REVIEW

Epithelial spindle orientation diversities and uncertainties: recent developments and lingering questions [version 1; referees: 3 approved]

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Abstract
Mitotic spindle orientation is a conserved, dynamic, and highly complex process that plays a key role in dictating the cleavage plane, fate, and positioning of cells within a tissue, therefore laying the blueprint for tissue structure and function. While the spindle-positioning pathway has been extensively studied in lower-model organisms, research over the past several years has highlighted its relevance to mammalian epithelial tissues. Although we continue to gain critical insights into the mechanisms underlying spindle positioning, many uncertainties persist. In this commentary, we will review the protein interactions that modulate spindle orientation and we will present important recent findings that underscore epithelial tissue-specific requirements and variations in this important pathway, as well as its potential relevance to cancer.

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Referee Status: ✔ ✔ ✔

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version 1
published
23 Jun 2017

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Competing interests: The authors declare that they have no competing interests.

How to cite this article: Seldin L and Macara I. Epithelial spindle orientation diversities and uncertainties: recent developments and lingering questions [version 1; referees: 3 approved] F1000Research 2017, 6(F1000 Faculty Rev):984 (doi: 10.12688/f1000research.11370.1)

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Grant information: This work was supported in part by grant CA197571 from the National Cancer Institute, National Institutes of Health, Department of Health & Human Services.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

First published: 23 Jun 2017, 6(F1000 Faculty Rev):984 (doi: 10.12688/f1000research.11370.1)
Introduction

Robust regulation of mitotic spindle positioning is required for the proper development and maintenance of many epithelial tissues among a diverse array of organisms. Spindle orientation dictates both tissue architecture (lung branching and epidermal layering) as well as cellular diversity (symmetric versus asymmetric divisions) and also is thought to function in tumor suppression\(^5\). Recent work has demonstrated the importance of spindle orientation in multiple mammalian tissues, including brain, retina, and epidermal appendages\(^6\). Nevertheless, whether this process is a universal requirement for epithelial morphogenesis remains unclear. Although the proteins that dictate spindle orientation are relatively well conserved across phyla, recent findings suggest that the requirements and mechanism of this process can vary according to tissue type. Furthermore, although several studies correlate defective spindle orientation with tumorigenesis, no work to date demonstrates a direct causal link between these processes.

A more thorough understanding of the tissue-specific signaling and regulation involved in spindle orientation could provide critical insights into developmental, stem cell, and cancer biology as well as divulge novel disease targets. In this commentary, we will discuss important recent developments in the spindle orientation field as well as highlight persisting controversies and critical unanswered questions.

Spindle orientation mechanism

Although multiple factors are known to regulate epithelial structural and functional robustness, mitotic spindle orientation is particularly important because it dictates where each daughter cell is situated within a tissue. In simple epithelia, spindles normally orient parallel to the basement membrane, causing cells to divide in the plane of the epithelial sheet. Perpendicular divisions, on the other hand, are necessary to create stratified epithelia. Nevertheless, defective spindle orientation that causes oblique or perpendicular divisions to occur inappropriately could ultimately disrupt normal epithelial organization and generate daughter cells unconstrained by contact with neighbors, resulting in hyperplasia. Importantly, there appears to be no checkpoint for spindle orientation, so defects in this process have no direct effect on the cell cycle. Although our current understanding of the spindle-positioning mechanism was initially elucidated in lower-model organisms such as the Drosophila melanogaster fruit fly, the nematode Caenorhabditis elegans, and budding yeast Saccharomyces cerevisiae as well as in mammalian cell lines, extensive recent in vivo work in mouse models has suggested that the same protein machinery is also responsible for orchestrating spindle orientation in multiple complex tissues.

Mitotic spindle positioning in most epithelia is controlled by astral microtubules (MTs) that emanate from the metaphase mitotic spindle toward the cell cortex. These MTs interact with a complex of cortical proteins at the plasma membrane, including Inscuteable (Insc), LGN (Partner of Insc/Pins in Drosophila), nuclear mitotic apparatus (NuMA, Mud in Drosophila), the G-protein subunit G\(\text{oi}\), and dynein, which together transduce pulling forces that guide the spindle into its appropriate position. LGN tethers to the cell membrane by interacting through its C-terminal GoLoco domains with G\(\text{oi}\) and simultaneously links to the spindle machinery by binding to NuMA via its N-terminal tetra-tricopeptide repeat (TPR) motifs\(^8\). In addition, LGN can interact directly with the polarity protein Discs Large (Dlg) and with the adherens junction protein E-cadherin, both of which will recruit it to the lateral cortex\(^8\). LGN competes with p120-catenin for binding to the intracellular domain of E-cadherin, which will likely decrease the stoichiometry of LGN binding. NuMA binds to dynein via its N-terminus and to both LGN and MTs via its C-terminus, and each of these interactions is required for robust spindle orientation\(^6\). Notably, the LGN- and MT-binding domains of NuMA overlap and promote mutually exclusive interactions, so it remains unclear how these proteins cooperate at the cell cortex to direct spindle positioning\(^7\) (Figure 1).

In most epithelia, LGN is excluded from the apical cortex by apically localized factors such as the polarity protein atypical protein kinase C (aPKC), which phosphorylates LGN, and SAPCD2, which competes with NuMA for binding to LGN, thus orienting spindles parallel to the epithelial plane\(^8\). In some systems, however, LGN is recruited to the apical domain through binding to InsC, which interacts with the Par3 polarity protein\(^9\). In these specific cases, such as the mammalian epidermis, however, it remains unclear whether (1) an apical signal can override lateral cues to promote perpendicular over parallel spindle orientations, (2) parallel orientation is a default in the absence of apical cues, or (3) entirely separable mechanisms drive perpendicular versus parallel orientations. Findings from recent in vivo studies of spindle orientation proteins in mice support the latter two possibilities, where depletion of LGN or NuMA compromises perpendicular orientations and favors parallel ones, whereas depletion of upstream components mInsc or Par3 results in randomization due to LGN mislocalization\(^10\). Additional investigation is required to further dissect out whether instructive or permissive lateral cues underlie this behavior (Figure 1).

Spindle orientation requires phosphoregulation

Several recent studies have revealed the importance of phosphoregulation in ensuring appropriate protein interactions and localization throughout the spindle orientation process during both metaphase and anaphase. It should be noted that other post-translational modifications have been implicated in spindle orientation, such as deubiquitination of Disheveled by CYLD; however, here we will focus on phosphorylation\(^1\). In metaphase, LGN can be phosphorylated in the linker region between the N- and C-terminal domains by Aurora A and aPKC\(^12\). The phosphorylated form of the protein then is dissociated from the apical cortex by binding 14-3-3 and specifically...
associates with the guanylate kinase-like (GUK) domain of Dlg, a polarity protein on the lateral membrane of epithelial cells. This LGN/Dlg interaction relies on removal of lethal giant larvae (Lgl) from the plasma membrane via Aurora B phosphorylation \[^{23}\] (Figure 1 and Figure 2).

Additionally, both ABL1 and Aurora A have been shown to phosphorylate the C-terminus of NuMA to promote its release from spindle poles and recruitment to the cortex in metaphase, where its interactions with the membrane-associated factor 4.1 help stabilize its residence at the cortex.\[^{24-26}\] Cdk1, conversely, phosphorylates the C-terminus of NuMA to maintain its localization to spindle poles in metaphase, which can be counterbalanced by PPP2CA phosphatase activity, while anaphase-driven Cdk1 inactivation promotes extensive NuMA and dynein cortical accumulation.\[^{25,27}\] Notably, this anaphase cortical recruitment is mediated by interactions between NuMA and membrane lipids instead of LGN or 4.1.\[^{25,28,29}\]

An additional level of regulation at the spindle pole involves phosphorylation by the pole-enriched Polo-like kinase 1 (Plk1) that can promote cortical dynein/dynactin dissociation from NuMA-LGN.\[^{30}\] However, it remains unclear whether this is due to NuMA or dynactin phosphorylation or both, since both are Plk1 targets (Figure 1 and Figure 2).

These findings raise two important questions: (1) How do these multiple kinases coordinate with one another to maintain an appropriate balance of cortical and spindle pole NuMA pools? (2) Why do NuMA cortical accumulation and stability rely on two entirely separable mechanisms in metaphase and anaphase? One possibility is that metaphase NuMA must engage with dynamic cortical partners to promote continuous fine-tuning of spindle positioning, while cortical NuMA tethering to membrane phospholipids in anaphase is essential for driving efficient chromosome segregation and cell division. Future studies addressing these questions, as well how
other post-translationally modifying enzymes (for example, CYLD deubiquitinase) may collaborate, would fill important gaps in our understanding of the spindle orientation mechanism and how to potentially manipulate this process in a therapeutic context.

Is spindle orientation a universal requirement in epithelia?

Many studies, including those most recently on the hair follicle, tongue, and prostate, have demonstrated the key importance of oriented cell divisions for the proper morphogenesis, structure, and function of mammalian epithelial tissues. Nevertheless, other findings contradict and challenge this paradigm. First, LGN knockout mice are viable. Second, embryonic mouse kidney, zebrafish neuroepithelial cells, and many Drosophila tissues can tolerate non-planar divisions and maintain tissue integrity by reintegrating displaced cells back into the epithelium. This raises the question of why spindle orientation is required in some tissues but dispensable in others.

The mechanism of spindle orientation also appears to diverge in a tissue-, cell type-, or temporal-specific context (or a combination of these). For example, recent work demonstrates that Pins/LGN is dispensable in the Drosophila imaginal wing disc epithelium because of a Pins-independent recruitment of Mud/NuMA but that Pins is required for Mud recruitment in neuroblasts and follicle epithelial cells. Furthermore, whereas aPKC promotes apical exclusion and lateral recruitment of Pins in both Madin-Darby canine kidney (MDCK) cells and Drosophila larval wing disc epithelium, Pins lateral localization is Dlg-dependent but aPKC-independent in both Drosophila follicle epithelium and chick neuroepithelium.

Other recent studies further support these mechanistic variations. Work in the retina revealed that although LGN inactivation increases progenitor number outside the ventricular zone in the developing neocortex, it has no effect on the position or number of progenitors in the retina. Furthermore, randomizing spindle orientation in embryonic radial glial cells (RGCs) by overexpressing either Insc or a dominant-negative form of LGN reduces asymmetric and increases symmetric divisions, thus reducing adult neural stem cell (aNSC) numbers. Nevertheless, Insc overexpression in either post-natal RGCs or aNSCs does not impact aNSC numbers.

An additional study in mice revealed a differential requirement and function for LGN in tongue and hair follicle morphogenesis. In most regions of the mouse tongue as well as in interfollicular epidermis, stratification is dictated by apical LGN-driven orthogonal
divisions. In the dorsal tongue, however, LGN localization varies and instead promotes planar divisions. Additionally, whereas filiform papillae rely on LGN, embryonic hair follicle development, which requires perpendicular divisions in the hair placode for proper Sox9-positive stem cell specification, is LGN-independent. Nevertheless, depletion of LGN compromises perpendicular divisions in the lower region of peg stage follicles. In addition, perpendicular divisions in the adult hair follicle matrix, which are important for driving proper differentiation programs, are NuMA-dependent. It remains unclear whether distinct proliferative populations within the adult hair follicle vary in their reliance on canonical spindle orientation regulation.

**Does inaccurate spindle orientation promote tumorigenesis?**

A key feature of epithelial cancers is the loss of tissue organization, even though individual cells might preserve epithelial characteristics. The importance of spindle orientation for tissue integrity in certain contexts has led to speculation that it plays a role in cancer suppression. There are strong correlations between spindle misorientation and tumorigenesis in Drosophila. Perturbation of spindle orientation in Drosophila neuroblasts causes invasive tumor-like overgrowths, caused by uncontrolled self-renewal stem cell divisions. In the wing disc, epithelial cells with misaligned spindles primarily apoptosis. However, inhibition of apoptosis in these cells enables them to escape the epithelium by undergoing an epithelial-to-mesenchymal transition (EMT), which ultimately promotes the formation of tumor-like masses. Therefore, spindle misorientation in this system severely disrupts normal epithelial tissue architecture and can promote both EMT and hyperproliferation.

Although spindle misorientation has been observed in multiple mammalian cancer cell types, evidence for a causative role in tumorigenesis is at best correlative. Differential expression of components of the core spindle orientation machinery has been correlated with specific cancers. For example, although LGN and NuMA are not mutated in breast cancer, patients with luminal breast cancers expressing high levels of LGN have significantly worse survival rates than those with low LGN. Additionally, the Par3 polarity protein is essential for normal spindle orientation, and its loss promotes tumor growth and metastasis in the skin and mammary gland. Furthermore, many studies have drawn correlations between oncogenic activation (or tumor suppressor silencing), spindle orientation, and cancer, yet none has established a direct causal link. Mutations in the tumor suppressor adenomatous polyposis coli (APC), which are common in colorectal cancer, cause spindle misorientation. In addition to having a role as part of the β-catenin destruction complex in the WNT pathway, APC can bind to the plus ends of MTs through End-binding 1 (EB1), and there are several examples in C. elegans and Drosophila in which APC plays an important role in spindle orientation. Nevertheless, there is no evidence that APC-driven tumorigenesis is due to an effect on spindles rather than a constitutive activation of Wnt signaling.

Phosphatidylinositol 3-kinase (PI3-K) is an example of an oncogene that is significantly upregulated in several cancers and has been associated with spindle misorientation phenotypes. A recent study in HeLa cells revealed that integrin-mediated adhesion orients the spindle parallel to the substratum through accumulation of PtdIns(3,4,5)P3 to the mid-cortex and that the inhibition of PI3-K, which produces this phospholipid, can perturb spindle orientation in the z-direction. However, it remains unclear whether similar mechanisms operate in epithelial cells. In another study, overexpression of the tyrosine phosphatase-encoding Shp2 oncogene disrupted both epithelial integrity and spindle orientation in cultured cells.

These correlative data have incited discussion in several reviews regarding a potential link between spindle orientation and tumorigenesis. Important goals of future research will be to determine whether oncogenic activation can disrupt spindle orientation and to definitively test the role, if any, of spindle orientation defects in epithelial cancer initiation or progression.

**Conclusions**

Research over the past several years has revealed key insights into the mechanism and necessity of the conserved spindle orientation pathway across diverse mammalian epithelia. Many recent studies add further complexity to our understanding of the spindle orientation mechanism by revealing the involvement of additional factors (for example, SAPCD2, microRNAs, and peroxisomes); however, it remains unclear precisely how these components incorporate into and facilitate this process. Additional studies have revealed interesting and unexpected context-dependent variations in pathway regulation. Nevertheless, many lingering questions and controversies persist, and extensive future work is required to fill the remaining black boxes that we have highlighted throughout this review. A particularly pressing question is whether (1) spindle-positioning defects are sufficient, (2) they synergize with other processes to drive tumorigenesis, or (3) both apply, as this information could provide significant mechanistic insight into cancer initiation. This would ultimately elucidate whether spindle orientation does in fact provide an important tumor-suppressive function in adult epithelial tissues. The findings yielded from these studies could inform the development of increasingly sophisticated and targeted treatments to impede early tumorigenic events.

**Competing interests**

The authors declare that they have no competing interests.

**Grant information**

This work was supported in part by grant CA197571 from the National Cancer Institute, National Institutes of Health, Department of Health & Human Services.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
References

1. El-Hashash AH, Turcatel G, Al Alam D, et al.: Eya1 controls cell polarity, spindle orientation, cell fate and Notch signaling in distal embryonic lung epithelium. Development. 2011; 138(7): 1395–407.

2. Williams SE, Berona S, Pasoli HA, et al.: Asymmetric cell divisions promote Notch-dependent epidermal differentiation. Nature. 2011; 470(7344): 353–8.

3. Poulsen ND, Lechler T: Robust control of mitotic spindle orientation in the developing epidermis. J Cell Biol. 2010; 191(5): 915–22.

4. Falk S, Bugeno S, Ninkovic J, et al.: Time-Specific Effects of Spindle Positioning on Embryonic Progenitor Pool Composition and Adult Neural Stem Cell Seeding. Neuron. 2017; 93(4): 777–91.e3.

5. Lacomme M, Tarchini B, Boudreau-Pinsonneault C, et al.: The LGN protein promotes planar proliferative divisions in the neocortex but apico basal asymmetric terminal divisions in the retina. Development. 2016; 143(4): 757–81.

6. Selin L, Murayama A, Lechler T: NuMA-microtubule interactions are critical for spindle orientation and the morphogenesis of diverse epithelial structures. eLife. 2016; 5 pii: el2504.

7. Byrd KM, Lough KJ, Patel JH, et al.: LGN plays distinct roles in oral epithelial stratification, filiform papilla morphogenesis and hair follicle development. Development. 2016; 143(5): 2903–17.

8. di Pietro F, Chard A, Morin X: Regulation of mitotic spindle orientation: an integrated view. EMBO Rep. 2016; 17(8): 1106–30.

9. Golserich M, Biancini JM, Siemens KA, et al.: Cell division orientation is coupled to cell-cell adhesion by the E-cadherin/LGN complex. Nat Commun. 2017; 8: 13996.

10. Haren L, Merdes A: Direct binding of NuMA to tubulin is mediated by a novel sequence motif in the tail domain that bundles and stabilizes microtubules. J Cell Sci. 2002; 115(Pt 9): 1815–24.

11. Kotak S, Busso C, Gönçzy P: Cortical dynein is critical for proper spindle positioning in human cells. J Cell Biol. 2012; 199(1): 97–110.

12. Du Q, Taylor L, Compton DA, et al.: LGN blocks the ability of NuMA to bind and stabilize microtubules. A mechanism for mitotic spindle assembly regulation. Curr Biol. 2002; 12(19): 1929–33.

13. Hao Y, Du Q, Chen X, et al.: Par3 controls epithelial spindle orientation by aPKC-mediated phosphorylation of apical Pins. Curr Biol. 2010; 20(20): 1809–18.

14. Chiu CW, Monat C, Robitaille M, et al.: SAPC2D Controls Spindle Orientation and Asymmetric Divisions by Negatively Regulating the Gui-LGN-NuMA Terminator Complex. Dev Cell. 2016; 36(1): 50–62.

15. Lechler T, Fuchs E: Asymmetric cell divisions promote stratification and differentiation of mammalian skin. Nature. 2005; 437(7066): 275–80.

16. Williams SE, Ratliff LA, Postiglione MP, et al.: Par3/mnsce and Gα cooperate to promote oriented epithelial cell divisions through LGN. Nat Cell Biol. 2014; 16(8): 758–69.

17. Nguyen-Ngo T, Alshar K, Gönçzy P: Coupling of cortical dynein and G protein-coupled receptors with spindle positioning in Caenorhabditis elegans. Nat Cell Biol. 2007; 9(11): 1294–302.

18. Gompel SK, Neumuller RA, Novatchkova M, et al.: The Drosophila NuMA Homolog Mud regulates spindle orientation in asymmetric cell division. Dev Cell. 2006; 10(6): 731–42.

19. dé Nobres A, Ramyer K, Vechio JD, et al.: A complex of NuMA and cytoplasmic dynein is essential for mitotic spindle assembly. Celn. 1996; 87(3): 447–58.

20. Yang Y, Liu M, Li D, et al.: CYLD regulates spindle orientation by stabilizing astral microtubules and promoting disheveled-NuMA-dynein/dynactin complex formation. Proc Natl Acad Sci U S A. 2014; 111(6): 2158–63.

21. Bell GP, Fletcher GC, Brain R, et al.: Aurora kinases phosphorylate Lgl to induce mitotic spindle orientation in Drosophila melanogaster. Curr Biol. 2015; 25(1): 61–8.

22. Gollini S, Carminati M, De Mattia F, et al.: NuMA Phosphorylation by Aurora A Orchestrates Spindle Orientation. Curr Biol. 2016; 26(4): 458–69.

23. Seidin L, Poulsen ND, Foote HP, et al.: NuMA localization, stability, and function in spindle orientation involve 4.1 and Cdk1 interactions. Mol Biol Cell. 2013; 24(23): 3651–62.

24. Matsumura S, Haramaki M, Yamamoto T, et al.: ABL1 regulates spindle orientation in adherent cells and mammalian skin. Nat Commun. 2012; 3: 626.

25. Takot S, Busso C, Gönçzy P: NuMA phosphorylation by cdk1 couples mitotic progression with cortical dynein function. EMBO J. 2013; 32(18): 2517–29.

26. Zheng Z, Wan Q, Meikong G, et al.: Cell cycle-regulated membrane binding of NuMA contributes to efficient anaphase chromosome separation. Mol Biol Cell. 2014; 25(6): 606–19.

27. Takot S, Busso C, Gönçzy P: NuMA interacts with phosphoinositides and links the mitotic spindle with the plasma membrane. EMBO J. 2014; 33(16): 1815–30.

28. Kiyomitsu T, Cheeseman I: Chromosome- and spindle-pole-derived signals generate an intrinsic code for spindle position and orientation. Nat Cell Biol. 2012; 14(3): 311–7.

29. Fraser D, Shioi G, Shitamukai A, et al.: Neuroepithelial progenitors undergo LGN-dependent planar divisions to maintain self-renewability during mammalian neurogenesis. Nat Cell Biol. 2008; 10(1): 93–101.

30. Tarchini B, Jolicoeur C, Cayouette M: A molecular blueprint at the apical surface establishes planar asymmetry in cochlear hair cells. Dev Cell. 2013; 27(1): 89–102.

31. Packard A, Georgas K, Michos O, et al.: Luminal mitosis drives epithelial cell dispersal within the branching ureteric bud. Dev Cell. 2013; 27(3): 319–30.

32. Cünna B, Jenny A, Lee D, et al.: Planar cell polarity signalling couples cell division and morphogenesis during neurotubulation. Nature. 2006; 439(7073): 229–4.

33. Bergstrahl DT, Lovegrove HE, St Johnston D: Lateral adhesion drives reintegration of misplaced cells into epithelial monolayers. Nat Cell Biol. 2015; 17(11): 1497–503.

34. Bergstrahl DT, Lovegrove HE, Kuwaiki I, et al.: Pins is not required for spindle orientation in the Drosophila wing disc. Development. 2016; 143(14): 2573–81.

35. Peyre E, Jaouen F, Saadoua M, et al.: A lateral belt of cortical LGN and NuMA guides mitotic spindle movements and planar division in neuroepithelial cells. J Cell Biol. 2011; 193(1): 141–54.

36. Saadoua M, Machcoane M, di Pietro F, et al.: Dvl1 controls planar spindle orientation via Gα signaling in the neuroepithelium through direct interaction with LGN. J Cell Biol. 2014; 200(6): 707–17.

37. Gulli LG, Prunicio P, Ferreira T, et al.: Drosophila aPKC is required for mitotic spindle orientation during symmetric division of epithelial cells. Development. 2012; 139(3): 503–13.
Par3 for Epidermal Homeostasis through Regulation of Barrier Function, Keratinocyte Differentiation, and Stem Cell Maintenance. J Invest Dermatol. 2016; 136(12): 2406–16. PubMed Abstract | Publisher Full Text | F1000 Recommendation

51. Cabello J, Neusumm LJ, Guenrodogan U, et al.: The Wnt pathway controls cell death engulfment, spindle orientation, and migration through CED-10/Rac. PLoS Biol. 2010; 8(2): e1000297. PubMed Abstract | Publisher Full Text | Free Full Text

52. Yamashita YM, Jones DL, Fuller MT: Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome. Science. 2003; 301(5639): 1547–50. PubMed Abstract | Publisher Full Text | F1000 Recommendation

53. Lu B, Roegers F, Jan LY, et al.: Adherens junctions inhibit asymmetric division in the Drosophila epithelium. Nature. 2001; 408(6819): 522–5. PubMed Abstract | Publisher Full Text

54. Kang S, Bader AG, Vogt PK: Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proc Natl Acad Sci U S A. 2005; 102(3): 802–7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

55. Toyoshima F, Matsumura S, Morimoto H, et al.: PtdIns(3,4,5)P3 regulates spindle orientation in adherent cells. Dev Cell. 2007; 13(6): 796–811. PubMed Abstract | Publisher Full Text | F1000 Recommendation

56. Tien SC, Lee HH, Yang YC, et al.: The Shp2-induced epithelial disorganization defect is reversed by HDAC6 inhibition independent of Cdc42. Nat Commun. 2016; 7: 10420. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

57. Fedorov AP, Eski C, Mierzwa B, et al.: MicroRNA-34/449 controls mitotic spindle orientation during mammalian cortex development. EMBO J. 2016; 35(22): 2386–98. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

58. Asare A, Lavorese J, Fuchs E: Coupling organelle inheritance with mitosis to balance growth and differentiation. Science. 2017; 355(6324): pii eaah4701. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
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Competing Interests: No competing interests were disclosed.

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Competing Interests: No competing interests were disclosed.