BIOCELL
2022 46(11): 2357-2361

Tech Science Press

Possible mechanisms of bidirectional nuclear transport during neuronal migration

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Key words: Nesprin-2, Nucleus, Microtubules, Kinesin, Dynein

Abstract: Neuronal migration is a fundamental process of mammalian brain development. In migrating neurons, the nuclear membrane protein Nesprin-2 has been shown to serve as an adaptor to pull the nucleus along microtubule tracks. Current evidence has shown that Nesprin-2 binds to both the minus-end-directed motor dynein as well as the plus-end-directed motor kinesin. However, translocation of neuronal nucleus has long been thought to be primarily driven by dynein motors. Intriguing questions could be raised about the role of kinesin in nuclear transport and how the activities of opposing motors are coordinated through interactions with Nesprin. Combining evidence from recent studies, we propose that Nesprin-2 serves as a switchboard in mediating bidirectional neuronal nuclear movements.

Main Text

The positioning of cell nucleus is essential in many developmental events, including the multinucleated arrangement in myoblast syncytium, apicobasal polarization of epithelial cells in the cochlea, and pronuclear migration in fertilized zygotes (Bone and Starr, 2016; Gundersen and Worman, 2013). Especially in highly polarized cells like neurons, nuclear movements and positioning are tightly aligned with developmental stages and cellular functions. One important example is the interkinetic nuclear migration of neuroepithelial progenitor cells, where the apicobasal movements of the nucleus is coupled with the cell division cycle to produce neurons and glia in the brain (Bertipaglia *et al.*, 2018; Taverna and Huttner, 2010). Following neurogenesis, the migration of post-mitotic neurons during the formation of the laminated cortex also requires active nuclear movements (Nakazawa and Kengaku, 2020; Tsai *et al.*, 2007). Here we focus our discussion on how nuclear movements are regulated in mammalian neuronal migration, which would hopefully provide new insights into nucleocytoskeletal interactions under normal and pathological conditions in different tissue types.

The forward translocation of the cell nucleus is a critical step of neuronal migration, which was first described in detail by Rakic (1972) in the developing cerebral cortex. Pioneering studies using the cerebellar granule cells identified perinuclear microtubule network which connects to microtubule bundles in the leading process, and proposed the preliminary hypothesis that the polarized microtubules may create forces for nuclear displacement (Fig. 1) (Rivas and Hatten, 1995; Rakic *et al.*, 1996). Breakthrough was made by the discovery of the causal genes for type I lissencephaly, a heterogeneous group of disorders of cortical formation caused by abnormal neuronal migration. LIS1 (official symbol PAFAH1B1, for platelet-activating factor acetylhydrolase isoform 1b regulatory subunit 1) was identified as a causal gene product, which binds to the motor domain of cytoplasmic dynein and regulates dynein-dependent transport of the nucleus along intracellular microtubule tracks (Hirotsune *et al.*, 1998; Tanaka *et al.*, 2004; Shu *et al.*, 2004). Later, more dynein-related mutations that lead to neuronal migration defects were identified, contributing to the common view that the cytoplasmic dynein complex (dynein hereafter) drives forward nuclear translocation in neurons (Ayala *et al.*, 2007; Tsai and Gleeson, 2005). Since dynein transports cargoes towards microtubule minus ends, it is in line with the observation that most peri-nuclear microtubules have their minus ends pointing forward (Fig. 1) (Tsai *et al.*, 2007). Nonetheless, recent studies further revealed that perinuclear microtubules are of mixed polarity and that KIF5, the microtubule plus-end-driven kinesin-1 motor, is also involved in facilitating neuronal nuclear translocation during cerebellar granule cell migration (Umeshima *et al.*, 2007; Wu *et al.*, 2018). Due to the opposite nature of dynein

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Received: 05 January 2022; Accepted: 18 April 2022

Doi: 10.32604/biocell.2022.021050

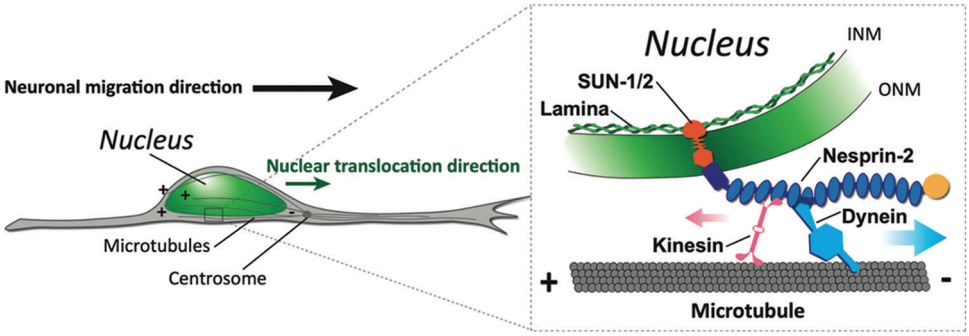

FIGURE 1. The forward translocation of nucleus during neuronal migration is driven by microtubule motors via LINC complex. In migrating neurons, the cell nucleus is transported along migration direction towards the minus ends of perinuclear microtubules which are embedded in the centrosome in front (left). The LINC complex of INM (inner nuclear membrane)-locating SUN proteins and ONM (outer nuclear membrane)-locating Nesprin-2 mediates recruitment of kinesin and dynein motors onto nuclear envelope (right).

and kinesin motilities on microtubules, a consensus has not been reached on the role of kinesin in driving nuclear movements (Kengaku, 2018). In the case of bidirectional interkinetic nuclear migration of neuroepithelial cells, kinesin-3 motor KIF1A and dynein are responsible for basal (away from centrosome) and apical (towards centrosome) nuclear movements, respectively, at distinct cell cycle stages (Tsai *et al.*, 2010). However, in the case of one-way nuclear translocation of migrating neurons, novel mechanisms need to be proposed to explain the biological significance of kinesin involvement.

Meanwhile, increasing evidence suggests that the LINC complex (Linker of Nucleoskeleton and Cytoskeleton) acts as a key mediator in nuclear transport driven by microtubule motors. The LINC complex is composed of SUN proteins located on the inner nuclear membrane which interact with Lamin A/C of the nuclear lamina and KASH (Klarsicht/ANC-1/Syne Homology) family proteins traversing the outer nuclear membrane (Fig. 1). The binding between SUN and KASH domains anchors the C-terminus of KASH protein to the nuclear envelope while its gigantic N-terminus extends out to the cytoplasm, providing a scaffold for interactions with cytoskeletons (Starr and Fridolfsson, 2010; Friedl *et al.*, 2011; Rajgor and Shanahan, 2013). KASH proteins in vertebrates are known as nesprins, for nuclear envelope spectrin repeat protein (Zhang *et al.*, 2001). Human nesprin mutations defective in nucleus-cytoskeleton coupling are associated with muscular, neurological, pre-mature aging diseases and cancer in human (Zhang *et al.*, 2007; Attali *et al.*, 2009; Young *et al.*, 2021; Gros-Louis *et al.*, 2007; Kandert *et al.*, 2007; Dawe *et al.*, 2009; Doherty *et al.*, 2010; Östlund *et al.*, 2019; Bone and Starr, 2016). Among the nesprin family, Nesprin-2 has been shown to recruit both dynein and KIF5 motors onto the nucleus during neuronal migration in the developing mouse brain (Zhang *et al.*, 2009). While the kinesin-binding motif has been identified to be the LEWD sequence near the C-terminus of the cytoplasmic stretch, the dynein-binding regions are still unclear (Wilson and Holzbaur, 2015). Zhu *et al.* (2017) have presented the initial evidence that the dynein and/or dynactin-binding sites are within a region in close proximity to the LEWD motif, followed by another study reporting that the same region also recruits BICD2, a key component of dynein/dynactin complex (Gonçalves *et al.*, 2020).

Although the recruitment of both dynein and kinesin by Nesprin-2 is evident, the mechanism of motor activation remains unknown. In addition to serving merely as a docking site for motor recruitment, spectrin repeats in the cytoplasmic stretch of Nesprin-2 might also play regulatory roles by adopting conformational transformations or post-translational modifications upon interactions with cytoskeletal or signaling molecules (Djinovic-Carugo *et al.*, 2002). One possibility is that Nesprin-2 acts as a molecular switch to selectively turn on/off the activities of dynein and kinesin in response to spatiotemporal cues. Another possibility is that Nesprin-2 mediates new modes of cooperation between dynein and kinesin while both motors are simultaneously attached and active. In fact, continuous progress has been made to characterize the coordinating roles of adaptor or scaffolding proteins which link dynein and kinesin simultaneously to specific intracellular organelles or vesicles (Olenick and Holzbaur, 2019; Fu and Holzbaur, 2014). For instance, phosphorylation/dephosphorylation of HAP-1 (Huntingtin-associated protein 1, a motor-adaptor protein for neuronal intracellular vesicles) can enhance or lessen recruitment of the kinesin-1 light chain in competition with dynein, which determines the direction of cargo transport (Colin *et al.*, 2008). Likewise, TRAK1/2 proteins (the adaptors responsible for mitochondria trafficking) are capable of recruiting both dynactin p150 and KIF5 to generate bidirectional cargo movements along microtubules, but their association with KIF5 can be downregulated when TRAK proteins adopt a head-to-tail folded structure (van Spronsen *et al.*, 2013). Another bidirectional adaptor protein HOOK3 forms a complex with dynein/dynactin and KIF1C, which can adjust the frequency of plus-end-directed runs depending on the local concentration of KIF1C motors (Kendrick *et al.*, 2019). Although the large size and complexity of Nesprin-2 make it challenging to fully understand its functional interactions with motors, Nesprin-2 shares some similarities with those characterized bidirectional adaptors, including the extended coiled-coil structures and physical proximity between kinesin and dynein binding motifs. Therefore, it is tempting to speculate that Nesprin-2 might function not only as a physical linker, but also a coordinating moderator between opposing microtubule motors.

By forming an integrated complex with motors and motor accessory proteins, cargo adaptors may also acquire

new motility properties rather than a simple stochastic combination of motor activities (Elshenawy *et al.*, 2019; Mckenney *et al.*, 2014). It is particularly interesting to find out whether kinesin plays an inhibitory, subsidiary, or assistive role with dynein in neuronal nuclear translocation. There are different theories about the function of kinesin in dynein-dominating cargo transport (Fig. 2):

1. *Brake control*: by interfering kinesin function in migrating cerebral neurons, Gonçalves *et al.* (2020) showed that nuclear translocation and neuronal migration were accelerated, implying that kinesin restrains forward nuclear movements while dynein moves it forward.
2. *Increase flexibility*: studies in myotubes demonstrated that kinesin generates dynamic nuclear rotation and backward stepping of the nucleus, which may help to untangle the nucleus from roadblock and to enable smooth transport through crowded cytoplasm and to finetune its correct positioning (Wilson and Holzbaur, 2012). In migrating cerebellar granule cells, downregulation of kinesin activities has been shown to decrease nuclear rotation and impede cell migration (Wu *et al.*, 2018).
3. *Microtubule tethering*: kinesin may also help with cargo attachment onto microtubules to facilitate dynein-mediated transport. The mitochondria adaptor protein TRAK2 has been shown to have a higher affinity to microtubule tracks when kinesin is also present, which, in turn, enables a higher frequency of active dynein-driven movements (Fenton *et al.*, 2021).
4. *Mechanical activation*: some evidence from *in vitro* studies suggested that the presence of opposite pulling force by kinesin enhances dynein stalling force, which resembles a catch-bond mechanism (reviwed in Hancock, 2014).
5. *Steric disinhibition or hinderance*: conformational changes could occur when kinesin and dynein bind to cargo adaptors (Hancock, 2014). It should be noted that these hypothesized models are not mutually exclusive and multiple mechanisms might be applied to dictate how nuclear transport is achieved coordinately by opposing motors.

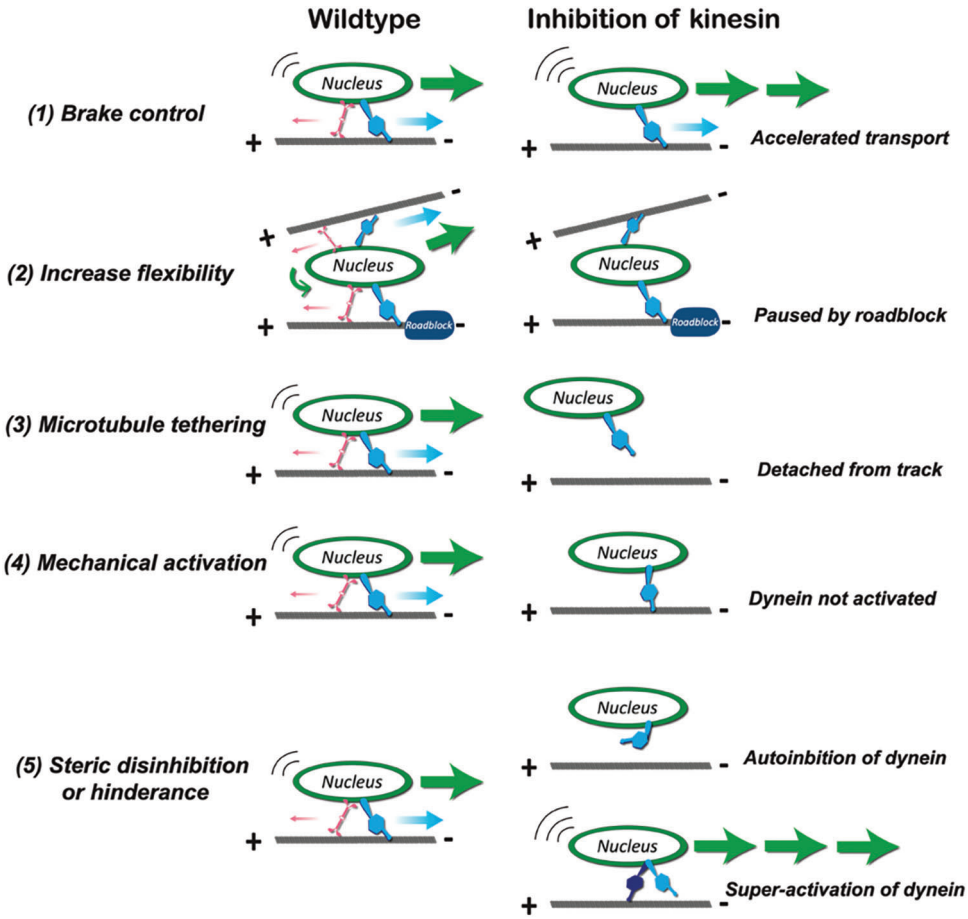

FIGURE 2. The hypothesized roles of kinesin in dynein-dominating nuclear transport. (1) When functioning as brake control, kinesin competes with dynein. Under kinesin inhibition, nucleus moves faster towards microtubule minus ends due to the absence of opposite forces. (2) When functioning to increase flexibility of transport, kinesin generates nuclear rotation and backward stepping to overcome roadblocks or to switch to another microtubule track. Under kinesin inhibition, nuclear movement is impeded by roadblocks or crowded intracellular environment. (3) When functioning to tether nucleus to microtubule tracks, kinesin enhances attachment between dynein-bound nucleus to microtubules. Under kinesin inhibition, nucleus detaches from tracks and fails to be transported. (4) When functioning as mechanical activator, the opposite stalling forces generated by kinesin activates dynein activities. Under kinesin inhibition, dynein motor is not activated, and nuclear transport is suppressed. (5) When functioning as steric disinhibition or hinderance effector, the presence of kinesin either relieves auto-inhibition or suppress super-activation of dynein. Under kinesin inhibition, dynein remains at auto-inhibited state or resumes to super-activated conformation (Adapted from Hancock, 2014).

To test the hypothesized mechanisms of nesprin-mediated nuclear transport, complex intracellular environment and multiple players should be considered. Kinetics of neuronal migration show great diversity depending on neuronal types and trajectories. This may be caused by diverse roles of kinesin in different cell types and stages with different microtubule arrangement, types of microtubule-associated proteins, and post-translational modifications of tubulin. In addition, depending on the distinct properties of dynein and kinesin, including processivity, detachment rate and stalling force, they probably behave differently under intracellular environment with highly polarized parallel microtubule assemblies, or a more mixed-oriented microtubule tracks with frequent intersections. Moreover, the availability of dynein regulators, including LIS1, NDE1/NDEL1 and BICD2 also affects transport. Combinatorial approach with molecular biophysics, high temporospatial imaging, and structural analysis of macromolecular protein complex will be required to reveal detailed motor dynamics regulated by nesprins in various neuronal migration, including radial migration of excitatory neurons and tangential migration of interneurons in the telencephalon.

In summary, we think that Nesprin-2 acts as the core adaptor protein of a complex with kinesin and dynein motors to facilitate nuclear translocation during neuronal migration. Understanding the mediator function of Nesprin-2 could be a promising direction leading to mechanistic understanding of neuronal migration.

Author Contribution: Both authors contributed to conceptualizing, researching, writing, and editing the manuscript.

Funding Statement: This work was supported by KAKENHI grant from the Japan Society for the Promotion of Science (JSPS) to MK (20H00483). CZ was supported by the Otsuka Toshimi Scholarship Foundation.

Conflicts of Interest: The authors declare no conflicts of interest.

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