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Interkinetic nuclear migration

Reciprocal activities of dynein and kinesin

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A hallmark of neurogenesis in vertebrates is the apical-basal fluctuation of radial glia nuclei. Such a phenomenon, called INM, has been known for decades and is closely associated with mitosis but still puzzles scientists. An impressive step in the molecular understanding of INM has recently been achieved by Tsai and coworkers. Using RNA interference associated with time-lapse imaging, these authors demonstrated a dual motor system that can push/pull the nuclei accordingly with the cell cycle stages.

Key words: interkinetic nuclear migration (INM), radial glial progenitor cells (RGPCs), dynein (Dyn), kinesin (Kin), neurogenesis

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Introduction

Formation of a layered structure in the developing vertebrate brain requires intense neurogenesis in the proliferative layer called ventricular zone (VZ). This neurogenesis is mediated by radial glial progenitor cells (RGPCs) whose nuclei demonstrate a cell cycle dependent movement termed interkinetic nuclear migration (INM): during mitosis the nuclei stay at the apical surface of the VZ, at G_1 phase they move to the basal side, where they undergo S phase, and then return back to the ventricular surface during G_2 phase (**Fig. 1**).

Although the first histological studies predicting INM date back to 1935,[1] until recently its underlying mechanisms were poorly understood. Studies with pharmacological inhibitors suggest that actin and microtubule (MT) cytoskeleton may be involved in INM.[2,3] One possible explanation for this is that RGPCs nuclei are transported along MTs by motor proteins, like dynein (Dyn).[4,5] Evidence for this comes from two recent works showing that a minus end-directed MT-associated Dyn/dynactin motor protein complex is implicated into the INM.[6,7] The first work[6] demonstrates that the reduction of Dyn-regulating protein Lis1 levels blocks INM, while the second[7] shows that mutations in dynactin-1 lead to perturbed INM and mitoses throughout the VZ. However, these studies do not exclude the possibility that other cytoskeletal components also influence INM. Alternatively, actomyosin networks that generate forces in many different cellular contexts might also be involved in INM.[8,9]

The recent work by Tsai et al.[10] provides a detailed analysis of INM. Using live imaging of nuclei, centrosomes and MTs in embryonic rat brain slices, coupled with RNA interference (RNAi) and the myosin inhibitor blebbistatin, the researchers described INM and the MT organization in RGPCs and evaluated the contribution of MT- and actin-based motors to INM, identifying its unusual mechanism.

Live Imaging Reveals INM Mechanisms

For live imaging, the authors used in utero electroporation to express cyan fluorescent histone 1 to tag the oscillating nuclei along with green fluorescent protein (GFP), while MTs were labeled by either GFP-tubulin or GFP-EB3, which tags growing MT plus-ends. The authors revealed an unusual nuclear behavior during INM: the basal-to-apical movement was fast, but discontinuous in time, while movement in the opposite direction was slow and steady. Moreover, INM was found to be independent of centrosomes (by direct monitoring of a centrosomal protein

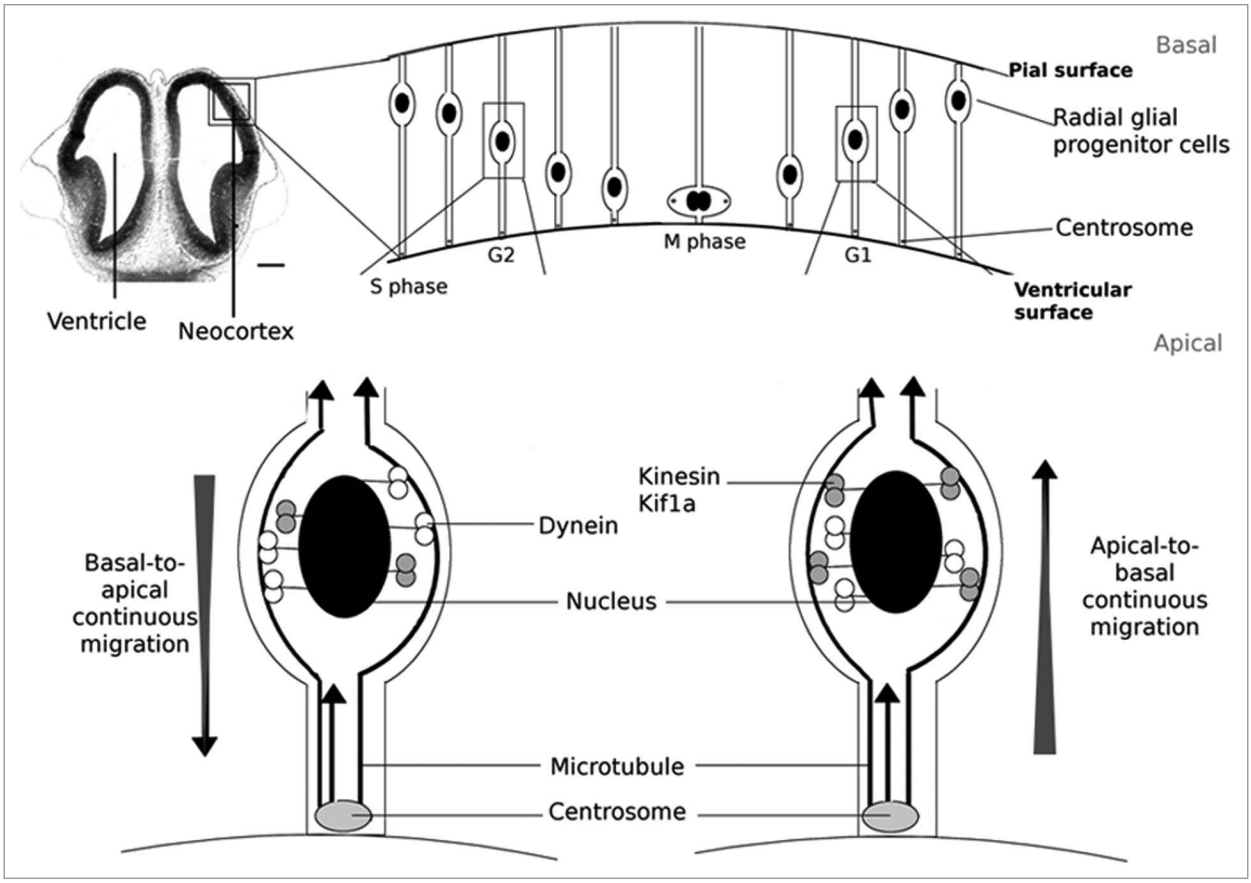

Figure 1. Molecular mechanisms of INM. Position of the RGPC's nucleus in the VZ depends on the phase of the cell cycle. The nucleus stays at the pial surface until the end of the S phase. During the G_2 phase Dyn transport the nucleus along uniformly directed microtubules toward the ventricular surface, where it undergoes mitosis (M phase). This nuclear movement is fast, but intermittent. After mitosis, at the G_1 phase the nucleus is driven back to the pial surface by Kin. Unlike basal-to-apical INM, apical-to-basal nuclear translocation is slower, but continuous in time. The centrosomes remain at the ventricular surface during the whole cycle.

DsRed-centrin II) and occur along uniformly oriented MTs spanning the entire length of the RGPCs. By complete and partial RNA-mediated inhibition of Dyn, the researchers confirmed that apically but not basally directed INM is mediated by this motor protein. Then, by RNAi screen of 36 plus end-directed kinesins (Kin), the authors revealed that KIF1A, a member of the Kin-3 family, is essential for basally directed INM but not for mitosis or migration of newly generated neurons, identifying it as a key basal nuclear transport motor. Unlike others,[8,9] the researchers did not see any effect of myosin II inhibition neither by RNAi nor by blebbistatin.

INM: Underlying Mechanisms and Functional Significance

Together the results suggest that INM is powered by oppositely directed motor proteins (Dyn and Kin) that transport the nuclei in RGPCs along uniformly directed MTs toward and away from the centrosome in a cell cycle-dependent manner (**Fig. 1**). The lack of effect of myosin inhibition on INM contradicts some previous findings,[8,9] but this discrepancy could be explained by differences in the studied species (fish vs. rodents) and tissues (retina vs. cortex) or analysis technologies.

The presented model implies that motor proteins act from the nuclear surface and INM requires factors that anchor them to the nucleus. It was shown that KASH proteins Syne-2/nesprin-2, which mediate the interactions between the nucleus and the cytoskeleton, interact with both Kin and Dyn and play essential role in INM.[11] Dyn is also bounded to the nucleus by adaptors like Lis1 and NUDEL.[12] However, the mechanism of INM deserves further investigation. We still don't know the molecular pathway that regulates Dyn and Kin activity, but as INM is cell cycle-dependent the signal may come from the cell itself. Beyond Kif1a, other screened kinesins also affected neuronal redistribution orienting future research on their role in neurogenesis.

Furthermore, a controversy still exists regarding the type of mechanisms that push/pull nuclei in phase with the cell cycle stage. Indeed recent reports in reference 13 by Kosodo et al. suggest that both active and passive movements coexist during INM. Using magnetic fluorescent microbeads coupled to state of the art imaging technology, they identified the microtubule-nucleating/binding Tpx2 protein as a candidate for basal-to-apical migration of G_2-phase nuclei. In addition these authors develop a computational model that identifies the nuclear displacement by apically migrating G_2-phase

nuclei as the main driving force for basal migration during G_1-phase, while the opposite nuclear migration in G_1-phase remained a non-autonomous passive process, corroborating their observation of a specific apical accumulation of nuclei in G_1-phase of the progenitor cells overexpressing $p18^{Ink4c}$, one of the four members of the cycline-dependent kinase inhibitors (Ink).

Another important issue is the functional significance of INM. The main theory is that INM is required for cell cycle progression in a limited space, improving proliferation rate and resulting in the epithelium's pseudostratified appearance.[5] Efficient space allocation might be mediated by the synchronization of the INM. Indeed, evidence shows that gap-junctions between RGPCs mediate calcium transients and ATP release which help to synchronize apically directed INM between adjacent cells.[14] Synchrony also has its place in regulating the duration and the level of exposure of progenitor nuclei to neurogenic signals,[7] possibly shaping the well described wavefronts of the migrating neurons populating the cortical layers.[15] Similarily, INM may be an important mechanism by which MT-regulating proteins maintain the neural progenitor pool during neocortical development.[4] Failures in the synchronization or alterations in the INM duration may severely affect neurogenesis leading to developmental defects and diseases, such as lissencephaly.[6,16] Thereby, the role of INM in the development is of exceptional importance and future studies of it are likely to shed more light on the understanding of corticogenesis.

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