# Dynamic Interaction Between Microtubules and the Nucleus Regulates Nuclear Movement During Neuronal Migration

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**ABSTRACT:** Fine structures of the mammalian brain are formed by neuronal migration during development. Newborn neurons migrate long distances from the germinal zone to individual sites of function by squeezing their largest cargo, the nucleus, through the crowded neural tissue. Nuclear translocation is thought to be orchestrated by microtubules, actin, and their associated motor proteins, dynein and myosin. However, where and how the cytoskeletal forces are converted to actual nuclear movement remains unclear. Using high-resolution confocal imaging of live migrating neurons, we demonstrated that microtubule-dependent forces are directly applied to the nucleus via the linker of nucleoskeleton and cytoskeleton complex, and that they induce dynamic nuclear movement, including translocation, rotation, and local peaking. Microtubules bind to small points on the nuclear envelope via the minus- and plus-oriented motor proteins, dynein and kinesin-1, and generate a point force independent of the actin-dependent force. Dynamic binding of microtubule motors might cause a continuously changing net force vector acting on the nucleus and results in a stochastic and inconsistent movement of the nucleus, which are seen in crowded neural tissues.

**KEYWORDS:** Neuronal migration, nucleus, microtubules

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Neuronal migration is an essential step of mammalian brain development. Because neural stem cells are distributed only in the germinal zones in limited regions of the brain, newborn neurons need to migrate to their final destination in the cortex or nucleus to form correct neuronal networks. Impairment of neuronal migration thus causes brain malformation and neurological disorders.[1,2] Neurons typically migrate by repeating 2 distinct steps. They first extend a long leading process tipped with a growth cone that directs the migration. Next, the nucleus in the cell soma is translocated into the process. It has been shown that these steps are independently regulated in some neurons.[3]

The nucleus is the largest cargo in the neuron, and therefore some force is required for its transport. It has been demonstrated that the actin and microtubule cytoskeletons are involved in the regulation of nuclear translocation. Actomyosin is found to accumulate in either the proximal leading process or rear of the cell soma depending on the cell type, and local inactivation by drug treatment or laser ablation has demonstrated that the contractile tension of actomyosin is converted to a pulling or pushing force to the nucleus.[4-9] Microtubules have been shown to emanate from the leading process, where the centrosome is typically positioned, with the plus ends toward the cell soma. These microtubules are thought to associate with the nucleus and work as rails on which the cytoplasmic dynein motor carries the nucleus into the leading process by its minus end–directed motor activity.[5,10-13] The linker of nucleoskeleton and cytoskeleton (LINC) complex mediates the interaction between the nucleus and cytoskeletons because its loss or inhibition results in the failure of neuronal migration.[14,15] However, it should also be noted that the force generated by the cytoskeletons does not always directly act on the nucleus; it has been reported that actomyosin regulates the position of the centrosome by interacting with microtubules in the leading process.[6,16] Other reports have also demonstrated that microtubule sliding in the leading process is implicated in nuclear translocation.[17] Differences in model systems as well as invasiveness of pharmacologic perturbation and laser ablation approaches also partly contribute to the ambiguity of general conclusions. Thus, the interplay between actin, microtubules, and the nucleus is not fully clarified, and the precise driving force for nuclear translocation remains to be elucidated.

To better understand the dynamics of the nucleus and associated cytoskeletons in intact condition, we have adopted spinning-disk confocal microscopy for live imaging of migrating cerebellar granule cells at a high spatiotemporal resolution.[18] We have recently identified nuclear rotation, a yet uncharacterized motion of the nucleus during neuronal migration, by labeling heterochromatin spots with fluorophore-tagged HP1β instead of the nuclear localization signal, which diffuses throughout the nucleoplasm. In migrating neurons, the nucleus exhibits highly dynamic motion, including intermittent translocation, frequent rotation, and transient deformation. These phenomena are observed in cerebellar granule cells migrating

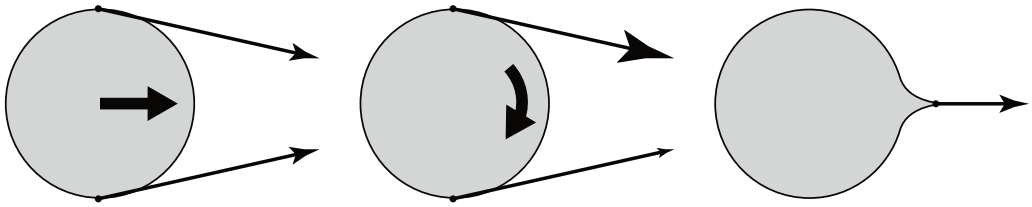

**Figure 1.** When multiple forces act on the ball, the resultant movement is determined by the direction and strength of the net force. Balanced forces and unbalanced forces acting on the ball induce translocation and rotation, respectively.

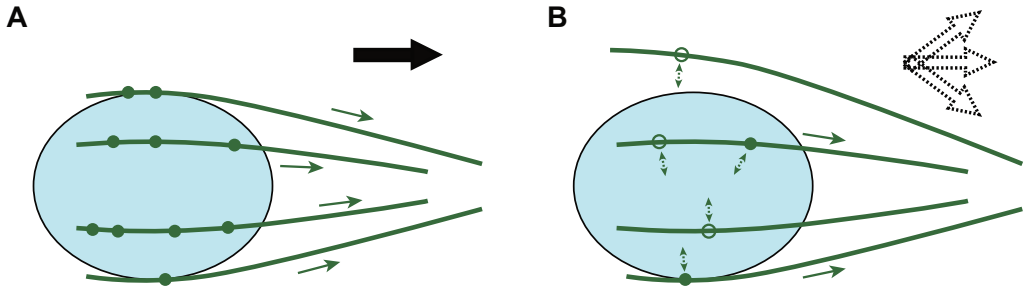


**Figure 2.** The interaction between microtubules and the nucleus. (A) The microtubules stably interact with the nucleus along multiple points, where force is generated locally. Thus, the net force is consistent and similarly directed. (B) Individual microtubules continuously attach and detach to the nucleus. A transient force is generated at each interaction point and thus the net force vector changes over time.

on a flat surface in in vitro cultures as well as in organotypic brain slice cultures. The nuclei of postmigratory neurons stay still and do not show any of these motions, indicating that these nuclear dynamics are driven by forces generated in neurons in the migratory stage. The granule cell nucleus exhibits stepwise movement composed of moving and resting phases, like many other neurons.[4,19,20] Nuclear rotation is often observed in the resting phases, suggesting that migrating neurons generate and transmit force to the nucleus even with no apparent nuclear translocation. In addition, we occasionally noticed a sharp deformation at the nuclear front that persisted for only a few minutes. Such peaking suggested a pulling force acting locally at small points on the nucleus. We have thus analyzed these nuclear dynamics as readouts of the properties of the forces applied to the nucleus during neuronal migration.

We envision a simple physical model comprising a large soft ball (nucleus) associated by multiple wires (cytoskeletal components) (Figure 1). When multiple forces generated by individual cytoskeletal components act on the nucleus, the resultant nuclear movement will be determined by the vector of the net force. The nucleus will undergo translocation if the net force acts on the center of mass, or else a torque will be generated and cause rotational motion. Furthermore, deformation will be induced if the nucleus is soft, and its elasticity will return the nucleus to its original shape when the force is released.

An interesting feature of the nuclear dynamics we can observe during neuronal migration is its inconsistency; the translocation occurs only intermittently, the rotation frequently changes its axis, and the nuclear shape is not always consistent. This suggests that the force acting on the nucleus changes dynamically over time. The force vector may even instantly reverse, as we have occasionally observed short-step rearward nuclear translocation and sharp nuclear peaking on the rear side.

We have demonstrated that nuclear rotation requires microtubule-dependent forces generated by dynein and kinesin-1 bound to the LINC complex. Consistently, some perinuclear microtubules labeled with green fluorescent protein–conjugated doublecortin appeared to closely associate with the nucleus and moved with the same direction and speed as the nuclear rotation. Each microtubule followed the nuclear rotation only transiently and then started to move independent of the nuclear movement. These observations support the idea that each microtubule does not continuously bind to the nucleus, but instead transiently attaches and detaches. Such dynamic interaction may underlie the inconsistency of the force applied to the nucleus.

In the classic view, microtubules are thought to stably bind to multiple points along the surface of the nucleus (Figure 2A). Assuming that the force generation among individual microtubules is not largely unbalanced, the net force applied to the nucleus would be constant and unbiased. Here, the nucleus would be transported in one direction without showing recurrent rotational motion. We instead propose a novel view of the microtubule-based regulation of nuclear movement. Each motor protein produces a point force directed toward the front or rear, depending on their directionality and the microtubule polarity. Thus, the erratic and transient binding of motor proteins to the LINC complex and microtubules results in a continuously changing vector of the net force, leading to movements of the nucleus such as translocation, rotation, and deformation (Figure 2B). It is also possible that the movement of the nucleus

could alter the interaction among the nucleus, motor proteins, and microtubules, by changing the relative positions of these components. In such a dynamic state, nuclear translocation is driven when cytoskeletal components and the nucleus stochastically adopt a suitable conformation to generate a forward force. However, these microtubule-based directional forces may not be sufficient to allow the nucleus to move into the narrow leading process, which has a diameter several folds smaller than the nucleus. Although our data negate the involvement of actomyosin in generation of the point forces driving the rotation of the nucleus or formation of the sharp nuclear peak, its strong contractile force may still contribute to nuclear movement coordinately with microtubules.

Considering neurons navigate through tissues crowded with many other cells and extracellular components, a force fixed toward a single direction may not always be desirable. Once migration is disturbed by some obstacle on the path, a force generated only to achieve smooth translocation may not be helpful for the neuron in this situation. Dynamic interactions among the nucleus and cytoskeletons and generation of an inconsistent force may appear to be an inefficient mechanism, but may be favorable in crowded environments.

## Author Contributions

YKW and MK wrote the manuscript.

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## REFERENCES


1. Manzini MC, Walsh CA. What disorders of cortical development tell us about the cortex: one plus one does not always make two. *Curr Opin Genet Dev*. 2011;21:333–339.
2. Moon HM, Wynshaw-Boris A. Cytoskeleton in action: lissencephaly, a neuronal migration disorder. *Wiley Interdiscip Rev Dev Biol*. 2013;2:229–245.
3. Tsai LH, Gleeson JG. Nucleokinesis in neuronal migration. *Neuron*. 2005;46:383–388.
4. Bellion A, Baudoin JP, Alvarez C, Bornens M, Métin C. Nucleokinesis in tangentially migrating neurons comprises two alternating phases: forward migration of the Golgi/centrosome associated with centrosome splitting and myosin contraction at the rear. *J Neurosci*. 2005;25:5691–5699.
5. Schaar BT, McConnell SK. Cytoskeletal coordination during neuronal migration. *Proc Natl Acad Sci U S A*. 2005;102:13652–13657.
6. Solecki DJ, Trivedi N, Govek EE, Kerekes RA, Gleason SS, Hatten ME. Myosin II motors and F-actin dynamics drive the coordinated movement of the centrosome and soma during CNS glial-guided neuronal migration. *Neuron*. 2009;63:63–80.
7. Martini FJ, Valdeolmillos M. Actomyosin contraction at the cell rear drives nuclear translocation in migrating cortical interneurons. *J Neurosci*. 2010;30:8660–8670.
8. Jiang J, Zhang ZH, Yuan XB, Poo MM. Spatiotemporal dynamics of traction forces show three contraction centers in migratory neurons. *J Cell Biol*. 2015;209:759–774.
9. Umeshima H, Nomura KI, Yoshikawa S, et al. Local traction force in the proximal leading process triggers nuclear translocation during neuronal migration [published online ahead of print April 5, 2018]. *Neurosci Res*. doi:10.1016/jneures.2018.04.001.
10. Solecki DJ, Model L, Gaetz J, Kapoor TM, Hatten ME. Par6alpha signaling controls glial-guided neuronal migration. *Nat Neurosci*. 2004;7:1195–1203.
11. Shu T, Ayala R, Nguyen MD, Xie Z, Gleeson JG, Tsai LH. Ndel1 operates in a common pathway with LIS1 and cytoplasmic dynein to regulate cortical neuronal positioning. *Neuron*. 2004;44:263–277.
12. Tanaka T, Serneo FF, Higgins C, Gambello MJ, Wynshaw-Boris A, Gleeson JG. Lis1 and doublecortin function with dynein to mediate coupling of the nucleus to the centrosome in neuronal migration. *J Cell Biol*. 2004;165:709–721.
13. Umeshima H, Hirano T, Kengaku M. Microtubule-based nuclear movement occurs independently of centrosome positioning in migrating neurons. *Proc Natl Acad Sci U S A*. 2007;104:16182–16187.
14. Zhang X, Lei K, Yuan X, et al. SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. *Neuron*. 2009;64:173–187.
15. Yu J, Lei K, Zhou M, et al. KASH protein Syne-2/Nesprin-2 and SUN proteins SUN1/2 mediate nuclear migration during mammalian retinal development. *Hum Mol Genet*. 2011;20:1061–1073.
16. Trivedi N, Stabley DR, Cain B, et al. Drebrin-mediated microtubule-actomyosin coupling steers cerebellar granule neuron nucleokinesis and migration pathway selection. *Nat Commun*. 2017;8:14484.
17. Rao AN, Falnikar A, O'Toole ET, et al. Sliding of centrosome-unattached microtubules defines key features of neuronal phenotype. *J Cell Biol*. 2016;213:329–341.
18. Wu YK, Umeshima H, Kurisu J, Kengaku M. Nesprins and opposing microtubule motors generate a point force that drives directional nuclear motion in migrating neurons. *Development*. 2018;145:dev158782.
19. Edmondson JC, Hatten ME. Glial-guided granule neuron migration in vitro: a high-resolution time-lapse video microscopic study. *J Neurosci*. 1987;7:1928–1934.
20. Nadarajah B, Brunstrom JE, Grutzendler J, Wong RO, Pearlman AL. Two modes of radial migration in early development of the cerebral cortex. *Nat Neurosci*. 2001;4:143–150.