© 2017. Published by The Company of Biologists Ltd | Journal of Cell Science (2017) 0, 1-5 doi:10.1242/jcs.192997

CELL SCIENCE AT A GLANCE

Pseudostratified epithelia – cell biology, diversity and roles in organ formation at a glance

Caren Norden*

ABSTRACT

Pseudostratified epithelia (PSE) are widespread and diverse tissue arrangements, and many PSE are organ precursors in a variety of organisms. While cells in PSE, like other epithelial cells, feature apico-basal polarity, they generally are more elongated and their nuclei are more densely packed within the tissue. In addition, nuclei in PSE undergo interkinetic nuclear migration (IKNM, also referred to as INM), whereby all mitotic events occur at the apical surface of the elongated epithelium. Previous reviews have focused on the links between IKNM and the cell cycle, as well as the relationship between IKNM and neurogenesis, which will not be elaborated on here. Instead, in this Cell Science at a Glance article and the accompanying poster, I will discuss the cell biology of PSEs, highlighting how differences in PSE architecture could influence cellular behaviour, especially IKNM. Furthermore, I will summarize what we know about the links between apical mitosis in PSE and tissue integrity and maturation.

KEY WORDS: Epithelial biology, Nuclear movements, Cytoskeleton, Tissue maturation

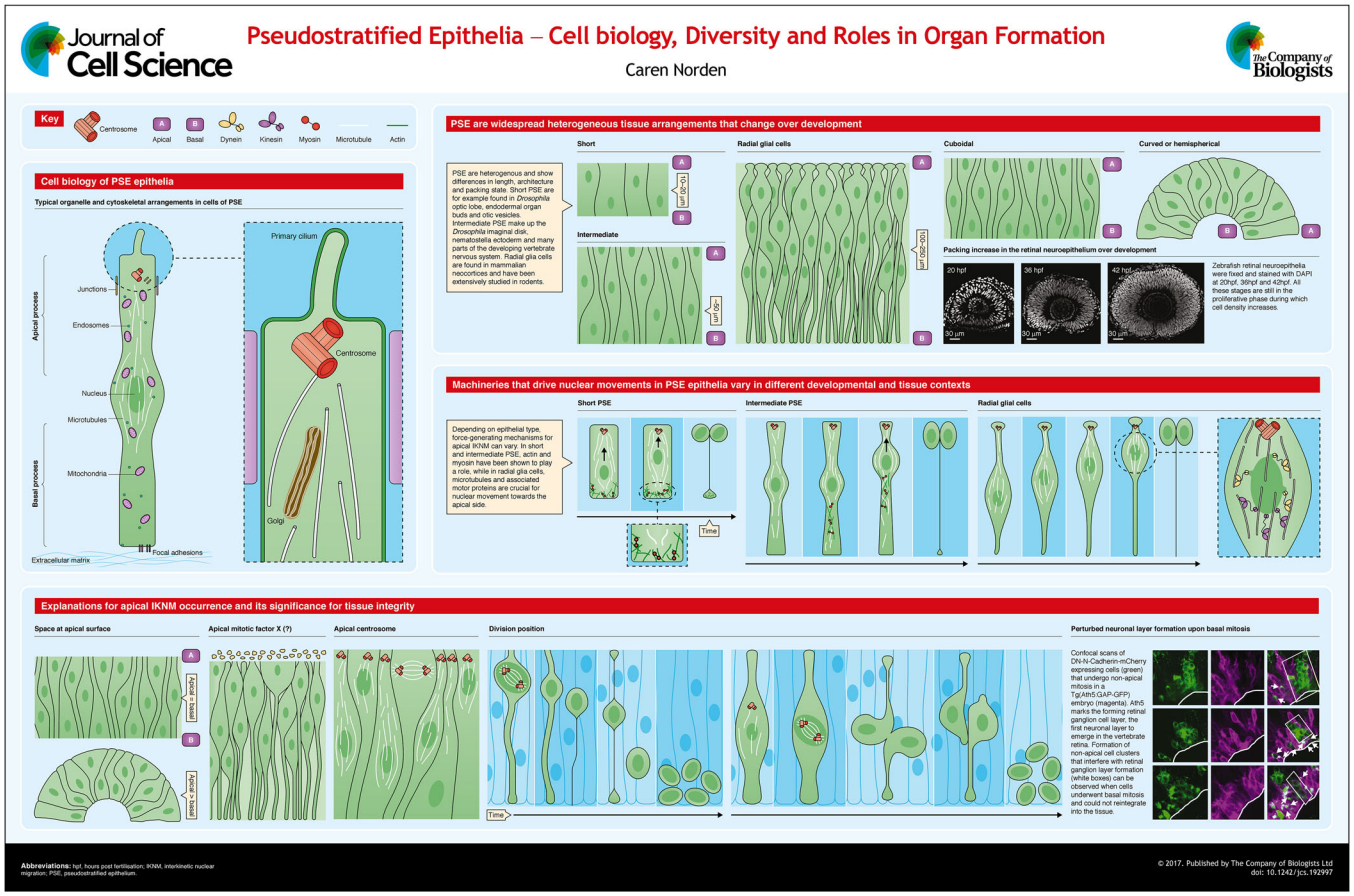
Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstraße 108, Dresden 01307, Germany.

*Author for correspondence (norden@mpi-cbg.de)

C.N., 0000-0001-8835-1451

Introduction

Epithelia are found in all metazoans and often serve as a selective barrier between body compartments or between the organism and its environment. All epithelia have a typical apico-basal polarity but their morphologies range from flat or squamous, to cuboidal or columnar. Furthermore, epithelia can either consist of a single cell layer, which are referred to as simple epithelia, or host multiple cell layers, referred to as stratified epithelia. A particular type of epithelium is the so-called pseudostratified epithelium (PSE). Because nuclei in this columnar epithelium were found to be



JCS Advance Online Article. Posted on 28 April 2017

Journal of Cell Science (2017) 0, 1-5 doi:10.1242/jcs.192997

positioned at different depths within the epithelial monolayer using the low magnification microscopes available in the late 19th century, it was initially assumed that the tissue was stratified. However, it was later revealed that all cells within the epithelium are attached to both laminae (Sauer, 1935; Smart, 1972), hence the term 'pseudostratified'. In contrast to other epithelia, PSE do not fulfil any obvious barrier functions, but instead are highly proliferative tissues and can often be seen as organ precursors. For instance, PSE in invertebrates include precursors of the embryonic ectoderm in the sea anemone *Nematostella* (Meyer et al., 2011), the imaginal discs of fly larvae that later form legs, wings or antennae (Meyer et al., 2011), as well as the fly optic lobe epithelium, which develops into the visual processing centre (Rujano et al., 2013). In vertebrates, PSE are also the building blocks of the epiblast of the gastrulating mouse embryo (Ichikawa et al., 2013), lung-, liver- and pancreatic-buds, and otic and lens placodes as well as all for areas of the central nervous system (reviewed in Strzyz et al., 2015). Interestingly, several *ex vivo* organoid tissues initially feature a pseudostratified appearance. In particular, organoids that give rise to different brain structures are originally pseudostratified, including the neural tube, retinal and cerebral organoids, thus reflecting the *in vivo* situation (Eiraku et al., 2011; Lancaster et al., 2013; Ranga et al., 2016). Surprisingly, given the overall importance of this widespread and diverse tissue type, we are still only beginning to assess their biology and significance for developmental programs.

It is important to note that PSE are a diverse tissue type. Different PSE span a broad range of heights from tens to hundreds of micrometres and vary in their 3D architecture (see poster). Furthermore, the 'packing state' of a PSE, meaning their nuclear density, varies depending on the tissue and the developmental stage. More developed PSEs usually show a higher 'packing state' upon continuous proliferation (see the related image on the poster). Interestingly, the nuclear position within single cells of PSE is not fixed, but fluctuates depending on cell cycle stage. These nuclear movements were initially discovered in the 1930s and are known as interkinetic nuclear migration (IKNM, also frequently referred to as INM) (Sauer, 1935). The particularities of these movements can vary between tissues, but in all PSE, apical nuclear movement occurs before mitosis and cell division always takes place at the apical side of the epithelium (Kosodo et al., 2011; Leung et al., 2011; Meyer et al., 2011; Norden et al., 2009; Okamoto et al., 2014; Tsai et al., 2010).

In this Cell Science at a Glance and the accompanying poster, I will introduce what we know and discuss what we still need to learn about PSEs. To that end, I will present the general cell biology of PSEs and discuss their heterogeneity. I will also examine apical nuclear migration and highlight its importance for tissue integrity and maintenance.

Cell biology of pseudostratified epithelia

Cells within a PSE share many features with other epithelial cells. They are attached to the apical and basal lamina via apical and basal processes (see poster). Furthermore, they show clear apico-basal polarity (Drubin and Nelson, 1996), and apical polarity markers, including the Par complex, ZO-1 (also known as TJP1) and Crumbs proteins are found at their apical membrane. PSE feature apical junctions, namely septate junctions in *Drosophila* and adherens and tight junctions in vertebrates (Liang et al., 2014; Strzyz et al., 2015). In all PSE, the centrosome is found at apical positions during the entire cell cycle (see poster). While this is most likely linked to the fact that the centrosome serves as a basal body for the apically emerging primary cilium in vertebrates (Kosodo et al., 2011; Leung et al., 2011; Meyer et al., 2011; Norden et al., 2009; Okamoto et al., 2014; Tsai et al., 2010), the relevance of the apical centrosome position in *Drosophila* PSE that lack primary cilia (Meyer et al., 2011) is less clear. In interphase, microtubules emanate from this apical centrosome meaning that all microtubule plus-ends point basally (Kosodo et al., 2011; Leung et al., 2011; Meyer et al., 2011; Norden et al., 2009; Okamoto et al., 2014; Tsai et al., 2010). Only upon entry into mitosis, the duplicated centrosomes leave apical positions and travel basally to meet the nucleus. They then guide the formation of a bipolar spindle that is arranged perpendicular to the apical surface (Dzafic et al., 2015; Strzyz et al., 2015).

Like the centrosome, the Golgi complex is also confined to the apical process in cells of zebrafish neuroepithelia, as well as the mouse neocortex PSE; however, Golgi and centrosome are not connected to each other (Hinds and Hinds, 1974; Taverna et al., 2016). In contrast, the endoplasmic reticulum can be found in both apical and basal processes (Taverna et al., 2016). The same appears to be true for mitochondria (my unpublished observations) and many types of endosomes (Clark et al., 2011). While the cell biology of the apical process is well defined (see poster), much less is known about the composition of the basal process, which is linked to the basal lamina through integrin-based focal adhesion complexes (Stuermer and Bastmeyer, 2000). Interestingly, in the zebrafish retinal neuroepithelium, it appears that these basal adhesions are more stable than the adhesions of emerging neighbouring neurons (Icha et al., 2016). It has further been shown that regrowth of the basal process is more directed and faster than regrowth of the apical process (Icha et al., 2016). However, the reasons for these differences in adhesion or growth potential are not yet clear.

Pseudostratified epithelia heterogeneity

As noted above, cells in PSE share many cell biological characteristics independently of where they occur; however, PSE are a heterogeneous group of tissues. While all PSE show layered nuclear arrangements with nuclei dispersed along the apico-basal axis, they vary extensively in height, spanning distances of less than 30 µm in the *Drosophila* optic lobe (Rujano et al., 2013) to hundreds of micrometres in the rodent neocortex (Tsai et al., 2010), even reaching millimetres in the primate neocortex (Rakic, 1972). Alongside an increase in epithelial height, the number of nuclear layers stacked within a PSE also increases and, concurrently, so does the distance the nuclei have to travel to reach apical positions before mitosis (also see the images on the poster). Depending on the cell length and number of nuclear layers, I will here categorize PSE into short, intermediate and extended PSE (see poster) (Strzyz et al., 2016).

Short PSE (below 30 µm) are seen in both invertebrates and vertebrates. For example, cells in the optic lobe in *Drosophila* that give rise to parts of the fly eye are less than 30 µm high, and nuclei are arranged basically in a top and a bottom layer (Rujano et al., 2013). Similar PSE heights are found in some vertebrate tissues, including endodermal organ buds (Bort et al., 2006), otic vesicles (Hoijman et al., 2015), the neural plate (Schoenwolf and Alvarez, 1989) and zebrafish photoreceptor cell precursors (Weber et al., 2014).

Intermediate PSE span an apico-basal distance of between 30 µm and 60 µm, with nuclei stacked into four to six layers. Consequently, cells are less columnar and become more spindle shaped (see poster). In turn, both, apical and basal processes are thinner than in short PSE with less cytoplasm and a denser packing of nuclei. Examples of such intermediate epithelia are fly imaginal discs (Meyer et al., 2011), *Nematostella* ectoderm (Meyer et al., 2011),

Journal of Cell Science (2017) 0, 1-5 doi:10.1242/jcs.192997

zebrafish retinal and hindbrain neuroepithelia (Leung et al., 2011; Norden et al., 2009), mouse intestine (Grosse et al., 2011) and the mammalian neural tube (Sauer, 1935).

Extended PSE that span ∼100 µm and feature eight to nine nuclear layers do exist, but they are less common. Examples are the more developed neural tube and retinal neuroepithelia in mammals (Iulianella et al., 2008). One particular case of an extended PSE is the PSE of mammalian neocortices that consist of radial glia cells (see poster). These cells are extremely elongated, spanning about 250 µm in mouse and up to 1 mm in primates (Miyata, 2008; Rakic, 1972). In these cells, the only bulky region is the nucleus, while processes are extremely thin and almost devoid of any cytoplasm. This gives radial glia cells a 'bead on a string' appearance. In contrast to other PSEs, here nuclei are not found along the entire apico-basal axis, but instead reside in a restricted zone that spans ∼150 µm from the apical surface where they arrange into ten or more layers.

In addition to their differences in length and nuclear layer arrangements, PSE can also vary in their overall shape and architecture. The majority of PSE have a straight surface and a rectangular morphology, as seen in the ectoderm of *Nematostella* and PSE in the neocortex. However, some PSEs are apically or basally bent, for example parts of the *Drosophila* wing disc and the vertebrate retina (see poster). Whether this different architecture is linked to differences in nuclear arrangements and packing states, or even influences how nuclei move within epithelia has not yet been explored. Furthermore, it is not fully understood whether differences in tissue height or tissue packing can influence cellular processes within PSE (see poster). While many of these areas still need investigations, some correlations are found with regard to the observed links between epithelial length and the machineries that drive nuclear dynamics during IKNM (Lee and Norden, 2013; Miyata et al., 2015; Strzyz et al., 2016), which will be discussed and elaborated in the next chapter.

Machineries driving nuclear movements in PSE – possible dependence on tissue context

IKNM is the most studied hallmark of PSE. For almost a century, researchers have investigated why and how nuclei move in PSE during the cell cycle. The phenomenon of IKNM was already discovered in the 1930s when Sauer noted that all cell divisions occur at apical positions and nuclei vacate this space in other phases of the cell cycle (Sauer, 1935). I will not elaborate on the basal movements of nuclei here, as they have been discussed in detail in previous reviews (Lee and Norden, 2013; Miyata et al., 2015; Strzyz et al., 2016), but focus on the apical nuclear movement before mitosis.

It is now clear that the apical nuclear movement that brings nuclei to the apical surface before mitosis is a fast, directed and active process that is driven by cytoskeletal elements in all PSE. However, the molecular machineries responsible for these movements can vary depending on tissue context. So far, a combination of studies hints that the length of a PSE might be linked to the particular molecular machinery used.

In PSE of short and intermediate length, actin and myosin have been shown to be involved in apical IKNM (Leung et al., 2011; Meyer et al., 2011; Norden et al., 2009; Rujano et al., 2013). Nevertheless, differences are seen in how actin and myosin are used. In the short PSE of the *Drosophila* optic lobe, for example, where nuclei have to travel only one nuclear length to reach the apical surface, it appears that actomyosin-based cell rounding is sufficient to move nuclei into apical positions for mitosis. In line with this argument, in these epithelia, myosin is seen only at the basal cortex, and contractility of this actomyosin assembly, which appears to occur concurrently with cell rounding, might be sufficient to move nuclei to apical positions (see poster) (Rujano et al., 2013). A similar movement is seen in zebrafish photoreceptor cell precursors, which have a comparable length to cells of the optic lobe (Weber et al., 2014). However, here, the cytoskeletal arrangements involved have not yet been explored.

In PSE of intermediate length, such as the zebrafish retinal neuroepithelium or the imaginal disk of the fly wing, mitotic rounding and IKNM can occur independently of each other, indicating that, here, IKNM is an additional process. Interestingly, mitotic rounding can take place at basal positions in the epithelium in cases where IKNM is impaired due to genetic manipulation or interference with the actin pool that drives the movement (Liang et al., 2014; Strzyz et al., 2015). This argues that in these epithelia, in which nuclei have to travel up to three times their length to reach the apical surface, additional mechanisms other than cell rounding that are based on actin and myosin have evolved. The finding that myosin and actin follow the nucleus as it moves apically underlines this notion (Meyer et al., 2011; Norden et al., 2009). However, how exactly actin and myosin generate force to translocate the bulky nucleus in these tissues is still not well understood. In the fly wing, Rho-associated protein kinase (Rock)-dependent mechanisms have been suggested, implying that actomyosin contractility could be the driving force (Meyer et al., 2011). For a brief discussion of the role of microtubules in these tissues, see Box 1.

Finally, in the very elongated radial glia cells of the neocortex, in which nuclei have to move up to ten times, or even more, their own length to reach apical positions, microtubules and their associated motors are actively involved in apical nuclear movement before mitosis (see poster). Microtubules are arranged as apico-basal arrays that form a cage surrounding the nucleus (see Box 1) (Xie et al., 2007). If this cage is compromised by either depolymerising microtubules or by interference with centrosome integrity, apical movements are disturbed (Ge et al., 2010; Xie et al., 2007). It has been shown that dynein serves as an apically-directed motor and the

Box 1. Roles of microtubule arrangements in different PSE

In all PSE studied so far, microtubules emanate from the apically positioned centrosome with a clear apico-basal polarity where all minus-ends point towards the apical side and plus-ends towards the basal side (Norden et al., 2009; Tsai et al., 2010). It has also been shown that in some tissues these microtubules can be stabilized by acetylation (Norden et al., 2009). However, it is only in a subset of PSE, the elongated radial glial cells, that these microtubules appear to play an active role in apical translocation of nuclei in combination with the microtubule motor protein dynein and links to the nuclear envelope (see main text and poster). In contrast, in the short and intermediate PSE investigated so far, microtubules do not appear to be the main driver of apical IKNM (Norden et al., 2009; Meyer et al., 2011) and rather have a supportive role, such as in the *Nematostella* ectoderm (Meyer et al., 2011). Nevertheless, to date it has not been excluded that microtubules might be otherwise involved in the apical nuclear movement in intermediate PSE. Although apical nuclear movement still takes place in *Drosophila* wing disk and zebrafish retinal neuroepithelium upon microtubule depolymerisation (Meyer et al., 2011; Norden et al., 2009), it should be noted that, at least in the zebrafish neuroepithelium, additional microtubule destabilization upon actomyosin interference increased the effect on apical IKNM (Norden et al., 2009). Thus, it is possible that even in tissues, in which microtubules are dispensable for overall nuclear apical movement, they potentially stabilize nuclear positions during interphase and thereby ensure smooth apical migration (Del Bene et al., 2008; Meyer et al., 2011; Norden et al., 2009).

Journal of Cell Science (2017) 0, 1-5 doi:10.1242/jcs.192997

plus-end-directed kinesin motor Kif1A moves nuclei basally in the rodent neocortex (Tsai et al., 2010). Dynein is recruited to the nuclear envelope by the nuclear pore complex proteins Nup133 and BicD2, which then link the nucleus to the microtubule network through dynein (Hu et al., 2013).

Overall, the data acquired to date could suggest that the observed switch from an actomyosin-based force-generating mechanism to one that involves microtubule-mediated transport is connected to tissue height. If this speculation is correct, actin and myosin might not be able to generate sufficient force to move nuclei to apical positions as overall length increases, and microtubule-based transport could be a more robust mechanism for extremely elongated cells. So far, however, this idea is purely speculative. Future studies using newly established 3D culture models for PSE, including organoids, could help to investigate this question in more detail.

Apical IKNM and its significance for tissue integrity

In addition to elucidating how nuclei move apically before mitosis it is also important to understand why mitosis and cell division always occur at apical positions in the PSE (see poster). One hypothesis, initially raised in the 1970s, is that rounded mitotic cells occupy more space and moving them to the apical surface could thus 'outsource' them from the rest of the epithelium (Fish et al., 2008; Smart, 1972). However, it is only in outward curved PSE, such as the retinal neuroepithelium, that the apical side indeed has a greater apical than basal surface area (see poster). Therefore, in the majority of straight PSE, having a larger surface area available for mitotic events is most likely not the main reason for apical mitosis. In addition, non-apical mitosis can occur despite dense nuclear packing when apical IKNM is disturbed or when committed precursors arise in later retinal development (Liang et al., 2014; Strzyz et al., 2015; Weber et al., 2014); this further argues that eventual space constraints are not the main reasons for apical mitosis.

Another hypothesis has suggested an apical 'mitotic zone' is present in the very elongated rodent neocortex PSE. Here, it was proposed that apical signalling cues allow for a spatial control of mitotic entry (Hu et al., 2013). So far, the exact nature of these apical signals remains elusive and needs further investigation. It is possible that such mitotic entry signals are specific to extended PSE, as, as mentioned above, in shorter PSE, cells can enter mitosis at non-apical positions (Liang et al., 2014; Strzyz et al., 2015; Weber et al., 2014). Another consideration is that the apically positioned centrosome could be instructive for apical IKNM. Apical nuclear movement before mitosis could facilitate the interaction between the centrosome and nucleus, which is important for bipolar spindle formation. This might well be true in the very elongated cells of the neocortex PSE, in which the centrosome is also actively involved in nuclear movement. However, apical IKNM in the zebrafish retinal PSE takes place even when the centrosome is mispositioned or ablated (Strzyz et al., 2015). In addition, in PSE of the *Drosophila* wing disc, apical IKNM is still observed when centrosomes are genetically depleted (Poulton et al., 2014). Thus, centrosome position, and even its presence, can be decoupled from apical IKNM, at least in some tissues.

In most PSE investigated so far, apical IKNM is followed by a cell division that features a perpendicular cleavage plane (see poster) (Cui et al., 2007; Das et al., 2003; Kosodo et al., 2004; Nakajima et al., 2013). As such divisions bisect the apical membranes, correct cleavage angles could be important for the distribution of apical components into the two daughter cells. In some PSE, including the *Drosophila* wing disc, the chick neural tube and the mouse neocortex, a perturbation of cleavage plane orientation can result in cell delamination and a misregulation of cell fates (Morin et al., 2007; Nakajima et al., 2013). In the retinal neuroepithelium, however, a perpendicular cleavage plane is not absolutely necessary for cells to re-integrate into the tissue (Dzafic et al., 2015; Strzyz et al., 2015). Here, as long as divisions still occur in apical regions, both daughter cells will be included in the tissue and continue to proliferate. However, when apical IKNM is perturbed in this tissue (Strzyz et al., 2015), and cells divide at more basal locations, at least one of the daughter cells does not re-establish bipolar PSE morphology. Such a cell ectopically proliferates and interferes with tissue integrity and consecutive retinogenesis (Strzyz et al., 2015) (see related images on the poster). Taken together, these studies show that an important role of apical IKNM is to ensure apical divisions, which in turn are necessary and important for daughter cells to re-integrate into the tissue, and thus ensure tissue integrity before differentiation and maturation.

Conclusions

PSE give rise to many organs in a multitude of organisms and are thus important for diverse developmental programs. Remarkably, pseudostratification is also a hallmark of many organoid systems, including the neural tube and retinal and cerebral organoids, before the cells in these organoids undergo final differentiation (Eiraku et al., 2011; Lancaster et al., 2013; Ranga et al., 2016). Thus, this tissue arrangement is so general that it is important to understand it in all its flavours and intricacies.

So far, we have made headway in deciphering the cell biological machineries that drive apical IKNM in diverse types of PSE. As it has become clear that PSE are a diverse tissue type, it is now time to evaluate in more detail the similarities and differences resulting from different tissue heights and shapes. For example, it would be very exciting to test how nuclei are moved in a tissue that increases its height and packing state over development. Organoids would be a highly accessible tool for such studies. Another important future direction in PSE research is to shed light on why PSE are so widespread in development. Understanding the advantages of pseudostratification prior to differentiation will be important to understand morphogenesis and organogenesis in various contexts.

Acknowledgements

I thank M. Matejcic and I. Yanakieva for extremely valuable input to this manuscript and on-going discussion about pseudostratification. P. Strzyz is thanked for many of the initial thoughts leading to this review and the whole Norden laboratory for discussion. J. Eichhorn is thanked for illustrations.

Competing interests

The author declares no competing or financial interests.

Funding

Work essential for this review was supported by the Human Frontier Science Program (CDA-00007/2011) and the Deutsche Forschungsgemeinschaft (DFG).

Cell science at a glance

A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.192997.supplemental

References

Bort, R., Signore, M., Tremblay, K., Barbera, J. P. M. and Zaret, K. S. (2006). Hex homeobox gene controls the transition of the endoderm to a pseudostratified, cell emergent epithelium for liver bud development. *Dev. Biol.* **290**, 44-56.

Clark, B. S., Winter, M., Cohen, A. R. and Link, B. A. (2011). Generation of Rab-based transgenic lines for in vivo studies of endosome biology in zebrafish. *Dev. Dyn.* **240**, 2452-2465.

Cui, S., Otten, C., Rohr, S., Abdelilah-Seyfried, S. and Link, B. A. (2007). Analysis of aPKClambda and aPKCzeta reveals multiple and redundant functions during vertebrate retinogenesis. *Mol. Cell. Neurosci.* **34**, 431-444.

Das, T., Payer, B., Cayouette, M. and Harris, W. A. (2003). In vivo time-lapse imaging of cell divisions during neurogenesis in the developing zebrafish retina. *Neuron* **37**, 597-609.
Del Bene, F., Wehman, A. M., Link, B. A. and Baier, H. (2008). Regulation of neurogenesis by interkinetic nuclear migration through an apical-basal notch gradient. *Cell* **134**, 1055-1065.
Drubin, D. G. and Nelson, W. J. (1996). Origins of cell polarity. *Cell* **84**, 335-344.
Dzafic, E., Strzyz, P. J., Wilsch-Bräuninger, M. and Norden, C. (2015). Centriole amplification in Zebrafish affects proliferation and survival but not differentiation of neural progenitor cells. *Cell Rep.* **13**, 168-182.
Eiraku, M., Takata, N., Ishibashi, H., Kawada, M., Sakakura, E., Okuda, S., Sekiguchi, K., Adachi, T. and Sasai, Y. (2011). Self-organizing optic-cup morphogenesis in three-dimensional culture. *Nature* **472**, 51-56.
Fish, J. L., Dehay, C., Kennedy, H. and Huttner, W. B. (2008). Making bigger brains-the evolution of neural-progenitor-cell division. *J. Cell Sci.* **121**, 2783-2793.
Ge, X., Frank, C. L., Calderon De Anda, F. and Tsai, L.-H. (2010). Hook3 interacts with PCM1 to regulate pericentriolar material assembly and the timing of neurogenesis. *Neuron* **65**, 191-203.
Grosse, A. S., Pressprich, M. F., Curley, L. B., Hamilton, K. L., Margolis, B., Hildebrand, J. D. and Gumucio, D. L. (2011). Cell dynamics in fetal intestinal epithelium: implications for intestinal growth and morphogenesis. *Development* **138**, 4423-4432.
Hinds, J. W. and Hinds, P. L. (1974). Early ganglion cell differentiation in the mouse retina: an electron microscopic analysis utilizing serial sections. *Dev. Biol.* **37**, 381-416.
Hoijman, E., Rubbini, D., Colombelli, J. and Alsina, B. (2015). Mitotic cell rounding and epithelial thinning regulate lumen growth and shape. *Nat. Commun.* **6**, 7355.
Hu, D. J.-K., Baffet, A. D., Nayak, T., Akhmanova, A., Doye, V. and Vallee, R. B. (2013). Dynein recruitment to nuclear pores activates apical nuclear migration and mitotic entry in brain progenitor cells. *Cell* **154**, 1300-1313.
Icha, J., Kunath, C., Rocha-Martins, M. and Norden, C. (2016). Independent modes of ganglion cell translocation ensure correct lamination of the zebrafish retina. *J. Cell Biol.* **215**, 259-275.
Ichikawa, T., Nakazato, K., Keller, P. J., Kajiura-Kobayashi, H., Stelzer, E. H. K., Mochizuki, A. and Nonaka, S. (2013). Live imaging of whole mouse embryos during gastrulation: migration analyses of epiblast and mesodermal cells. *PLoS ONE* **8**, e64506.
Iulianella, A., Sharma, M., Durnin, M., Vanden Heuvel, G. B. and Trainor, P. A. (2008). Cux2 (Cutl2) integrates neural progenitor development with cell-cycle progression during spinal cord neurogenesis. *Development* **135**, 729-741.
Kosodo, Y., Röper, K., Haubensak, W., Marzesco, A.-M., Corbeil, D. and Huttner, W. B. (2004). Asymmetric distribution of the apical plasma membrane during neurogenic divisions of mammalian neuroepithelial cells. *EMBO J.* **23**, 2314-2324.
Kosodo, Y., Suetsugu, T., Suda, M., Mimori-Kiyosue, Y., Toida, K., Baba, S. A., Kimura, A. and Matsuzaki, F. (2011). Regulation of interkinetic nuclear migration by cell cycle-coupled active and passive mechanisms in the developing brain. *EMBO J.* **30**, 1690-1704.
Lancaster, M. A., Renner, M., Martin, C.-A., Wenzel, D., Bicknell, L. S., Hurles, M. E., Homfray, T., Penninger, J. M., Jackson, A. P. and Knoblich, J. A. (2013). Cerebral organoids model human brain development and microcephaly. *Nature* **501**, 373-379.
Lee, H. O. and Norden, C. (2013). Mechanisms controlling arrangements and movements of nuclei in pseudostratified epithelia. *Trends Cell Biol.* **23**, 141-150.
Leung, L., Klopper, A. V., Grill, S. W., Harris, W. A. and Norden, C. (2011). Apical migration of nuclei during G2 is a prerequisite for all nuclear motion in zebrafish neuroepithelia. *Development* **138**, 5003-5013.
Liang, L., Haug, J. S., Seidel, C. W. and Gibson, M. C. (2014). Functional genomic analysis of the periodic transcriptome in the developing drosophila wing. *Dev. Cell* **29**, 112-127.
Meyer, E. J., Ikmi, A. and Gibson, M. C. (2011). Interkinetic nuclear migration is a broadly conserved feature of cell division in pseudostratified epithelia. *Curr. Biol.* **21**, 485-491.
Miyata, T. (2008). Development of three-dimensional architecture of the neuroepithelium: role of pseudostratification and cellular 'community'. *Dev. Growth Differ.* **50** Suppl. 1, S105-S112.
Miyata, T., Okamoto, M., Shinoda, T. and Kawaguchi, A. (2015). Interkinetic nuclear migration generates and opposes ventricular-zone crowding: insight into tissue mechanics. *Front. Cell Neurosci.* **8**, 473.
Morin, X., Jaouen, F. and Durbec, P. (2007). Control of planar divisions by the G-protein regulator LGN maintains progenitors in the chick neuroepithelium. *Nat. Neurosci.* **10**, 1440-1448.
Nakajima, Y.-I., Meyer, E. J., Kroesen, A., McKinney, S. A. and Gibson, M. C. (2013). Epithelial junctions maintain tissue architecture by directing planar spindle orientation. *Nature* **500**, 359-362.
Norden, C., Young, S., Link, B. A. and Harris, W. A. (2009). Actomyosin is the main driver of interkinetic nuclear migration in the retina. *Cell* **138**, 1195-1208.
Okamoto, M., Shinoda, T., Kawaue, T., Nagasaka, A. and Miyata, T. (2014). Ferret–mouse differences in interkinetic nuclear migration and cellular densification in the neocortical ventricular zone. *Neurosci. Res.* **83**, 25-32.
Poulton, J. S., Cuningham, J. C. and Peifer, M. (2014). Acentrosomal Drosophila epithelial cells exhibit abnormal cell division, leading to cell death and compensatory proliferation. *Dev. Cell* **30**, 731-745.
Rakic, P. (1972). Mode of cell migration to the superficial layers of fetal monkey neocortex. *J. Comp. Neurol.* **145**, 61-83.
Ranga, A., Girgin, M., Meinhardt, A., Eberle, D., Caiazzo, M., Tanaka, E. M. and Lutolf, M. P. (2016). Neural tube morphogenesis in synthetic 3D microenvironments. *Proc. Natl. Acad. Sci. USA* **113**, E6831-E6839.
Rujano, M. A., Sanchez-Pulido, L., Pennetier, C., le Dez, G. and Basto, R. (2013). The microcephaly protein Asp regulates neuroepithelium morphogenesis by controlling the spatial distribution of myosin II. *Nat. Cell Biol.* **15**, 1294-1306.
Sauer, F. C. (1935). Mitosis in the neural tube. *J. Comp. Neurol.* **62**, 377-405.
Schoenwolf, G. C. and Alvarez, I. S. (1989). Roles of neuroepithelial cell rearrangement and in shaping of the avian neural plate. *Development* **106**, 427-439.
Smart, I. H. (1972). Proliferative characteristics of the ependymal layer during the early development of the mouse diencephalon, as revealed by recording the number, location, and plane of cleavage of mitotic figures. *J. Anat.* **113**, 109.
Strzyz, P. J., Lee, H. O., Sidhaye, J., Weber, I. P., Leung, L. C. and Norden, C. (2015). Interkinetic nuclear migration is centrosome independent and ensures apical cell division to maintain tissue integrity. *Dev. Cell* **32**, 203-219.
Strzyz, P. J., Matejcic, M. and Norden, C. (2016). Heterogeneity, cell biology and tissue mechanics of pseudostratified epithelia: coordination of cell divisions and growth in tightly packed tissues. *Int. Rev. Cell Mol. Biol.* **325**, 89-118.
Stuermer, C. A. O. and Bastmeyer, M. (2000). The retinal axon's pathfinding to the optic disk. *Prog. Neurobiol.* **62**, 197-214.
Taverna, E., Mora-Bermúdez, F., Strzyz, P. J., Florio, M., Icha, J., Haffner, C., Norden, C., Wilsch-Bräuninger, M. and Huttner, W. B. (2016). Non-canonical features of the Golgi apparatus in bipolar epithelial neural stem cells. *Sci. Rep.* **6**, 21206.
Tsai, J.-W., Lian, W.-N., Kemal, S., Kriegstein, A. R. and Vallee, R. B. (2010). Kinesin 3 and cytoplasmic dynein mediate interkinetic nuclear migration in neural stem cells. *Nat. Neurosci.* **13**, 1463-1U43.
Weber, I. P., Ramos, A. P., Strzyz, P. J., Leung, L. C., Young, S. and Norden, C. (2014). Mitotic position and morphology of committed precursor cells in the zebrafish retina adapt to architectural changes upon tissue maturation. *Cell Rep.* **7**, 386-397.
Xie, Z., Moy, L. Y., Sanada, K., Zhou, Y., Buchman, J. J. and Tsai, L.-H. (2007). Cep120 and TACCs control interkinetic nuclear migration and the neural progenitor pool. *Neuron* **56**, 79-93.

Journal of Cell Science • Advance article