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Review

Nuclear migration in mammalian brain development

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ABSTRACT

During development of the mammalian brain, neural stem cells divide and give rise to adult stem cells, glia and neurons, which migrate to their final locations. Nuclear migration is an important feature of neural stem cell (radial glia progenitor) proliferation and subsequent postmitotic neuronal migration. Defects in nuclear migration contribute to severe neurodevelopmental disorders such as microcephaly and lissencephaly. In this review, we address the cellular and molecular mechanisms responsible for nuclear migration during the radial glia cell cycle and postmitotic neuronal migration, with a particular focus on the role of molecular motors and cytoskeleton dynamics in regulating nuclear behavior.

Contents

Abbreviations: NE, nuclear envelope; RGP, radial glia progenitor; INM, interkinetic nuclear migration; oRGC, outer radial glia cell; MST, mitotic somal translocation.

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1. Introduction

Mammalian central nervous system development is a complex process requiring extensive nuclear movement and cell migration. During embryogenesis the neural plate, which is the precursor to the mammalian brain, folds to give rise to the neural tube, consisting of a pseudostratified neuroepithelium with stem-like properties [1]. The neuroepithelial cells are highly elongated and have a bipolar morphology, with the two processes spanning the distance between the pial and the ventricular surfaces of the cerebral neocortex [2,3]. In these cells the nucleus moves between the apical and basal surfaces of the neural tube. As brain development progresses, the basal process of the progenitor cells elongates, and the cells are now referred to as radial glial progenitors (RGPs). The nucleus of both the neuroepithelial and RGP cells exhibits an unusual form of cell cycle-dependent oscillatory behavior known as interkinetic nuclear migration (INM). Following mitosis at the ventricular surface, during G1 the nucleus migrates "basally" toward the subventricular zone. The RGP cell undergoes S-phase, and then the nucleus migrates "apically" during G2 to return to the lumen of the neural tube or, subsequently in development, the ventricular surface for the next mitotic division (Fig. 1 and Supplemental movie 1) [4,5].

The RGPs persist during most of cortical development, and have stem-like properties: they can divide either symmetrically, giving rise to new RGPs, or asymmetrically, generating intermediate progenitors or postmitotic neurons [3]. Intermediate progenitors do not exhibit INM nor have elongated processes, and reside in the subventricular zone, ultimately dividing to form two postmitotic neurons [6,7]. These cells then migrate toward the pial surface of the cortical plate, as discussed for postmitotic neurons in general below.

Nuclear migration during either neurogenesis or subsequent postmitotic neuronal migration is controlled by the cytoskeleton and involves the centrosome directly or indirectly. In this review, we discuss our current understanding of the cellular and molecular mechanisms that govern nuclear and centrosomal behavior in mammalian neuronal cells, with an emphasis on molecular motors and their regulatory factors and cargo adaptors.

2. Interkinetic nuclear migration in radial glial progenitors

Throughout the cell cycle the RGP nucleus exhibits an unusual form of oscillatory behavior, referred to as INM. Once the basal process has begun to elongate dramatically, nuclear migration distance of the RGP cell is limited to the ventricular zone. Mitosis is restricted to the ventricular surface, after which the nucleus moves basally. S-phase is thought to occur when the nucleus is away from the ventricle. Then, during G2 the nucleus returns apically to the ventricular surface where a new mitotic event takes place (Fig. 1 and Supplemental movie 1) [4,5].

Although the phenomenon of INM had been known for a long time [8–10], its developmental purpose and underlying mechanisms remained unknown. Live imaging analysis of INM in organotypic brain slice culture began to reveal the bidirectional behavior of individual RGP nuclei in detail [11–13]. Apical migration was found to be relatively fast though intermittent ($0.14 \pm 0.02\ \mu m\ min^{-1}$ with pauses of 0.5–2 h and bursts of up to $1\ \mu m\ min^{-1}$) [13]. Basal migration was much slower ($0.063 \pm 0.009\ \mu m\ min^{-1}$) but continuous [13,14], making it more difficult to characterize (Fig. 1b and Supplemental movie 1). Such different kinetics suggested the possibility of distinct motor-based mechanisms controlling the apical versus basal movement. Importantly, in each case, once initiated, nuclear migration was unidirectional.

2.1. Organization of microtubule cytoskeleton during INM

In view of evidence that microtubules might be involved in INM [15,16], it seemed important to test the orientation of microtubules in the RGP cells. This was accomplished by expressing the microtubule-plus end tracking protein EB3, which associates predominantly with the growing microtubule end. Strikingly, microtubules were observed to be largely unidirectional in the RGP cells, with 93% showing their plus ends to be oriented basally (Fig. 1a) [13]. Thus, if nuclei were freely moving, directly along the microtubules, apical migration toward the centrosome would be expected to require cytoplasmic dynein, a minus end-directed motor protein, and basal migration a plus end-directed motor protein, perhaps one of the many kinesins.

In RGPs the restricted localization of the centrosome to the apical end of the cell also suggested that nuclei might migrate along microtubules under their own power, rather than being pulled along by the microtubule cytoskeleton

The centrosome remained exclusively associated with the apical end of the RGP throughout the cell cycle (Fig. 1a) [5,13]. The RGP nucleus departed from the centrosome during G1, and its entire excursion away from and back to the ventricular surface was virtually centrosome-independent.

2.2. Role of microtubule motor proteins during INM

The first direct evidence of a role for microtubule motor proteins in INM came from analysis of the effects of Lis1 RNAi in rat embryonic brain [15]. LIS1 is responsible for classic lissencephaly (smooth brain), a severe brain developmental disease [17]. It is also a key regulator of the microtubule minus-end directed molecular motor cytoplasmic dynein [18–21]. LIS1 had been speculated to participate in neuronal migration, to account for the more-or-less normal brain mass, but altered cortical lamination, of lissencephaly patients [17]. *In utero* electroporation of Lis1 shRNAs into embryonic rat brain revealed, in fact, a near complete arrest of postmitotic neuronal migration in rat embryonic brain [15]. In addition, it completely blocked INM in the RGP cells. These results suggested that Lis1 and, by extension, cytoplasmic dynein might be involved in INM, which was directly confirmed by later studies [5,13]. Indeed, *In utero* electroporation of rat embryonic brain with shRNA against dynein heavy chain abolished apical migration, though basal migration could still be detected [13].

Evidence for a role of motor proteins in INM was also reported in zebrafish retina, in which mutation or altered expression of $p150^{Glued}$, a component of the dynein regulatory complex dynactin, altered both basal and apical INM [22].

Despite evidence for a dynactin role in zebrafish basal INM, the orientation of microtubules in rat RGPs suggested a role for a microtubule plus end-directed motor, i.e., a kinesin, in basal INM. To test this possibility 11 rat plus end-directed kinesin heavy chains were screened for this role. Although several kinesins were found to contribute to over-all neuronal distribution, basal INM was specifically inhibited by knockdown of the kinesin 3 Kif1a [13]. An important consequence of this effect was accumulation of the nuclei near the ventricular surface, causing newborn nuclei to persist at the ventricular surface following mitosis [13]. Surprisingly, there was little effect on cell cycle progression, as judged by staining with cell cycle-specific markers. Live imaging of mitotic progression revealed that the inhibited RGP cells continued to divide [23]. Finally, the ratio of asymmetric to symmetric mitotic divisions was clearly reduced by Kif1a knockdown, leading to an increase in the ratio of progenitor cells to neurons. Furthermore, the orientation of the cytokinetic cleavage plane was remarkably shifted from horizontal to vertical, suggesting a role for Kif1a in mitotic spindle orientation [23], though this remains to be tested directly.

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