamamoto et al., 2008). Hence, the introduction of new planar polarity genes may reflect an expanded role for Wnt signalling in vertebrates.

Typical planar polarity phenotypes also arise in mice and zebrafish that lack Scribble (Montcouquiol et al., 2003; Murdoch et al., 2003; Wada et al., 2005). The *Drosophila scribble* gene is primarily required for apicobasal polarity (Bilder and Perrimon, 2000), possibly indicating that vertebrate cells rely more heavily on proper apicolateral localisation of the core proteins. However, in zebrafish Scribble is required for convergent extension of mesenchymal cells (Wada et al., 2005) that lack apicobasal polarity, suggesting additional functions for Scribble in planar polarity patterning.

Downstream effectors

Planar polarity signalling can lead to diverse cellular consequences, from directed migration of intracellular organelles to dynamic actin cytoskeleton changes. Hence, it is not surprising that downstream effectors vary between organisms and tissues. By analogy to the original observations in *Drosophila* (Strutt et al., 1997), the molecules most often assigned this role in vertebrates are small Rho family GTPases. Consistent with this, RhoA (Wünnenberg-Stapleton et al., 1999; Tahinci and Symes, 2003), Rac1 (Sugihara et al., 1998; Tahinci and Symes, 2003; Habas et al., 2003), Cdc42 (Djiane et al., 2000; Choi and Han, 2002), the RhoA effector Rok (Wei et al., 2001; Marlow et al., 2002; Ybot-Gonzalez et al., 2007) and the Rok target Myosin II (Skoglund et al., 2008) have all been described as being planar polarity effectors during gastrulation. Moreover, Rac1 contributes to the polarisation and morphogenesis of hair cells in the mouse inner ear (Grimsley-Myers et al., 2009), whereas Myosin II is implicated in convergent extension of the cochlea (Yamamoto et al., 2009b).

A direct connection between the core proteins and RhoA activation has been established in frogs through the identification of the formin Daam1, which binds to both Dsh and RhoA (Habas et al., 2001), leading to RhoA activation by a Daam1-interacting GEF (Tanegashima et al., 2008). However, as in *Drosophila*, it should be noted that Rho family proteins are central regulators of actin dynamics, and so the disruption of a particular planar polarity pathway-dependent process does not necessarily imply that Rho GTPases are acting directly as planar polarity effectors. Interestingly, although there is a Daam1 homologue in flies, it does not play a role in planar polarity (Matusek et al., 2006). These caveats should be considered before concluding that a morphogenetic process is controlled by 'planar polarity' or 'Wnt/PCP' signalling based on the involvement of Wnt/Frizzled, RhoA, Rac1 or Daam1 activity.

There is also no clear picture regarding the functions of the vertebrate homologues of the *Drosophila* effectors In, Fy and Frtz (see Table 1). Loss of their activity in frog and in mouse has only mild effects on gastrulation, but disrupts ciliogenesis, additionally causing defects in Hh signalling due to cilia loss (Park et al., 2006; Gray et al., 2009; Heydeck et al., 2009; Kim et al., 2010; Zeng et al., 2010). Furthermore, during frog gastrulation, Frtz loss affects the ability of cells to elongate but not their polarity (Kim et al., 2010). Interestingly, in some contexts proper ciliogenesis may be required for the morphogenetic response to the core proteins (see below). If so, the weak gastrulation defects seen upon loss of activity of In, Fy and Frtz homologues may be an indirect effect of their requirement for cilia formation. Thus, just as it has been difficult to dissociate the contributions of Wnt pathway components to polarity versus non-polarity events, defining the specific contributions even of conserved effectors is complicated by their activities in multiple pathways.

Cilia: upstream or downstream?

One of the key differences in planar polarity signalling between flies and vertebrates is the unique involvement of cilia: in contrast to fly cells, primary cilia are present on most vertebrate cells, where they serve several functions (for reviews, see Gerdes et al., 2009; Goetz and Anderson, 2010). The realisation that cilia participate in planar polarity-dependent morphogenesis came from studies of the Bardet Biedl Syndrome (BBS) proteins, which are required for cilia formation due to their roles in intraflagellar transport (for a review, see Blacque and Leroux, 2006). Mice and zebrafish that lack BBS gene activity have both ciliogenesis defects and mild planar polarity defects, which are enhanced by loss of core protein activity (Ross et al., 2005; Gerdes et al., 2007; May-Simera et al., 2010).

Although the link between cilia and planar polarity is indisputable, the nature of this relationship is still unclear (for reviews, see Fischer and Pontoglio, 2009; Wallingford, 2010). In some contexts, cilia may serve as downstream effectors of planar polarity, as two mutations that cause cilia loss [intraflagellar transport protein 88 (*Ift88*) and *Kif3a*] cause polarity defects in the mouse ear and brain without affecting core protein distribution (Jones et al., 2008; Guirao et al., 2010). This mimics the loss of *Drosophila* effector proteins, and connects to the roles of vertebrate In, Fy and Frtz in ciliogenesis. However, such a role may be tissue or organism specific as *Ift88* mutant zebrafish that lack cilia show normal convergent extension (Huang and Schier, 2009), as do mice that lack cilia (for a review, see Eggenschwiler and Anderson, 2007). One alternative interpretation is that cilia participate in an as yet unidentified parallel polarising pathway. Cilia have also been implicated in upstream signalling mechanisms, because their mechanical deflection in a specific direction can refine the alignment of cells in the frog skin and mouse ependyma (Mitchell et al., 2007; Guirao et al., 2010). Again, this is unlikely to be a universal role, given the normal polarisation of cells in the inner ear and node when cilia are absent or immotile (Nonaka et al., 2005; Jones et al., 2008). How planar polarity proteins function in the cilia is also a puzzle, with conflicting reports regarding which proteins are present in basal bodies and whether they are required for ciliogenesis (Ross et al., 2005; Park et al., 2008; Borovina et al., 2010; May-Simera et al., 2010; Song et al., 2010; Tissir et al., 2010), in addition to their well-documented functions in cilia orientation, asymmetric positioning of the cilium and the alignment of ciliated cells (Mitchell et al., 2009; Antic et al., 2010; Borovina et al., 2010; Hirota et al., 2010; Hashimoto et al., 2010; Song et al., 2010). More work is needed to determine whether a single conserved planar polarity pathway mediates all of these effects or whether a subset of polarity proteins promote cilia formation independent of their more traditional roles in planar polarity.

Conclusion

Planar polarity is a fundamental property of cells in many – if not most – tissues, and is absolutely required for proper morphogenesis of structures ranging in size from tiny hairs to whole organisms. Consequently, understanding the underlying mechanisms of planar polarity establishment is of intense interest. However, a lack of clarity in the field about what constitutes a planar polarity-dependent process presents a barrier to progress. With regard to this, we have put forward a practical definition of planar polarity as referring to processes in which heterophilic cell-cell interactions lead to mutually coordinated planar polarisation, which fits well with the known molecular mechanisms.

One of the best understood manifestations of planar polarity is when cells in a sheet adopt coordinated polarities, which provides the basis for almost all the morphogenetic processes reviewed here. A major challenge is to elucidate planar polarity processes that occur outside cell sheets, and which perhaps occur only transiently and only between a few cells – for example, during the exquisitely complex wiring of the mammalian nervous system. Other important issues include understanding the relationship between the core and Ft/Ds systems, and the roles of Ft/Ds-related proteins in vertebrates, a largely unexplored issue that is further complicated by the multiple functions of the Ft/Ds system in flies.

The remarkable conservation of the basic mechanisms that establish planar polarity tends to obscure the dearth of knowledge regarding how these pathways are deployed in a range of contexts. In both flies and vertebrates there is only a limited knowledge of the upstream patterning cues, which makes it difficult to identify conserved principles. Similarly, it will be important to identify bona fide downstream effectors and understand how they permit a vast array of morphological outcomes. As we have seen for cilia, which seem to act both up- and downstream of planar polarity proteins, many features of planar polarity specification are highly context specific, with upstream signals and downstream effectors varying from tissue to tissue. Although *Drosophila* is likely to continue to be a powerful organism for investigating the molecular activities of the core and Ft/Ds systems, most of the questions relating to upstream signals and effectors will be vertebrate specific. As such genes are likely to participate in many different developmental events, their discovery will require a major research endeavour. Based on our experience to date, such efforts will probably lead us to new and surprising examples of how planar polarisation influences animal development.

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Competing interests statement

The authors declare no competing financial interests.

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