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The Ups and Downs of Neural Progenitors: Cep120 and TACCs Control Interkinetic Nuclear Migration

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The nuclei of dividing neural progenitors undergo a cell-cycle-dependent change in position along the apico-basal axis known as interkinetic nuclear migration (INM). The functional relationship between INM and the mode of division of neural progenitors remains elusive, in part because its regulation at the molecular level is poorly understood. In this issue of *Neuron*, Xie et al. identify two centrosomal proteins (Cep120 and TACCs) regulating the INM of cortical neural progenitors.

Through careful examination of histological sections of embryonic chick neural tube and pig neural plate, Sauer was the first to recognize the nuclear movement characterizing neuroepithelial progenitors known as interkinetic nuclear migration (INM) in 1935 (Sauer, 1935). During cell-cycle progression, neuroepithelial progenitors have an elongated morphology with an apical and a basal attachment, but their nuclei undergo a systematic change in position along the apico-basal axis (Figures 1A–1C). After undergoing mitosis in the apical part of the pseudoepithelium, the nuclei of neural progenitors progress in G1 phase by translocating basally, away from the ventricle, and undergo DNA replication (S phase) in the basal part of the ventricular zone. Finally, the nuclei migrate apically through G2 phase to undergo M phase in apical position along the ventricle (Figure 1C). Proper regulation of cell-cycle progression is critical for the proper amplification of the pool of neural progenitors ultimately generating the appropriate number of cortical neurons. Several recent studies have highlighted the importance of centrosome positioning and microtubule dynamics during mitotic spindle assembly for proper neurogenesis in the cerebral cortex (Buchman and Tsai, 2007). However, these studies did not address the role of centrosome and microtubule dynamics for INM and cell-cycle progression.

Recent reports have implicated microtubules as a potential regulator of INM. Tsai et al. demonstrated that depletion of Lis1 impaired INM. This is an interesting finding because it suggested that microtubules as well as motor proteins such as dynein regulate INM (Tsai et al., 2005). However, at this point, it remains unclear how Lis1 and other microtubule effectors control INM. In this issue of *Neuron*, a study from the Li-Huei Tsai group (Xie et al., 2007) provides novel molecular insights into the regulation of INM by the centrosome. Based on the pattern of nuclear movement during INM, one could hypothesize that the nucleus must be anchored by a fixed subcellular structure inside dividing neural progenitors. Interestingly, it is well established in many migrating cell types, including cortical and cerebellar neurons, that the centrosome is tightly associated with the nucleus during migration (Solecki et al., 2004; reviewed in Tsai and Gleeson, 2005). Moreover, the centrosome is localized apically in early dividing progenitors in the ventricular zone, making it an ideal candidate to regulate the type of nuclear movement that occurs during INM (Figure 1D). In order to identify proteins that are associated with the centrosome, Xie et al. performed a yeast two-hybrid screen using focal adhesion kinase (FAK) as a bait, as FAK was previously shown by the same group to regulate nucleus-centrosome coupling in migrating neurons (Xie et al., 2003). Using this approach, the authors isolated an uncharacterized protein of ~120 kD that was enriched in the centrosome of dividing neural progenitors that they called centrosomal protein (Cep)120. Using in utero cortical electroporation at early stages of development (E11.5), the authors show that depletion of Cep120 using short hairpin (sh)RNA specifically impairs INM and disrupts the ability of progenitors to undergo mitosis apically, close to the ventricle, and instead divide in a more basal position, i.e., away from the ventricle. Xie et al. found that the main consequences of this perturbation of INM and abnormal position of progenitors undergoing mitosis is to cause progenitors to prematurely exit the cell cycle and generate postmitotic neurons engaging radial translocation. Interestingly, the authors provide evidence that, despite this increased cell-cycle exit, the impairment of INM due to Cep120 downregulation has no effect on cell-cycle length. These data suggest that (1) the function of Cep120 is to regulate centrosome-mediated INM and thereby to regulate the mode of division of neural progenitors and (2) that abnormal INM does not change cell-cycle length, i.e., that one can

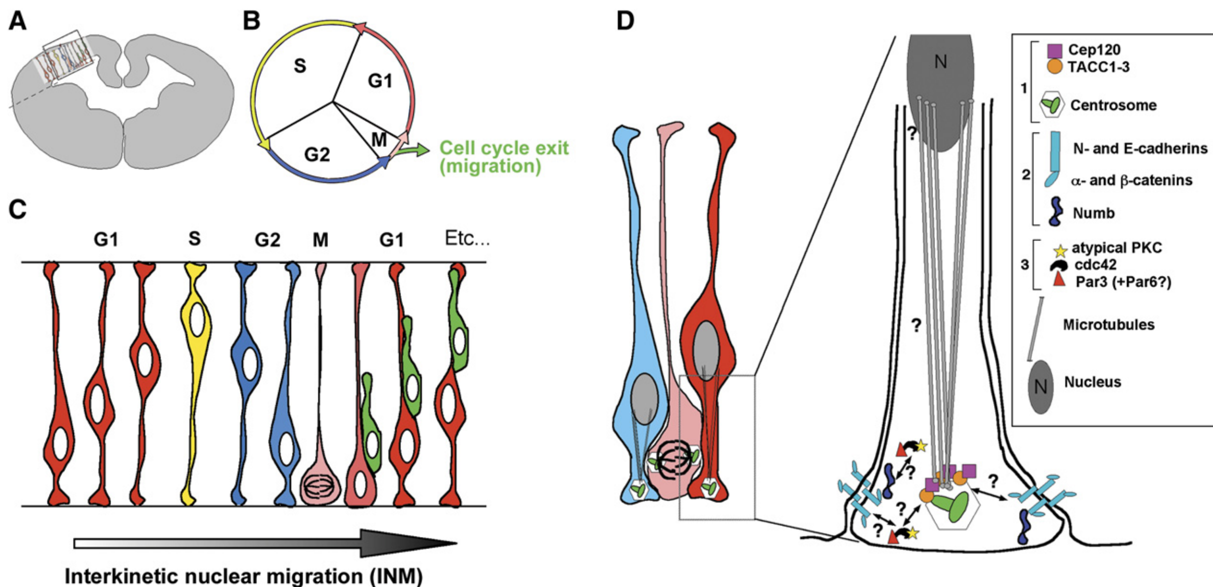

Figure 1. Toward a Cell and Molecular Biology of Intekinetic Nuclear Migration
(A) Cross-section of early mouse forebrain (E10-13) showing the region (box) of the dorsal telencephalon enlarged in (C).
(B and C) Cell-cycle phases (B) and their relation to the nucleus position during interkinetic nuclear migration (INM) of neuroepithelial progenitors (see text for details).
(D) Proposed model for Cep120-TACCs function in the control of centrosome-microtubule interaction. The right-hand side panel is attempting to incorporate some of the most recent advance in the molecular regulation of apical polarity of neural progenitors during early mouse cortical neurogenesis. Question marks point to unresolved issues with regard to the functional relationship between several protein complexes recently involved in apical polarity of INM, including (1) Cep120-TACCs-centrosome complex and microtubules, (2) Numb-regulated adherens junctions composed of cadherins and catenins, and (3) atypical protein kinase C (aPKC)-cdc42-Par3/6 (see text for details).

uncouple the physical position of nucleus along the apico-basal axis from the length of each cell-cycle phase.

Because Cep120 has no identifiable functional domain, Xie and colleagues performed a yeast two-hybrid screen for proteins that interact with Cep120 in order to identify how it actually regulates the centrosome and ultimately INM. Among other proteins, they isolated transforming acidic coiled-coiled proteins 1-3 (TACC1-3), a conserved family of proteins known to associate with both the centrosome and microtubules and previously implicated in nuclear migration (Raff, 2002). Using cortical electroporation of shRNA directed against TACC1-3, the authors were able to phenocopy the effects of Cep120 downregulation on INM, nuclear position, and mode of division, suggesting that, in fact, Cep120 and TACCs are in the same pathway. Interestingly, shRNA-mediated depletion of TACC (or Cep120) causes defects in microtubule organization in neurons, and overexpression of both TACC and Cep120 have additive effects on the growth of microtubule asters in COS7 cells, suggesting that Cep120 and TACCs act cooperatively to regulate microtubule dynamics.

How does Cep120 regulate TACC? The authors demonstrate that TACC localization to the centrosome is dependent on the presence of Cep120 in cortical progenitors, as the deletion of Cep120 causes mislocalization of TACC. Interestingly, mislocalization of TACC by Cep120 depletion has no effect on centrosome localization or apical polarity, suggesting that TACCs and Cep120 are not acting on the apical side of the centrosome. Importantly, the authors' data show that the nucleus-to-centrosome distance is increased by downregulation of Cep120 in neural progenitors. From these data, the authors propose a model where Cep120 regulates the localization of TACC to the centrosome, thereby regulating the growth of microtubules attached to the nucleus through a poorly understood mechanism (Figure 1D).

This study presents several provocative results and therefore raises several interesting questions. First, why does forcing progenitors to undergo mitosis before they reach their apical position along the ventricle result in cell-cycle exit and differentiation of progenitors into postmitotic neurons? Interestingly, inhibition of INM has been previously shown to promote neurogenesis. Cappello et al. showed that deletion of the small GTPase cdc42 impaired INM, increased the number of mitoses occurring basally, and prematurely increased the production of neurons (Cappello et al., 2006). However, in contrast to the present study, this was not a singular defect in INM, as loss of cdc42 also resulted in loss of cell/cell adhesions and apical polarity (Cappello et al., 2006). This might suggest that the determining factor in becoming a neuron is not the apical attachment but the position of the M phase nucleus inside the neuroepithelium. This effect could be a reflection of (1) spatial cues at the apical pole of progenitors might control cell-cycle re-entry, among these catenin-cadherin cell-cell junctions recently

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shown to be regulated by Numb and cdc42 (Cappello et al., 2006; Rasin et al., 2007) (Figure 1D) and/or (2) basally located signals that instruct progenitors to exit the cell cycle and adopt a specific cell fate during the G1/S transition (McConnell and Kaznowski, 1991). This is especially interesting in the context of abventricular mitosis occurring in what defines histologically the subventricular zone (SVZ). The SVZ first appears around E13, and increases progressively during mouse cortical neurogenesis relative to the ventricular zone (VZ) (reviewed by Dehay and Kennedy, 2007). Progenitors in the SVZ tend to divide symmetrically to generate two neurons, and therefore it is tempting to hypothesize that the fact that they do not undergo mitosis apically plays an instructive role on the outcome of cell division favoring cell-cycle exit, just like Cep120 or TACCs downregulation does.

Second, at a more cell-biological level, how does the nucleus physically move during INM? One of the most interesting contributions made by Xie et al. is the proposal of a cell-biological mechanism underlying INM. While it is clear from the data presented that proteins that bind the centrosome are required to allow for proper nuclear movement, it remains to be shown exactly how these work together during INM. One potential mechanism is that microtubule motors may regulate the basal and apical migration of the nucleus during INM. In support of this idea, Lis1, which has been shown to regulate INM, associates and regulates the activity of dynein, a minus-end microtubule motor protein (Shu et al., 2004). The authors speculate that nuclear movement might be controlled bidirectionally by minus-end directed motors such as dynein or plus-end directed motors such as kinesin. A second potential mechanism is that the movement of the nucleus may simply be regulated by directed microtubule polymerization and depolymerization.

Finally, what regulates the cell-cycle progression of progenitors in the subventricular zone, which by definition, do not undergo INM? Are centrosomal proteins such as Cep120 and TACCs operating in these abventricular mitoses, or is their expression downregulated in abventricular progenitors, thereby changing the mode of division of these progenitors by favoring neurogenic divisions?

The work of Xie et al. in this issue of *Neuron* provides new ground for the exploration of the molecular mechanisms regulating INM in neural progenitors and starts to provide mechanistic insights into the function of INM in the control of the mode of division of neural progenitors.

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