Pointing in the right direction: new developments in the field of planar cell polarity

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Abstract | Planar cell polarity (PCP) is observed in an array of developmental processes that involve collective cell movement and tissue organization, and its disruption can lead to severe developmental defects. Recent studies in flies and vertebrates have identified new functions for PCP as well as new signalling components, and have proposed new mechanistic models. However, despite this progress, the search to simplify principles of understanding continues and important mechanistic uncertainties still pose formidable challenges.

Sheets of cells often acquire a polarity that orients cells along an axis within the plane of the sheet, orthogonal to the apical–basal axis. Planar cell polarity (PCP) was originally described in epithelial cells but is also seen in non-epithelial cell sheets. Disruption of PCP can lead to developmental defects, including deafness, neural tube and heart defects, and polycystic kidney disease[1,2].

Much of our understanding of PCP comes from studies in flies, in which powerful approaches have provided important mechanistic insights. In epithelia across species, mechanistic features seem to be conserved; however, in non-epithelial cells, although the same genes are involved, conservation of mechanisms is less clear[2]. Adding to the complexity of vertebrate PCP signalling is an intimate link with cilia that cannot exist in flies[3].

Here, we review some of the recent progress in the field of PCP. We discuss new models for how polarity of *Drosophila* PCP components is established in relation to the tissue axis. We also describe newly identified roles for PCP in vertebrate developmental processes, including the collective cell movement phenomena of epidermal wound repair, the orientation of motile cilia and the breaking of left–right symmetry by polarized subcellular localization of cilia.

The fundamental machinery of PCP

Genetic and molecular analyses in *Drosophila* wing, eye and abdomen have provided a framework for understanding PCP. These studies have suggested a signalling mechanism that consists of several distinct sets, or modules, of proteins[4] (FIG. 1).

> “Although studies in *Drosophila* have continued to improve our understanding of the fundamental PCP machinery, recent studies in vertebrates have uncovered potential new roles for PCP”

A core module coordinates polarity between adjacent cells and amplifies subcellular asymmetry. Through a feedback mechanism functioning at cell boundaries, these proteins develop subcellular asymmetry, accumulating in proximal subsets (Flamingo (FMI; also known as Starry night), Prickle (PK) and Van Gogh (VANG; also known as strabismus)) and distal subsets (FMI, Frizzled (FZ), Dishevelled (DSH) and Diego (DGO)) on opposite sides of cell–cell junctions (reviewed in REFS 5,6). A second module consists of Fat (FT; also known as cadherin-related tumour suppressor), Dachsous (DS) and Four-jointed (FJ). Opposing expression gradients of DS and FJ are thought to provide global directional information (reviewed in REF. 6). In response to signals from the global and core modules, distinct downstream effector modules execute tissue-specific polarization events. A classic example is the distally oriented polymerization of actin observed in hair formation during wing development[7].

It is unclear to what extent PCP relies on similar mechanisms in different tissues — for example, asymmetric localization of core proteins has not been examined in the abdomen. In addition, although the global module is needed in all tissues that have been examined so far, the graded expression of DS and FJ that is needed to provide directional information in the eye is at least partially dispensable in the wing[8,9]. This suggests the possibility of another unidentified and partially redundant source of directional information in the wing. Furthermore, the connectivity between the modules is controversial. We have proposed that the global module signals directionality to the core module, whereas others have proposed that the global and core modules each signal independently to the downstream effector modules[6,10].

Recent insights into* Drosophila *Fat and Dachsous function. Much discussion has attended the nature of signals that orient PCP with respect to the tissue axes. Two recent studies propose fundamentally different mechanisms by which this might occur.

Eaton and colleagues previously reported that polarization of PCP components can be detected very early in fly wing development, even in the larval wing discs[11]. More recently, they showed that in the early pupal period, polarity is observed in a roughly radial pattern, with prospective proximal cortical domains of cells oriented towards the centre of the wing and prospective distal cortical domains oriented towards the wing margin. However, towards the end of the polarization period, cell polarities are nearly parallel, in a proximal to distal direction[12] (FIG. 2). In the intervening period, exogenously applied tension — driven by wing hinge contraction — leads to cell elongation, oriented cell divisions, coordinated changes in spatial

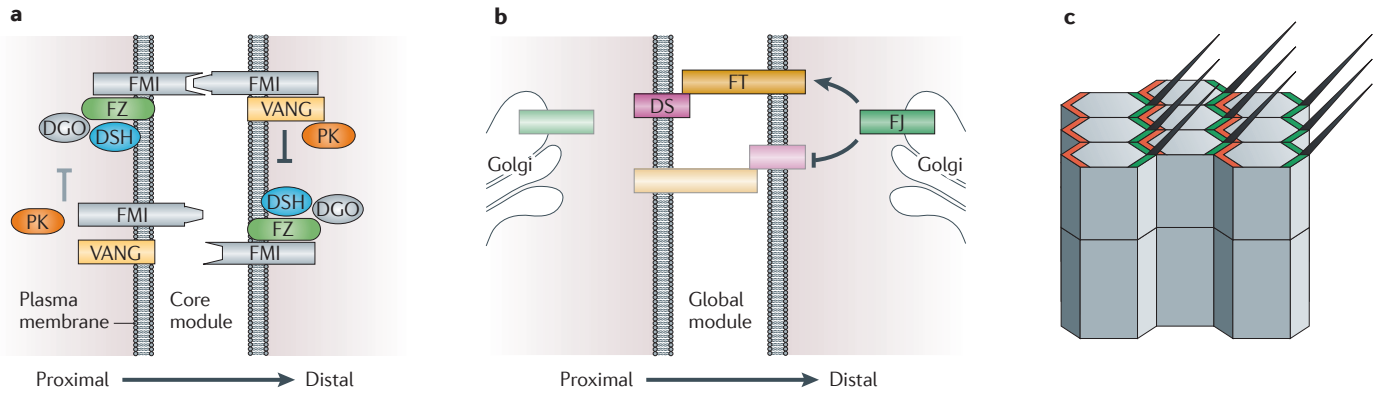

Figure 1 | **A model of the PCP signalling mechanism based on work in *Drosophila*.** The PCP signalling mechanism is proposed to consist of three functional modules: a core module, a global directional cue and one of many tissue-specific effector modules that respond to the upstream modules to produce morphological asymmetry in individual tissues. **a** | The core module acts to amplify asymmetry and to coordinate polarization between neighbouring cells, producing a local alignment of polarity (reviewed in REFS 5,6). Proteins in the core signalling module — including the serpentine receptor Frizzled (FZ), the multidomain protein Dishevelled (DSH), the ankyrin repeat protein Diego (DGO), the four-pass transmembrane protein Van Gogh (VANG; also known as strabismus), the LIM domain protein Prickle (PK) and the seven-transmembrane atypical cadherin Flamingo (FMI; also known as Starry night) — adopt asymmetric subcellular localizations that predict and have been proposed to (and in the case of wing, shown to) determine the eventual morphological asymmetry by orienting downstream effectors. These proteins communicate at cell boundaries, recruiting one group to the distal side of cells and the other to the proximal side, through a feedback mechanism that probably involves mutual antagonism of oppositely oriented complexes, thereby aligning the polarity of adjacent cells. **b** | The global module serves to convert tissue-level expression gradients to subcellular gradients of Fat (FT; also known as cadherin-related tumor suppressor)–Dachsous (DS) heterodimer expression[19–21,62]. It consists of the atypical cadherins FT and DS , which form heterodimers that may orient in either of two directions at any cell–cell boundary, and the golgi-resident protein Four-jointed (FJ). FJ acts on both FT and DS as an ectokinase[63], to make FT a stronger ligand and DS a weaker ligand, for each other[64,65]. Thus, the graded expression of FJ and DS results in a larger fraction of FT–DS heterodimers in one orientation relative to the other. **c** | Asymmetric core protein localization, with proximal proteins (shown in red) and distal proteins (shown in green) on opposite sides of cells. Localization of proteins corresponds to morphological polarity; in this example, polarized hair growth is shown.

relationships between neighbouring cells and anisotropic cell junction remodelling that, together, seem to reorient polarity. Inferred patterns of mechanical stress suggest that hinge contraction drives these movements. Indeed, severing the wing from the hinge alters the cell flows and the reorganization of polarity, strongly suggesting that the cell flows cause the changes in polarity. These events can be approximated by a computational model relating mechanical stress to polarity[12].

If bulk cell movement and rearrangement can reorganize polarity, might the 'global' polarity regulators FT, DS and FJ orient polarization through such a mechanism? In support of this possibility, perturbing DS, either by loss or gain of function, alters both the patterns of cell neighbour exchange and polarity[12]. Implying that this may be the sole mechanism by which the 'global' regulators affect PCP, the authors of this study also suggest that the early, radial pattern of polarity might arise by spontaneous alignment of local polarity, a property predicted by several mathematical models of polarity, including their own[12–16].

The idea that FT, DS and FJ might influence polarity by strictly mechanical means is a dramatic departure from alternative models. One previously proposed model suggests that opposing gradients of DS and FJ act through FT to orient microtubules with a distal plus-end bias that traffic FZ-containing vesicles towards the distal cell cortex, providing the necessary input bias to allow the core module to polarize in a specified direction[6,17]. Furthermore, these components orient polarity in the eye, abdomen and larval body wall[18–20], where no morphogenetic event similar to wing hinge contraction is known to occur. An alternative to Eaton's proposal is that FT, DS and FJ simultaneously modify both mechanical properties and polarization, but by different mechanisms. In line with this possibility, the expression of DS changes over time during pupal wing development, in patterns that are consistent with opposing gradients of FJ and DS directing both the early radial and late parallel patterns of polarity[8,21,22] (FIG. 2).

Another recent paper provides additional evidence for this gradient-based model. Harumoto and colleagues mapped the orientation of the apical microtubule network in the wing at several locations[23] and found reorganization of microtubules consistent with the reorganization of polarity observed by Eaton's group. Not surprisingly, in a *ds*-mutant wing, microtubule reorganization did not occur correctly. More dramatically, ectopic reversal of the *ds* gradient in the distal portion of the wing reversed hair polarity and that of the microtubule cytoskeleton. Wing morphology was not substantially altered, and it is hard to imagine how the observed effects might occur through alteration of mechanical properties. However, neither study provides definitive proof for the respective models. More detailed mechanistic descriptions of how this module either alters mechanical properties or biases core module function, will allow their selective disruption, enabling assessment of their relative contributions to polarization. Furthermore, it is important to keep in mind that neither model is likely to tell the whole story, as the gradients of DS and FJ are partially dispensable in the wing[8,9].

Although studies in *Drosophila* have continued to improve our understanding of the fundamental PCP machinery, recent studies in vertebrates have uncovered potential new roles for PCP, as discussed below.

Collective cell movement

In addition to polarizing cells within epithelia, vertebrate homologues of fly PCP genes are implicated in the control

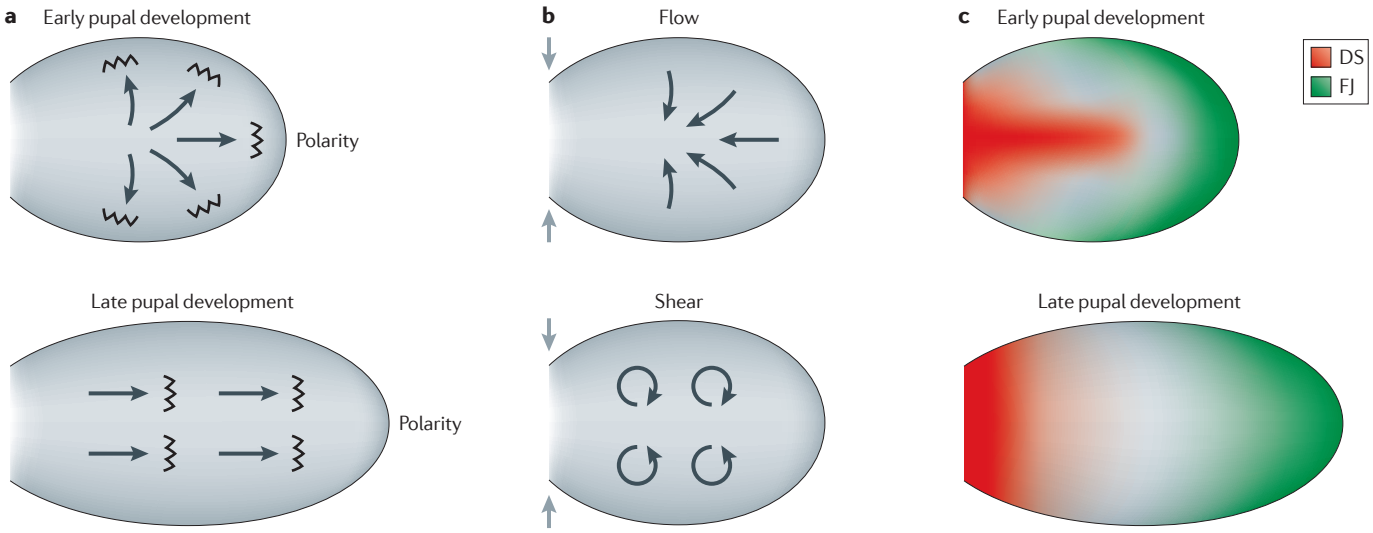

Figure 2 | **Reorganization of PCP in the pupal fly wing. a** | Polarity, as detected by the asymmetric orientation of PCP proteins, is in a radial pattern during early pupal stages (top panel) but reorganizes to a more parallel, proximal–distal pattern later in development[12] (bottom panel). Polarized PCP proteins that localize to the proximal–distal cell boundaries are shown by zigzags, and the direction of cell polarity from proximal to distal is shown by arrows. **b** | Tension (shown by light grey arrows), resulting from contraction of the wing hinge, causes cell flows (top panel; shown by dark grey arrows), cell elongation and junctional rearrangements (not shown). The resulting shear (bottom panel; shown by dark grey arrows) is proposed to cause reorientation of PCP domains. **c** | The relationship between Dachsous (DS; shown in red) and Four-jointed (FJ; shown in green) expression domains changes during pupal development[8,21,22]. The corresponding gradients might also be responsible for the difference in orientation of PCP from early (parts **a** and **c**, top panels) to later (parts **a** and **c**, bottom panels) pupal stages.

of a range of collective cell movements, including convergent extension — a process whereby cells intercalate between each other to drive tissue elongation along a particular axis. Originally observed during gastrulation and neurulation[24–26], indirect evidence suggests that convergent extension is required in various other vertebrate tissues, including the cochlea[27]. Although there is extensive genetic evidence that a conserved group of PCP genes control these events, it is unclear to what extent their mechanism of action is conserved, using asymmetric subcellular localization as an indicator of similar mechanism. In the organ of Corti, convergent extension is accompanied by a hallmark pattern of asymmetric subcellular localization[27]. During gastrulation, several examples of asymmetric subcellular localization have been reported, although these are different in character from the hallmark pattern observed in flies[28,29]. In other cases, no asymmetric subcellular localization has been reported, leaving open the possibility of differing mechanisms[2]. Additional characterization of PCP homologues in vertebrates has led to the identification of numerous other developmental processes involving planar polarized cell behaviours[1,2], including other examples of collective cell movement that are discussed below.

Epidermal wound repair and Grainyhead transcription factors. The integument is one of the more visually evident examples of PCP, as animal hairs, feathers and scales are oriented with respect to the body or limb axes. Orientation of mammalian hairs has been shown to depend on the PCP pathway[30,31], and indeed, the entire basal layer of the mouse epidermis shows molecular PCP, as evidenced by asymmetric subcellular localization of PCP proteins[31].

When the skin is wounded, keratinocytes undergo coordinated cell movement by crawling from the wound edge to close the gap[32]. Several lines of evidence suggest a role for PCP signalling in vertebrate wound healing. Caddy and colleagues recently showed that effective wound healing in the mouse depends on cadherin EGF LAG seven-pass G-type receptor 1 (CELSR1) and Scribble (SCRIB; also known as LAP4) — homologues of the fly PCP proteins FMI and SCRIB, respectively — and the vertebrate PCP component tyrosine-protein kinase-like 7 (PTK7)[33,34]. Additional links come from studies of grainyhead-like protein 3 homologue (GRHL3), a transcription factor associated with epithelial integrity in mice, the *Drosophila* homologue of which — grainyhead (GRH) — is involved in wound healing in flies[35,36]. Compound heterozygotes of vang-like 2 (*Vangl2*; homologue of *Drosophila* core protein VANG) and *Grhl3* implicate both of these genes in mouse wound healing[33]. Polarized migration of keratinocytes during wound healing requires regulation of the actin cytoskeleton by members of the RHO subfamily of GTPases: transforming protein RHOA and RAS-related C3 botulinum toxin substrate 1 (RAC1), as well as the RHO-associated kinase ROCK1. Although it is unclear precisely how their activity becomes polarized[37], members of the RHO GTPase family have been shown to interact with the PCP pathway[38,39]. It seems that the requirement for GRHL3 in mouse wound healing is to promote transcription of *Rhogef19* (also known as *Arhgef19*). GRHL3 directly binds to the proximal promoter region and activates transcription of *Rhogef19*, the overexpression of which is sufficient to rescue the phenotype observed in *Grlh3*-deficient keratinocytes[33].

Despite common roles as regulators of actin dynamics in wound healing, it is unclear whether murine GRHL3 and *Drosophila* GRH[35] share a common pathway. A function for fly GRH analogous to the regulation of *Rhogef19* by murine GRHL3 has not been tested. By contrast, although fly GRH was found to regulate PCP, at least partly, by controlling *fmi*

transcription[40], Caddy *et al.* found no evidence for regulation of *Celsr1, Celsr2* and *Celsr3* by GRHL3 in the mouse[33].

Vertebrate GRHL3 also functions in collective cell movement in other tissues. *Grhl3*$^{-/-}$ mouse mutants display defects in neural tube closure[41], a phenotype similar to that of many PCP pathway mutants. Again, *Grhl3* genetically interacts with the PCP pathway gene *Vangl2* during neural tube closure and in the development of hair cells in the inner ear[33]. Should GRHL3 therefore be considered a new component of the PCP pathway? Confounding such a conclusion, no evidence of wound-specific activation of *Rhogef19* has been shown in the mouse integument[33], in which GRHL3 is constitutively expressed[42]. In the neural tube and inner ear, the nature of the requirement for GRHL3 is not known. Therefore, GRHL3 might best be thought of as a constitutive regulator of a required downstream effector for at least some PCP-dependent events. However, GRH-dependent target genes are induced during *Drosophila* wound healing[35], and the conserved requirement but divergent function for GRH in mouse and fly PCP may be more than a remarkable coincidence. These interesting findings should motivate further characterization of GRHL3 in PCP signalling.

Convergent extension and septins. A recent report has revealed a requirement for the PCP effector secreted frizzled-related protein 3 (Fritz; homologous to *Drosophila* Fritz[43]) — a coiled-coil WD40 repeat protein — in convergent extension, and has identified an interaction between the PCP pathway and septins[44], a family of proteins that provide resilience to the plasma membrane and increase the overall structural integrity of the cell[45,46].

Kim *et al.* showed that in the absence of Fritz in *Xenopus*, convergent extension is perturbed. The observed disruption of convergent extension resulted not from the loss of individual cell polarity along the medial–lateral axis but from the inadequate lengthening of polarized cells. Although it is unclear how Fritz regulates cell lengthening, *fritz* morphants display dynamically undulating cell cortices and gaps between neighbouring cells[44]. These phenotypes suggested a possible role for septins in convergent extension, and indeed knockdown or inhibition of septins causes convergent extension defects and a specific failure of cell elongation. It was then found that Fritz physically interacts with, and is required for, the proper cortical localization and function of septin 2 and septin 7.

Symmetry breaking by motile cilia

PCP and ciliogenesis. Recent work has revealed an intriguing interdependence between PCP and primary cilia in vertebrates. Though general conclusions cannot yet be drawn, a requirement for primary cilia in at least some examples of PCP has been proposed. Conversely, a requirement for some Fritz-associated PCP components — including the vertebrate homologues of *Drosophila* genes *inturned* and *fuzzy* — in ciliogenesis of primary and motile cilia has also been observed[47,48] (reviewed in REF. 3).

In addition to their cortical localization, Fritz and septin 7 localize to the axoneme and base of cilia, with septin 7 appearing as a ring-like structure at the base[44]. Hu *et al.* also observed septin 2 in rings at the base of primary cilia *in vitro*, where it contributes to a diffusion barrier for the trafficking of particles into and out of the primary cilium[49]. In the absence of Fritz, the septin ring is altered in size and location but not disrupted[44]. It is unclear whether Fritz and septins have a regulatory or structural function in controlling trafficking in and out of the primary cilium, but the observation that the frog protein fuzzy is required for trafficking at least one cargo into cilia suggests that this may be a function of this group of PCP pathway effectors. In an additional parallel, VANGL2 was recently shown to genetically and physically interact with BBS8, a member of the BBSome, which is known to traffic membrane proteins to the cilium[50,51]. The possibility of shared mechanisms between convergent extension and regulation of the primary cilium is supported by the involvement of both Fritz and septins in these processes.

Orientation and migration of cilia in multiciliated cells. Along the lateral ventricles of the brain, multiciliated ependymal cells beat in a concerted fashion to propel cerebrospinal fluid (CSF) in a rostral direction. Impairment of CSF flow results in hydrocephalus. The beating orientation of each cilium correlates with the orientation of its basal foot, an appendage associated with the centrosome of each cilium. Ependymal motile cilia are randomly oriented within each cell in the first few days of postnatal life,

Glossary

Anisotropic
Having properties that depend on the direction of measurement.

Axoneme
The portion of the cilium projecting into the extracellular space. It is composed of a circular array of nine microtubule doublets plus many other proteins, and is enveloped by a specialized region of plasma membrane.

Basal foot
An appendage protruding asymmetrically from one side of the basal body (centriole) of motile cilia. The direction in which the basal foot points indicates the direction of the active stroke in the ciliary beat cycle.

BBSome
The stable complex of seven Barded–Biedl syndrome proteins involved in trafficking proteins to cilia.

Cell cortex
Region of the cytoplasm lying just interior to the plasma membrane.

Centrosome
An organelle consisting of a pair of centrioles that can nucleate cilia, and pericentriolar material that nucleates and organizes cytoplasmic and spindle microtubules.

Ciliopathies
A large group of diseases and developmental anomalies with overlapping manifestations that result from defects in cilia structure or function.

Ependymal cells
Cells of the ependyma — the epithelial lining of the ventricles of the brain.

Hydrocephalus
The inappropriate accumulation of cerebrospinal fluid in the brain ventricles.

Morphant
An organism treated with an antisense morpholino oligonucleotide resulting in a partial or total loss-of-function mutant.

Nodal cells
Cells in a transient structure at the anterior end of the primitive streak of a mammalian embryo, in which left–right asymmetry is established.

Organ of Corti
The structure in the inner ear that contains receptor cells that are sensitive to sound vibrations.

Rostral
In the direction of the top of the head.

Wing disc
A single-layered, sac-like epithelial structure in the larvae that, in holometabolous insects such as *Drosophila melanogaster*, gives rise to an adult wing after metamorphosis in the pupal stage.

but subsequently align themselves in each cell and orient to beat rostrally[52].

Reminiscent of the multiciliated cells on frog skin[53], this rostral orientation has recently been shown to depend on both PCP signalling and on fluid flow generated by the cilia themselves or from an exogenous source (FIG. 3). Loss of VANGL2, CELSR2, CELSR2 and CELSR3, or disruption of dishevelled 2 (DVL2; a homologue of *Drosophila* DSH) function results in misoriented cilia[54–56]. Loss of CELSR2 and CELSR3 interferes with the normal asymmetric localization of VANGL2 and frizzled 3, and surprisingly, also impairs ciliogenesis[56]. However, the ability of the PCP system to establish asymmetric cortical domains alone is insufficient for ciliary orientation; interfering with flow, and probably the ability of cilia to sense flow, by knocking down kinesin-like protein KIF3A (which is required for ciliogenesis), disrupts basal foot orientation but leaves the asymmetric localization of VANGL2 intact[54]. How might the PCP system contribute to orientation of cilia? VANGL2 localizes throughout the axoneme of ependymal motile cilia in addition to its asymmetric localization at the cell cortex, suggesting a possible direct role in ciliary function or orientation[54]. Experiments to dissociate a ciliary from a cortical function for VANGL2 will be very challenging, but the ability to separately test potentially distinct localized functions of PCP components within cells will be crucial for our understanding of what is mechanistically responsible for the coupling of flow and ciliary reorientation.

In addition to their directional orientation and beating, the motile cilia are found in clusters that are localized asymmetrically at the rostral end of ependymal cells[52,55]. This 'translational polarity' found in ependymal cells depends on events that occur much earlier in development. Before they differentiate into ependymal cells, neural progenitors (radial glia), which line the ventricular surface of the brain, possess a single primary cilium asymmetrically localized to the rostral side of the apical cell surface[52] (FIG. 3). Similar to the orientation of ependymal motile cilia, the rostral positioning of the basal body of a primary cilium within radial glial cells requires the cilium to be intact, although a requirement for the PCP pathway in translational polarity remains unclear[52].

Migration of single motile cilia. The planar polarized migration of cilia within radial glial cells is reminiscent of recent observations in the nodal cells of the mouse. Left–right asymmetry is acquired very early during development and involves a leftward flow of nodal fluid that is proposed to cause an asymmetric accumulation of an unknown signal on the left side of the embryo, ultimately resulting in the asymmetric expression of developmental control genes and a body plan with left–right asymmetry[57]. Most nodal cells possess a single motile cilium that beats with an intrinsic clockwise motion. Migration of cilia towards the posterior side of each cell is thought to be required to achieve leftward fluid flow[57].

Recently, several studies have shown a role for the PCP pathway in the posterior migration of motile cilia in mice, frogs and fish. In the absence of *Vangl1, Vangl1* and *Vangl2*, and in *Dvl1, Dvl2* and *Dvl3* compound mutant mice with five of six mutant alleles, the posterior migration of motile cilia within nodal cells was disrupted, resulting in impaired leftward flow and left–right patterning[50,58–60]. The same was observed in frog *vangl2* morphants[58]. In mice, VANGL1, VANGL2 and PK2 (homologue of *Drosophila* PK) were shown to localize asymmetrically at the anterior side, whereas DVL2 localizes to the posterior side of nodal cells before the posterior migration

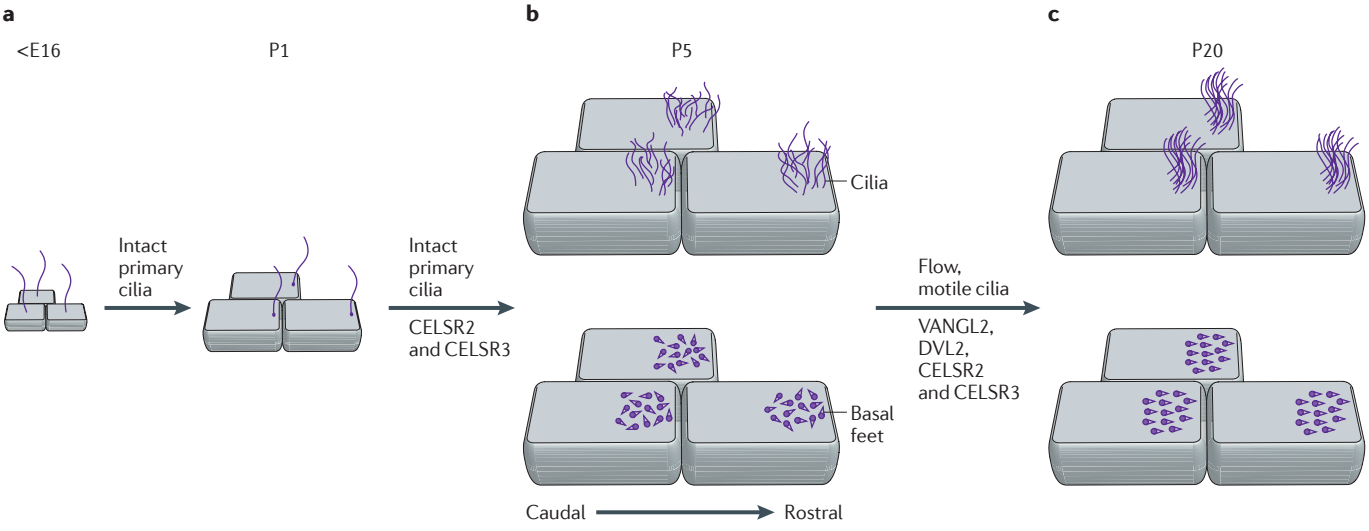

Figure 3 | **Development of ependymal PCP during mouse brain development.** In the developing cortex, progenitor cells called radial glia line the ventricular surface of the lateral ventricles, and some of these differentiate into ependymal cells. **a** | Each radial glial cell possesses a primary cilium that extends from the apical surface. From approximately embryonic day 16 (E16) until postnatal day 1 (P1), the apical surface area of radial glial cells increases and the primary cilium migrates towards the rostral end of each cell[52]. **b** | From approximately P1 to P5, radial glia begin to differentiate into ependymal cells, characterized by the continued increase in apical surface and the appearance of clusters of motile cilia[52]. Motile cilia are shown in the top panel and the basal feet of these cilia are shown in the bottom panel. The observed clusters are asymmetrically localized to the rostral side of the cell except when ciliary function is disrupted[52]. At this stage, motile cilia are not aligned in any one direction as determined by the orientation of their basal feet. In the absence of cadherin EGF LAG seven-pass G-type receptor 2 (CELSR2), or CELSR2 and CELSR3, ciliogenesis is partially disrupted, and most cilia that do form are improperly docked at the apical surface[56]. **c** | From approximately P5 until P20, the clusters of motile cilia become more densely packed (top panel), align with one another and orient in a caudal to rostral direction (bottom panel). The alignment of motile cilia is dependent on the PCP proteins vang-like protein 2 (VANGL2), segment polarity protein dishevelled homologue (DVL2), CELSR2 and CELSR3 (REFS 54–56). Additionally, the rostral flow of cerebrospinal fluid is required for their proper orientation in a process that is cilia-dependent[54].

of motile cilia[58–60]. Surprisingly, despite the seeming importance of VANG proteins in other species, only modest laterality defects were seen in *vangl2*-mutant zebrafish, but these were made much more profound with accompanying knockdown of *bbs8* (REF. 50). However, in this case, reduced numbers of shortened motile cilia were observed, and it is unclear whether asymmetric ciliary positioning is a factor in this phenotype. Thus, at least in the mouse and frog, planar polarization of nodal cells seems to direct posterior positioning of the cilium. It will be interesting to learn how the asymmetric accumulation of PCP components at the cell cortex enables the directed migration of motile cilia within nodal cells.

Concluding remarks and further questions

Despite substantial advances in our understanding of the PCP signalling mechanism, important unresolved questions remain. Advances will require mechanistic dissection of the various signalling modules, and determination of how they interact with each other. In the past several years, conservation of at least some features of the PCP pathway has been demonstrated in flies and vertebrates. However, the puzzling relationship between primary cilia and PCP signalling observed in vertebrates is absent from flies. Of additional interest will be to understand the apparent differences between epithelial and non-epithelial PCP. Future advances will therefore depend both on detailed mechanistic studies harnessing the power of *Drosophila* genetics, and on intensified characterization and mechanistic investigation of vertebrate PCP, with a particular focus on the relationship between cilia and PCP. So far, it is unclear to what extent unifying principles will emerge or to what extent we will discover that adaptations of a basic mechanism have resulted in a diversity of distinct processes that retain varying degrees of similarity to the mechanism originally characterized in flies. Because of the substantial list of developmental defects associated with PCP, as well as the recently recognized and phenotypically overlapping group of ciliopathies[61], these areas are bound to attract considerable attention.

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FURTHER INFORMATION
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