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Review

Cell division orientation and planar cell polarity pathways

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ABSTRACT

The orientation of cell division has a crucial role in early embryo body plan specification, axis determination and cell fate diversity generation, as well as in the morphogenesis of tissues and organs. In many instances, cell division orientation is regulated by the planar cell polarity (PCP) pathways: the Wnt/Frizzled non-canonical pathway or the Fat/Dachsous/Four-jointed pathway. Firstly, using asymmetric cell division in both *Drosophila* and *C. elegans*, we describe the central role of the Wnt/Frizzled pathway in the regulation of asymmetric cell division orientation, focusing on its cooperation with either the Src kinase pathway or the heterotrimeric G protein pathway. Secondly, we describe our present understanding of the mechanisms by which the planar cell polarity pathways drive tissue morphogenesis by regulating the orientation of symmetric cell division within a field of cells. Finally, we will discuss the important avenues that need to be explored in the future to better understand how planar cell polarity pathways control embryo body plan determination, cell fate specification or tissue morphogenesis by mitotic spindle orientation.

Contents

1. A framework to understand mitotic spindle orientation during development

At the turn of the 20th century, developmental biologists had already appreciated the stereotypical pattern of mitotic spindle orientation within the blastomere of the invertebrate blastula [1]. More than a 100 years later, the planar cell polarity (PCP) Wnt/Frizzled (Wnt/Fz) and Fat/Dachsous/Four-jointed (Fat/Ds/Fj) pathways have been identified as essential regulators of mitotic spindle orientation (for a review on PCP pathways see the paper by Jeff Axelrod in this issue). The PCP pathways act as extrinsic polarizing cues to orient the mitotic spindle relative to a cell–cell contact or to an embryo symmetry axis. In doing so, the PCP pathways have fundamental roles in body plan specification, in asymmetric cell division and in tissue morphogenesis. How PCP pathways control the mitotic spindle orientation has yet to be fully understood. However, the studies of two *PCP-independent* asymmetric cell divisions, the *C. elegans* first zygotic and the *Drosophila* neuroblast stem cell-like division, have established a conceptual framework to understand the mechanisms of mitotic spindle orientation.

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During both the *C. elegans* first zygotic division and the *Drosophila* neuroblast cell division, mitotic spindle orientation is dependent upon the polarized distribution of a conserved family of molecules that harbor Golocco domains: Partner of Inscuteable (Pins [2,3]) in *Drosophila* and GPR-1 or GPR-2 (hereafter referred to as GPR-1/2) in *C. elegans* (for review [4,5]). Their Golocco domains directly interact with the Gα subunit of the heterotrimeric G protein (HGP), thereby promoting the dissociation of Gαi from the Gβγ dimer [6–10]. The interaction of Pins or GPR-1/2 with Gα also promotes the interaction of Pins or GPR-1/2 with, respectively, Mud in *Drosophila* or LIN-5 in *C. elegans* [11–17]. Both LIN-5 and Mud belong to the NuMA family of molecules. They interact with the Dynein minus end microtubule motor. Thus, the asymmetric distribution of Pins or GPR-1/2 is transformed into the asymmetric activation of molecular motors. In *C. elegans*, elegant experiments of laser-mediated mitotic spindle severing show that the asymmetric position of the mitotic spindle depends on the number of active cortical "force generators" that pull on the astral microtubules [18]. Importantly, the activity of such "force generators" is dependent upon the activity of GPR-1/2, Gα, LIN-5 and Dynein [12–14]. Hence, the asymmetric activation of Dynein produces an asymmetry in the "force generators", which is sufficient to orient or position the mitotic spindle.

This molecular model provides a framework for understanding the mechanisms of mitotic spindle orientation whereby the local activation of molecular motors along the cell cortex orients the mitotic spindle by pulling on astral microtubules. Understanding the role of PCP pathways in mitotic spindle orientation can be summarized as (1) the identification of the microtubule motor(s) acting downstream of the PCP pathway and (2) the characterization of the mechanisms by which the PCP pathway triggers the asymmetric activation or localization of motor proteins within the cell. First, the *C. elegans* EMS blastomere division is reviewed to illustrate how the WNT/FZ pathway cooperates with the SRC kinase pathway to trigger a local enrichment of the Dynein motor. Second, the *Drosophila* sensory organ division is reviewed to illustrate how the cooperation between the Frizzled PCP pathway and the HGP pathway is necessary to control the orientation of the spindle along the anterior–posterior axis of the animal and within the plane of the epithelium. Finally, symmetric cell division in zebrafish, fruitfly and mouse are reviewed to illustrate the role of Wnt/Fz and Fat/Ds/Fj signalling in the regulation of tissue morphogenesis through oriented cell divisions.

2. Cooperation between the WNT/FRIZZLED and the SRC pathways orients cell division in the *C. elegans* EMS blastomere by regulating dynactin localization

The WNT/FZ signalling pathway plays several functions in numerous asymmetric cell divisions during *C. elegans* embryonic and post-embryonic development [19]. Three WNT/FZ signalling pathways have been "identified": The canonical and asymmetric WNT/FZ pathways, which both impact transcription via the POP-1 (*C. elegans* TCF/LEF-1) transcription factor and the PCP-like WNT/FZ pathway that regulates spindle orientation independently of transcription. The two first pathways have been recently reviewed ([19] see also [20]). Below, the role of the WNT/FZ non-transcriptional pathway in mitotic spindle orientation is reviewed in the EMS blastomere, where its mechanism of action is best understood.

In the four-cell *C. elegans* embryo, the EMS blastomere divides to produce the E and MS cells that generate endoderm and mesoderm cells, respectively. Blastomere recombination experiments demonstrate that the specification of the E cell depends upon the contact of the EMS cell with the adjacent P2 blastomere prior to the EMS cell division [21,22] (Fig. 1A). The P2 cell also orients the EMS spindle, which rotates to align with the contact site between the EMS and P2 blastomeres [23–25]. Both endoderm specification and mitotic spindle are controlled by the WNT/FZ signalling pathways. The two WNT/FZ transcriptional signalling pathways trigger the production of endoderm (reviewed in [19]), whereas WNT/FZ non-transcriptional signalling regulates spindle rotation in early prophase.

In wild-type embryos, the spindle of the EMS blastomere rotates to adopt an anterior–posterior (a–p) orientation in prophase (Fig. 1B). In embryos lacking the function of some WNT/FZ signalling components the spindle often fails to rotate along the a–p axis until the onset of anaphase. The WNT/FZ components involved in early spindle rotation are as follows: MOM-1, *C. elegans* Porcupine—an ER resident protein involved in WNT secretion [26,27]; MOM-2, a *C. elegans* WNT; DSH-2 and MIG-5, two *C. elegans* Dsh homologues that act redundantly; MOM-5 (*C. elegans* Fz) and GSK-3. Upon the secretion of MOM-2/WNT from the P2 blastomere and the activation of MOM-5/FZ, Dsh-2 and MIG-5 lead to the *activation* of GSK-3 which controls mitotic spindle orientation [24]. The activity of GSK-3 on the spindle also depends on KIN-19, *C. elegans* casein kinase I (CKI), which localizes on centrosomes [28]. The WNT/FZ signalling pathway that promotes correct spindle orientation in early prophase is transcription independent; spindle orientation is not affected by the blockade of either RNA polymerase II function or *pop-1* (*C. elegans* Tcf/Lef-1) or *vrm-1* (a *C. elegans* β-catenin related gene involved in WNT/FZ transcriptional response) [24]. A sizable body of evidence points toward a role for dynein in the regulation of mitotic spindle rotation downstream of the WNT/FZ pathway [29]. First, Dynactin, an activator of Dynein [30], is enriched at the EMS and P2 cortex along the EMS-P2 contact site. Second, loss of *mom-5* function reduces Dynactin accumulation. Finally the use of a *dynactin* temperature-sensitive conditional mutant demonstrates that Dynactin loss of function just prior to EMS division impairs spindle orientation.

Although the spindle is not correctly oriented in *mom* mutants in prophase, it rotates during anaphase to align with the EMS-P2 contact site. Such "rescue" of the mitotic spindle orientation in anaphase was proposed to be due to the constraints imposed by the eggshell, since the removal of the eggshell leads to a complete absence of spindle orientation in *mom-5* mutant [24]. Nevertheless, in the intact embryo, the rescue might be due to the action of the SRC-1 kinase pathway [23]. First, MES, a receptor tyrosine kinase localized between P2 and EMS is needed in both P2 and EMS cells for mitotic spindle rotation. Second, this receptor was proposed to signal through the SRC-1 kinase that is required in the EMS cell for spindle rotation. Finally, the removal of both SRC-1 and WNT/FZ activities results in a stronger phenotype suggesting that both SRC-1 and WNT/FZ signalling cooperate to orient the mitotic spindle [23]. The molecular mechanisms by which SRC-1 orients the mitotic spindle have been partially elucidated and they involve GPR-1/2, GPA-16, LIN-5 and Dynactin. SRC-1 recruits GPR-1/2 along the EMS-P2 contact site; SRC-1 does so, likely by excluding LET-99, a *C. elegans* protein harboring a DEP domain, from the EMS-P2 contact site [31]. In turn, GPR-1/2 is proposed to regulate mitotic spindle orientation with Gα and via LIN-5; loss of function of *Gpa-16*, one of the *C. elegans* Gα, or of *lin-5* prevents spindle rotation [31]. Accordingly, GPR-1/2 was shown to be important in regulating the cortical localization of Dynactin along the EMS-P2 contact site [29]. In agreement with the cooperation between WNT/FZ and SRC-1 signalling, the localization of Dynactin is reduced in either *mom-5*(*RNAi*) or *src-1*(*RNAi*) mutants and abolished in *mom-5*;*src-1* double RNAi mutant [29]. The current model therefore suggests that both WNT/FZ and SRC-1 act on mitotic spindle rotation by triggering the cortical enrichment of Dynactin along the P2-EMS contact site [29] (Fig. 1C). Importantly, *mom-5* loss of function does not affect GPR-1/2 localization, indicating that WNT/FZ regulates Dynactin localization independently of GPR-1/2 and LIN-5.

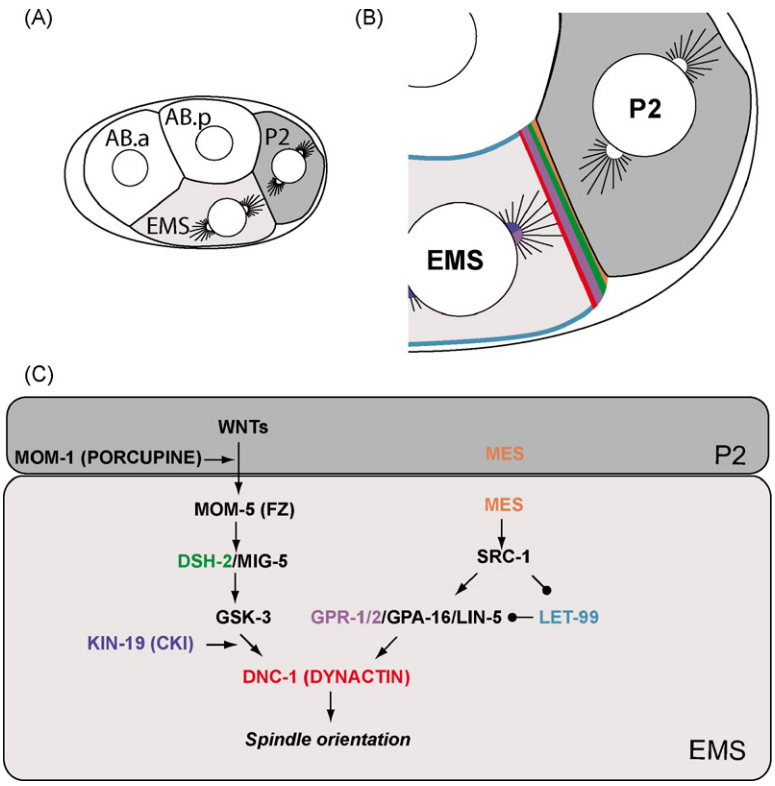

Fig. 1. The EMS cell division. (A) The four-cell stage blastomere of the *C. elegans* embryo. The spindles are only shown in the EMS and P2 blastomeres. (B) Distribution of MES (orange), DSH-2 (green), KIN-19 (blue), GPR-1/2 (purple), LET-99 (turquoise). DSH-2, MES and GPR-1/2 are likely to be present in both the EMS and P2 blastomere at the EMS-P2 contact site. (C) Regulation of the localization of Dynactin at the EMS-P2 contact site by the WNT/FZ and SRC-1 signalling pathways.

In parallel, the respective roles of the WNT/FZ and SRC-1 pathways in the EMS cell division were also studied using blastomere recombination experiments. Blastomere recombination experiments led to the proposal that the WNT/FZ non-transcriptional pathway plays an instructive role by providing a polarizing cue to orient the mitotic spindle whereas the SRC-1 pathway plays a more permissive role necessary for mitotic spindle rotation [32]. This proposal is consistent with the localization of DSH-2 at the EMS-P2 contact site and could be in agreement with the molecular data presented above if one assumes that SRC-1 recruits Dynactin to the cortex whereas the WNT/FZ signal essentially positions Dynactin along the EMS-P2 contact site. Further elucidation of the mechanism of recruitment of GPR-1/2 by SRC-1 and of positioning of Dynactin by both WNT/FZ signalling and SRC-1 will be essential to better understand how the WNT/FZ pathway orients the EMS cell division. Such mechanistic insights are crucial since the cooperation between the SRC-1 and the WNT/FZ pathway is needed for mitotic spindle orientation in other divisions such as the ABar blastomere division [28].

3. Cooperation between the Frizzled signalling pathway and heterotrimeric G protein orients division in *Drosophila* sensory cells

In the dorsal thorax (notum) of the *Drosophila* pupa, around one hundred sensory organ precursor (SOP or pI) cells each divide asymmetrically to produce a posterior cell, pIIa, and an anterior cell, pIIb, which will further divide to give rise to a mechanosensory organ [33]. During the division of the pI cell, its planar cell polarization (PCP) is evident by the anterior asymmetric localization of the cell fate determinants Numb and Neuralized as well as by the orientation of the mitotic spindle along the a–p pupal axis (Fig. 2A). The planar polarity of the pI cell was initially shown to be controlled by Frizzled (Fz) and Dsh [33]. In the *fz* or *dsh*^{1} (a missense *dsh* mutant that abrogates only its PCP activity) mutant pupa, the cell fate determinants localize asymmetrically but with a random position relative to the a–p axis; the spindle manifests a random orientation relative to the a–p axis (but remains correctly oriented relative to the cell fate determinants). Subsequently, the *flamingo*, *strabismus* (*stbm*) and *prickle* genes were shown to be required for PCP of the pI cell division [34,35]. Accordingly, the PCP proteins localize in a polarized manner at the posterior (Fz and likely Dsh) or at the anterior (Stbm and Pk) apical cortex of the pI cell prior to its division (Fig. 2B) [34].

In prophase, PCP proteins are necessary for the asymmetric localization of the Par-3/DaPKC/DmPar-6 complex and the Dlg/Pins/Gαi complex, which localize at the posterior and the anterior lateral cortex of the dividing pI cell, respectively (Fig. 2B and C) [6,36]. Pins and Gαi restrict the localization of the Par-3/DaPKC/DmPar-6 complex to the posterior cortex of the dividing pI cell. The Par-3/DaPKC/DmPar-6 complex, in turn, promotes the asymmetric localization of Numb by phosphorylating Numb, hence excluding Numb from the posterior cortex [37,38]. The asymmetric localizations established in late prophase remain unchanged until late anaphase, thereby leading to the asymmetric segregation of the cell fate determinants in the anterior pIIb daughter cell at telophase. How the PCP pathway dictates the anterior and posterior localization of the Par-3/DaPKC/DmPar-6 and Dlg/Pins/Gαi complexes remains unknown. Although mammalian Dsh has recently been shown to interact with mammalian aPKC [39], it remains to be established that this interaction is necessary to localize the Par complex at the posterior cortex of the pI cell in response to Fz signalling. Stbm interacts with the PDZ of the Dlg protein via its C-terminal PDZ binding motif. However, this motif is not necessary for the PCP of the pI cells [34].

The planar orientation along the a–p axis of the mitotic spindle depends upon cooperation between the Fz pathway and the het-

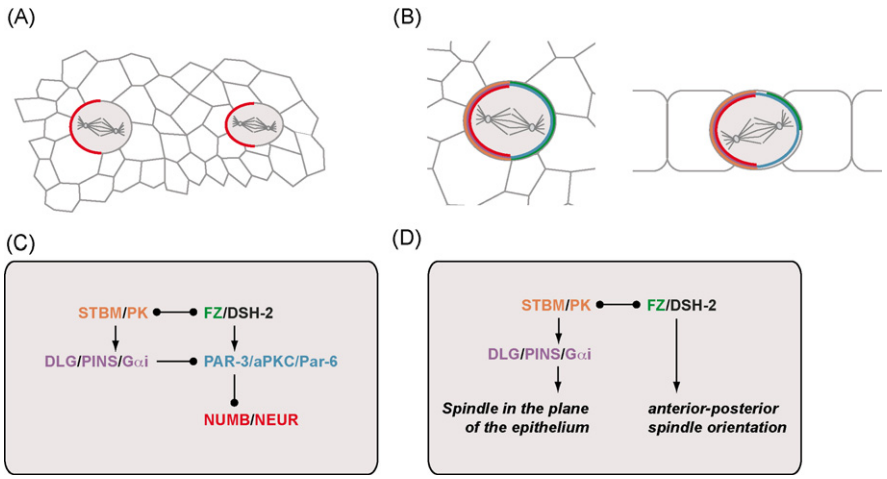

Fig. 2. The pI cell division. (A) Planar polarization of the pI cell. The Numb and the Neuralized cell fate determinants are shown in red. (B) Localization of the PCP proteins, the Par complex, the Dlg/Pins/Gαi complex during pI cell division (top view left; side view right). Note that the activity of Fz is localized more apically resulting in an apical–basal tilt of the spindle that is counterbalanced by the anterior lateral localization of Pins/Gαi. (C) Regulation of Numb asymmetric localization at the anterior pI cell cortex. (D) Regulation of the apical–basal and the a–p orientation of the mitotic spindle by both the HGP and the FZ pathways.

erotrimeric G protein (HGP) pathway [40]. In the absence of *pins*, *Gαi* or *Gγ-1*, or *Ric-8* (a putative GEF for Gαi [41,42]), the orientation of the spindle along the a–p axis is not affected. This indicates that a–p orientation of the spindle is independent of HGP signalling. While the a–p orientation is normal in "HGP mutant" animals, the spindle is strongly tilted along the *apical–basal* axis with the anterior centrosome being basally positioned. However, in absence of both HGP and PCP activity (i.e., in *fz*, *pins* double mutant), the mitotic spindle orientation becomes random relative to the a–p axis but is now within the plane of the epithelium. These data led to the proposal that PCP signalling aligns the spindle with the a–p axis but concomitantly tilts it relative to the apical–basal axis of the epithelium; the activity of the HGP counterbalances the apical–basal tilt induced by PCP signalling and therefore maintains the spindle in the plane of the epithelium (Fig. 2D). Whereas the Dlg/Pins/Gαi complex might regulate mitotic spindle planar orientation via Mud by analogy with its function downstream of Pins/Gαi in mitotic spindle orientation in neuroblasts, the mechanisms of action of the PCP pathway are unknown. The putative interaction between Dsh and aPKC is unlikely to be necessary for mitotic spindle orientation since loss of *par-3* function does not perturb mitotic spindle orientation [40]. Finally, the role of *Drosophila* GSK-3, CKI, Src and Dynactin are currently unknown during pI cell division.

4. Symmetric cell division and PCP pathways

The coordination between growth and morphogenesis of a tissue is a fundamental attribute of the development of a multicellular organism and one that underpins the homeostasis of tissue size and shape [43,44]. In the case of proliferating and growing tissues, important progress has been made in understanding how cell growth and cell division control the size, the cell number and the cell topology of animal tissues [44–49]. However less is known about how proliferating tissues acquire their shape. The observation of a stereotypical orientation of cell division along the axis of tissue elongation in multiple tissues have led to the proposal that oriented cell divisions could drive tissue elongation [50] (Fig. 3). The mechanisms controlling cell division orientation in tissue morphogenesis were first identified in Zebrafish gastrula and shown to be dependent on the Wnt/Fz PCP pathway. Later, the Fat/Ds/Fj pathway was shown to be essential in orienting cell division during tissue morphogenesis in both *Drosophila* and mouse.

4.1. Wnt/Frizzled pathway

During Zebrafish gastrulation, the epiblast, which gives rise to the neural ectoderm and the epidermis, dramatically elongates along the embryo's a–p axis. This elongation is known to be dependent upon cell–cell intercalation regulated by the Wnt/Fz PCP pathway, but the work of Gong et al. [51] (see also [52]) demonstrated that cell division orientation also plays an important role during this process. The orientation of cell division in the epiblast is biased along the a–p axis. This orientation is dependent upon the activity of Wnt-11, Dsh and Stbm but is not affected by disrupting β-catenin transcriptional activity. Importantly, the disruption of the PCP pathway affects cell division orientation and correlates with a reduction in elongation of the epiblast. Therefore, it is proposed that cell division orientation regulated by Wnt/Fz PCP promotes tissue elongation.

4.2. Fat/Dachsous/Four-jointed

The role of Fat/Ds/Fj signalling in the regulation of mitotic spindle orientation was first identified in Drosophila whose wings have an elongated shape along their proximal–distal (p–d) axis. It is well established that somatic clones in the wing are elongated along the p–d axis. The elongation of somatic clones indicates that the growth of this tissue is larger along the p–d axis. Furthermore, cell division orientation in the wing imaginal disc is also preferentially oriented along the p–d axis during wing development [53]. If one assumes that cells do not extensively rearrange during wing development this indicates that cell division orientation could be a driving force for wing elongation along the p–d axis. Strikingly, in either *fat* or *ds* mutant wings, cell division orientation is random relative to the p–d axis, somatic clones adopt a more round shape, and the elongation of the wing along the p–d axis is reduced [53]. Collectively these results indicate that cell division is oriented along the p–d axis by the Fat/Ds/Fj pathway, which thereby drives tissue elongation. The Fz PCP pathway is unlikely to play a role in cell division orientation in this tissue since it does not affect the overall wing shape.

The role of the Fat/Ds/Fj pathway in cell division orientation is conserved in vertebrates. Indeed, during mouse post-natal kidney development, somatic clone analysis reveals that somatic clones are dramatically elongated along the axis of tubule elongation. Accordingly cell division orientation is strongly biased along the direction

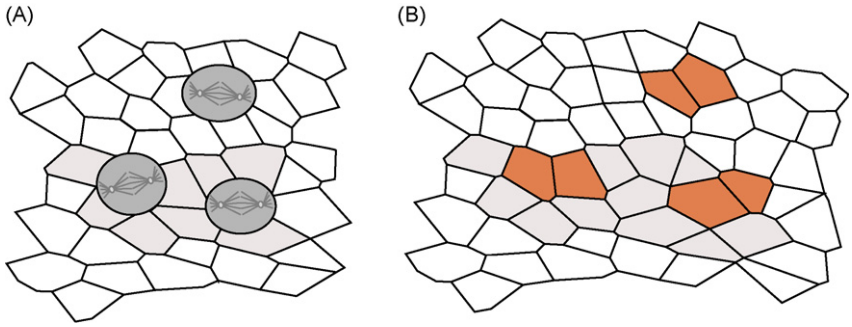

Fig. 3. Regulation of tissue morphogenesis by cell division orientation. Schematic representation of the elongation of a tissue due to the orientation of cell division. The figure illustrates the correlation between the elongated somatic clones (gray cells), the orientation of the mitotic spindle and the elongation of the tissue between two successive time points during development. Orange cells are the daughters of the dividing cells shown on the left panel.

of tubule elongation [54]. The disruption of the *Fat4* gene results in cell division misorientation and enlarged tubules [55]. This indicates that cell division orientation regulates tissue elongation as shown in the *Drosophila* wing. Strikingly, *Fat4*$^{-/-}$, *Vangl2*$^{-/+}$ tubules are even more affected [55]. The synergistic effect between the Wnt/Fz and Fat/Ds/Fj pathway might be due to an earlier function of the Wnt/Fz PCP pathway in cell division orientation. Indeed, during embryonic development, Wnt7b, secreted by the ureteric epithelium, regulates cell division orientation by activating the expression of PCP Wnts (Wnt5a, Wnt11, Wnt4) in the interstitial cells [56]. Therefore both Wnt/Fz and Fat/Ds/Fj pathways regulate cell division orientation at different stages of the development of the kidney tubule to promote its morphogenesis.

5. Current questions

5.1. Heterotrimeric G protein as a downstream effector of WNT/FZ signalling?

Fz receptors are seven transmembrane receptors and the role of HGP as a putative effector of the Fz receptors is a classic question [57]. In *Drosophila*, Gαo was shown to be necessary for both PCP and canonical Wnt/Fz signalling [58,59]. Its function in mitotic spindle orientation during pI cell division was studied by over-expression of Gαo GTP in the locked form. Such over-expression affects a–p orientation of the mitotic spindle [59]. Nevertheless, the interpretation of this result is cumbersome. While the over-expression of Gαi in the GTP locked form disrupts a–p orientation [6], Gαi loss of function has no effect on a–p mitotic spindle orientation, suggesting that over-expression of Gα in the GTP locked form is not appropriate to the rigorous study of the function of Gα in mitotic spindle orientation [40]. Accordingly, loss of Gγ-1 was observed to affect the orientation of the spindle in the apical–basal axis without significantly affecting its a–p orientation [40]. In the EMS *C. elegans* blastomere, Gα controls mitotic spindle orientation suggesting a possible role downstream of the WNT/FZ signalling pathway [31]. However, the asymmetric localization of *C. elegans* GPR-1/2 and its recruitment by SRC-1 more likely suggests that Gα is activated by GPR-1/2 independently of the WNT/FZ pathway [29].

5.2. Down to the mitotic spindle

While the function of Wnt/Fz signalling in spindle orientation is widely conserved, the exact molecular mechanisms underlying this function are unknown. The evidence in EMS cells would suggest that WNT/FZ signalling regulates Dynactin localization and therefore Dynein activity. Nevertheless, the molecular mechanism by which the Wnt/Fz pathway controls Dynactin localization remains completely unknown. Adenomatous Polyposis Coli (APC) is an additional putative candidate for the regulation of mitotic spindle orientation downstream of the WNT/FZ pathway. APC is part of the WNT canonical signalling pathway (for review [60]). It is known to regulate microtubule dynamics and has been shown to be involved in mitotic spindle orientation during the stem cell division of *Drosophila* spermatocytes [61]. The mechanisms of mitotic spindle orientation by the Fat/Ds/Fj signalling pathway in the regulation of tissue morphogenesis are even more obscure. A possible explanation for the lack of legitimate candidates is that Fat/Ds/Fj and Wnt/Fz signalling bias a pleiotropic mitotic spindle orientation mechanism, namely the one necessary for the maintenance of the spindle within the plane of the epithelium in the tissue. Therefore its genetic characterization downstream of the PCP signalling pathway is severely complicated.

5.3. Mitotic spindle orientation and morphogenesis

To date cell division orientation is the mechanism put forward to regulate tissue elongation of proliferative tissues. However, cell division misorientation induced by defects in planar cell polarity (PCP) pathways has been shown to be qualitatively associated with defects in tissue elongation in only three cases [51,53,55]. Furthermore, the function of cell division orientation has so far been studied independently of cell growth, cell–cell rearrangement and apoptosis, all of which could contribute to the shape of the tissue. In addition, the prevailing role of cell division orientation in anisotropic growth of a tissue is challenged by observations made in *Drosophila* imaginal discs. Indeed, a drastic reduction or increase of the cell division rate does not perturb tissue morphogenesis (reviewed in [62]). These results might suggest that anisotropic cell growth during the cell cycle rather than cell division is important in the regulation of tissue elongation. This emphasizes the need to quantitatively determine the contribution of the planar orientation of cell division to the elongation of the tissue to better understand the function of the PCP pathway in tissue morphogenesis.

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