Interkinetic nuclear migration: cell cycle on the move

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Interkinetic nuclear migration (INM) is a common feature of developing neuroepithelia, consisting of the periodic movement of the cell nucleus in phase with cell-cycle progression. In this issue of *The EMBO Journal*, Kosodo *et al* provide a first molecular mechanism to couple nuclear migration and cell cycle: the microtubule-associated protein Tpx2 redistributes from the nucleus to the apical process during the S-G2 transition, modulating microtubule organization to promote apical nuclear migration.

Developing neuroepithelia are tissues composed of neural progenitor cells, each spanning the entire thickness of the epithelium from the ventricular surface to the laminal side. Cell nuclei occupy different positions along the apical–basal axis of the tissue, but mitosis exclusively occurs close to ventricular surface (apical side). The nuclei then move to upper regions near the basal side where they proceed through S-phase. This nuclear movement is repeated at each cell cycle and is maintained by an apical-to-basal migration during G1-phase and a reverse basal-to-apical movement during G2-phase. Although this phenomenon, known as INM, was first described over 70 years ago (Sauer, 1935), its function has remained controversial. Initially, it had been proposed that a simple function of INM could be to maximize the number of mitoses at the limited apical surface to allow a more efficient progenitor expansion. As neural progenitor cells have a basal body/centrosome located at the apical surface during inter-phase, it has been suggested that the nucleus must reach this position in order to assemble the mitotic spindle. By moving the nuclei via INM, it is therefore possible to maximize the number of divisions per apical surface available (Fish *et al*, 2008). More recent data have supported an instrumental role of INM in determining the cell fate of neural progenitors, by moving their nuclei through signalling gradients along the apical–basal axis of the epithelium (Murciano *et al*, 2002; Baye and Link, 2007; Del Bene *et al*, 2008; Latasa *et al*, 2009). Experimental perturbations of INM lead to defects in neurogenesis with premature depletion of neuronal precursors and unbalanced neuronal cell fate decisions (Schenk *et al*, 2009).

Despite these and other recent progresses in understanding the function and the molecular machinery driving INM, an unresolved question remains concerning the link between INM and cell cycle, ensuring these two dynamic processes are tightly coupled. Several reports have indicated that INM is not required for cell-cycle progression and blocking or delaying the nuclear movement does not alter cell-cycle length

(Murciano *et al*, 2002; Schenk *et al*, 2009). Conversely, cell-cycle progression cannot be uncoupled from INM. Both blocking and delaying cell cycle result in either arrest or reduction of INM, respectively (Ueno *et al*, 2006; Baye and Link, 2007). These results are also confirmed by Kosodo *et al*:

Figure 1 Ensemble of forces proposed to drive INM. During G2-phase, the nucleus is moved towards the basal side by the concerted action of actomyosin constriction and dynein-mediated motility to the minus end of the microtubules, at the apical side of the neuroepithelium. Tpx2 organizes the apically distributed microtubules, increasing their packing to promote apical migration. During the G1-phase, the nucleus is moved towards the basal side by three alternative/concurrent forces. (i) Nuclei are pushed away from the apical side by nearby nuclei in G2-phase. (ii) Kinesin-3-mediated microtubule motility drives nuclei towards the microtubule plus end close to the apical side of the epithelium. (iii) Actomyosin constriction provides further force to the apical migration.

arresting neural progenitor in G1-phase by p18^{Ink4c} overexpression causes nuclear accumulation at the basal side. On the other hand, accelerating or retarding cell-cycle length does not alter the apical position of mitotic nuclei, suggesting that progenitor cells can adjust the speed of INM to the altered cell-cycle duration (Lange *et al*, 2009; Pilaz *et al*, 2009). From these data, we can conclude that nuclear migration is not essential for cell-cycle progression but that cell-cycle regulators also exert a tight control upon INM. In the present study, a first molecular mechanism that links between cell cycle and INM is described (Kosodo *et al*, 2011). The authors identify the microtubule-nucleating/binding Tpx2 protein as a candidate to mediate this function. In the embryonic mouse brain, Tbx2 is expressed in S-, G2- and M-phase neural progenitors. Specifically during G2-phase, Tpx2 was found to localize to the apical processes in a fiber-like pattern, probably associated with microtubules. Furthermore, Tpx2 depletion decreased the basal-to-apical migration of G2-phase nuclei of neural progenitors and lead to increased mitosis in a subapical position. Thus, G2-phase translocation of Tpx2 to the apical processes of neural progenitors alters microtubule organization, promoting the apically directed nuclear movement and ensuring that this occurs during the proper cell-cycle phase (G2-phase).

In the second part of their study, Kosodo *et al* develop a model that identifies the nuclear displacement by apically

migrating G2-phase nuclei as the main driving force for basal migration during G1-phase. These results are well supported by *in vivo* data including the passive basal displacement of fluorescent beads and cell non-autonomous apical accumulation of nuclei when the surrounding cells are arrested in G1-phase by p18^{Ink4c} overexpression. Nevertheless, other data support also alternative hypothesis including a microtubule/kinesin-mediated mechanism for the apical-to-basal migration (Tsai *et al*, 2010) and a actomyosin-driven nuclear migration in the same direction (Schenk *et al*, 2009). This apparent controversy will need to be addressed in detail, although it is possible that all three mechanisms contribute to a certain extent to proper nuclear movement and the difference observed may be due to specific experimental differences. It should be noted that similar contradicting results exist also for the main driving force responsible for the basal-to-apical migration, where both microtubule- and actomyosin-based motility seem to have a crucial role (see Figure 1).

The present study by Kosodo *et al* represents a milestone in the dissection of INM machinery, identifying a first molecular mechanism that provides cell cycle-coupled directionality to INM.

Conflict of interest

The author declares that he has no conflict of interest.

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