15. Gueiros-Filho, F.J., and Losick, R. (2002). A widely conserved bacterial cell division protein that promotes assembly of the tubulin-like protein FtsZ. Genes Dev. *16*, 2544–2556.
16. Hale, C.A., Rhee, A.C., and de Boer, P.A. (2000). ZipA-induced bundling of FtsZ polymers mediated by an interaction between C-terminal domains. J. Bacteriol. *182*, 5153–5166.
17. Singh, J.K., Makde, R.D., Kumar, V., and Panda, D. (2008). SepF increases the assembly and bundling of FtsZ polymers and stabilizes FtsZ protofilaments by binding along its length. J. Biol. Chem. *283*, 31116–31124.
18. Beuria, T.K., Mullapudi, S., Mileykovskaya, E., Sadasivam, M., Dowhan, W., and Margolin, W. (2009). Adenine nucleotide-dependent regulation of assembly of bacterial tubulin-like FtsZ by a hypermorph of bacterial actin-like FtsA. J. Biol. Chem. *284*, 14079–14086.
19. Tonthat, N.K., Arold, S.T., Pickering, B., Van Dyke, M.W., Liang, S., Lu, Y., Beuria, T.K., Margolin, W., and Schumacher, M.A. (2010). Molecular mechanism by which the SlmA nucleoid occlusion factor keeps cytokinesis in check. EMBO J., in press.
20. Judd, E.M., Comolli, L.R., Chen, J.C., Downing, K.H., Moerner, W.E., and McAdams, H.H. (2005). Distinct constrictive processes, separated in time and space, divide *Caulobacter* inner and outer membranes. J. Bacteriol. *187*, 6874–6882.

Department of Microbiology and Molecular Genetics, University of Texas Medical School at Houston, 6431 Fannin Street, Houston, TX 77030, USA.
*E-mail: William.Margolin@uth.tmc.edu

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Nuclear Migration: Rock and Roll Facilitated by Dynein and Kinesin

The nucleus encounters other organelles as well as high cytoplasmic pressures during its migration within the cell. A new study describes how the action of kinesin and dynein motors is coordinated at the nuclear envelope to rock and roll the nucleus in *Caenorhabditis elegans*.

Xiaochang Zhang[1,2] and Min Han[1,2,*]

Migration of the nucleus relative to a cell body is a prominent cellular process that occurs during development in almost all eukaryotes [1]. A failure in nuclear migration often causes severe developmental defects and human diseases, such as lissencephaly, which is characterized by the lack of sulci and gyri in the brain [2]. Taking vertebrate neurogenesis and neuronal migration as examples, microtubules and their associated proteins, such as Lis1, Ndel, DCX and centrosomal proteins, are known to function during nuclear movement [3]. Although both dynein and kinesin have been implicated in nuclear migration, it has long been unclear how these microtubule motors, which move along the microtubule in opposite directions, are coordinated to apply their forces to the migrating nucleus [4]. A new study published in the *Journal of Cell Biology* by Fridolfsson and Starr [5] investigates the specific roles of kinesin and dynein complexes at the nuclear envelope during the bidirectional movements and the rolling of nuclei during development of the *Caenorhabditis elegans* hypodermis.

Genetic studies in *C. elegans* identified functional interactions between the KASH-domain-containing proteins at the outer nuclear envelope and the SUN-domain-containing proteins at the inner nuclear envelope and established their roles in connecting the nuclei to different components of the cytoskeleton [6,7]. The essential functions of SUN–KASH protein complexes in connecting the nuclear envelope with microtubule and actin networks have also been studied in other model organisms as well as in mammalian tissue culture cells [4]. In the *Drosophila* eye and zebrafish retina, the KASH proteins have been proposed to link the dynein/dynactin protein complex to the nuclear envelope [8,9]. In the developing mouse brain, the KASH protein Syne-2/nesprin-2 was found to interact with both dynein/dynactin and kinesin motor complexes [10]. The most compelling evidence of interactions between KASH–SUN proteins and motor complexes came from studies in *C. elegans*: although a complex containing the KASH protein Zyg-12 and the SUN protein SUN1 interacts with dynein light chain and recruits the dynein–Lis1 protein complex to the nuclear envelope for pronuclear migration, germline nuclear anchorage/movement and other functions [11,12], a complex of the KASH protein UNC-83 and the SUN protein UNC-84 interacts with both kinesin and dynein complexes during nuclear migration in the hypodermal hyp7 cells [13,14] (Figure 1A).

The interaction of a nuclear envelope protein with both kinesin and dynein motors is intriguing and led the field to investigate how the action of two motors that move in opposite directions can be coordinated to drive the presumably unidirectional nuclear movement. Fridolfsson and Starr [5] have now addressed this question by time-lapse imaging of the nuclear migration process in worm hyp7 cells. They found that loss of UNC-83 or UNC-84 completely blocked the initiation of nuclear migration, which is consistent with the prediction that the adaptor for motor proteins at the nuclear envelope is essential for motor function. The high-resolution imaging allowed the authors not only to observe the fast and slow phases of nuclear movement, but also to detect the surprising backward movement of nuclei (Figure 1A). Also strikingly, the authors observed a fast rolling behavior in a certain percentage of migrating nuclei. The observed bidirectional and rolling movements are proposed to be the mechanism by which a migrating nucleus releases the cytoplasmic pressure created by a build-up of organelles in front of the nucleus in the narrow cell body.

Loss of kinesin function leads to a severe nuclear migration defect, including inhibition of the initiation of the movement. In comparison, the effect of losing dynein functions appears to be weaker and specific to certain aspects of the process. In worms with partially disrupted dynein function, the rolling of the nucleus was found to be compromised and the bidirectional nuclear movement was disrupted.
By generating a transgene that produces a kinesin–UNC-83 fusion protein, the authors cleverly created a system that presumably retains the connection between kinesin and the nuclear envelope, but not that between

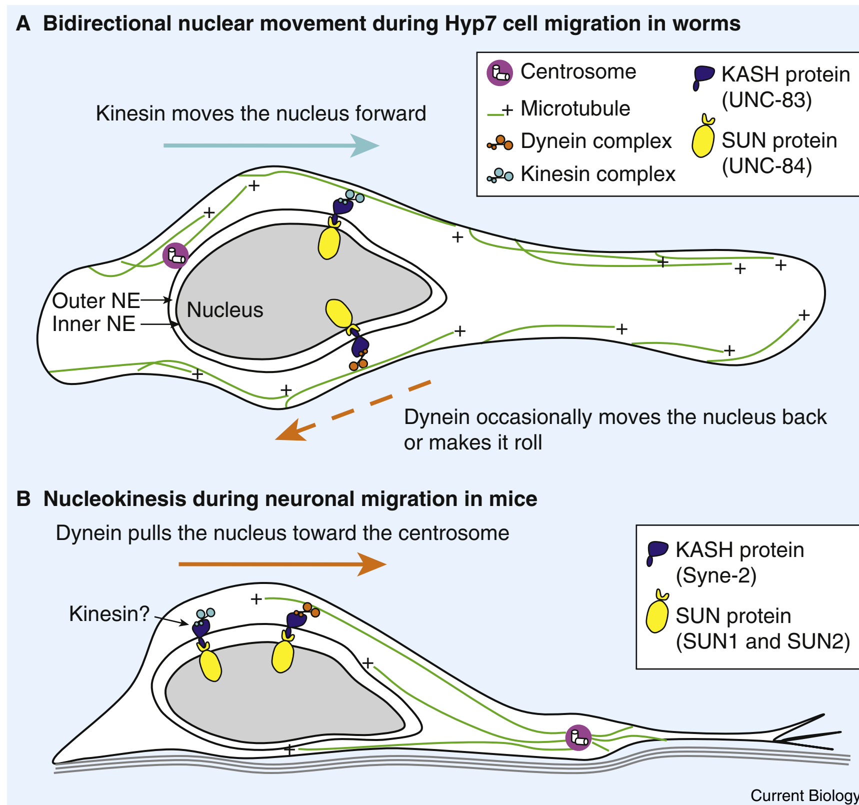

Figure 1. Kinesin and dynein during different modes of nuclear migration.

(A) A model for noncentrosomal-dependent nuclear migration during hyp7 cell migration in *C. elegans* [5]. The centrosome is in a random position around the nucleus. γ-tubulin is organized along the cell membrane, and the microtubules are polarized with the plus end pointing toward the direction of nuclear migration. While the plus-end-directed motor kinesin provides the major pulling force, dynein occasionally moves the nucleus back or makes it roll. Kinesin and dynein are anchored to the nuclear envelope by UNC-83–UNC-84 protein complexes. (B) A model for centrosome-dependent nuclear migration (nucleokinesis) during radial neuronal migration in mice [3]. The centrosome migrates ahead of the nucleus, and the nucleus is pulled forward toward the centrosome by dynein motors that are connected to the nuclear envelope by KASH–SUN proteins. A role for kinesin in this nuclear migration process is unknown.

dynein and the nuclear envelope [13]. In these transgenic worms, about half of the nuclei initiate nuclear migration normally, but none of them displayed either bidirectional movement or rolling. These observations indicated that kinesin provides the pulling force to move the nucleus forward and the UNC-83-dependent dynein activity at the nuclear envelope is required for the bidirectional movement and rolling behavior.

In hyp7 cells, microtubules were previously hypothesized to be noncentrosomal and organized into stable polarized bundles with the plus end pointing at the new tip of the cell [13,15]. The authors found that those noncentrosomal microtubules are highly dynamic during nuclear migration and polarized quickly after the initiation of nuclear migration. Specifically, over 90% of microtubules grow in the direction of migration, which is consistent with the proposal that the plus-end-directed motor kinesin provides the major force to move the nucleus. Furthermore, when nuclear migration is initiated, γ-tubulin relocates from a site adjacent to the nucleus to lining the cell membrane, which could facilitate the formation of noncentrosomal microtubule arrays.

Some further mechanistic questions have been raised by this study. For example, we may wonder how UNC-83 switches between working with kinesin and dynein. Previous work has shown that UNC-83 has two different domains that bind to kinesin- and dynein-related proteins separately [14]. Do kinesin and dynein bind to UNC-83 in a mutually exclusive manner? Is there a mechanism that regulates the interaction between UNC-83 and dynein complexes? Since UNC-83 has been shown to interact with GCK-4 (a Ste-like kinase) and MEL-11 (a phosphatase regulator) in a yeast two-hybrid assay [14], is it possible that the kinesin- and dynein-binding capacities of UNC-83 are subject to regulation by phosphorylation? Another intriguing question is how is the dynein-mediated backward migration and rolling behavior initiated? Is the pressure on the cytoplasmic membrane and nuclear envelope responsible for the regulation of dynein activity? A more challenging question is how the polarity of noncentrosomal microtubules is established and maintained. Specifically, what signal triggers the redistribution of γ-tubulin prior to nuclear migration, and what factors are involved in organizing γ-tubulin along the cell membrane?

UNC-83-mediated, noncentrosomal-microtubule-directed nuclear migration is not likely to be unique to *C. elegans*. Among several KASH-domain-containing proteins, nesprin-4 interacts with kinesin and appears to be the functional homolog of UNC-83 [16]. Nesprin-4 is highly expressed in mammalian epithelial cells where lateral bundles of microtubules exist in a manner similar to worm hyp7 cells [16]. It is thus conceivable that nesprin-4 and kinesin mediate similar nuclear migration events in mammalian epithelial cells, and it will be interesting to test the potential interaction between nesprin-4 and dynein and examine the rocking and rolling of the nucleus in these cells.

Unlike the nuclear migration process described here, the centrosomal microtubules are absolutely required in many important nuclear migration processes, such as pronuclear migration in *C. elegans* and nucleokinesis during neuronal migration in the vertebrate brain (Figure 1B) [4]. In these cases, the minus-end-directed dynein motor complex plays a dominant role in pulling the nucleus towards the centrosome and the leading edge of the cell. However, in some of these migration processes the nucleus also needs to deal with high resistance pressure and various organelles in the compressed cell body. It will thus be interesting to learn whether nuclear

rotation is also involved and whether any other motor proteins play a role. In the developing mouse brain, the SUN–KASH complexes also interact with the kinesin complex as well as dynein [10], but a prominent role of kinesin in neuronal migration has not been clearly demonstrated.

Interkinetic nuclear migration (INM) during vertebrate neurogenesis is currently another active research area where the roles of different motor proteins need to be clarified [17]. During INM, the nucleus moves away from the centrosome during G1 phase and migrates back toward the centrosome during G2 phase after DNA synthesis. Kinesin and dynein have been proposed to drive the nuclear migration processes during G1 and G2 phases, respectively [3], and the KASH protein Syne-2/nesprin-2 has been shown to interact with both kinesin and dynein in the developing mouse brain [10]. In the zebrafish retina, myosinII and dynactin have been suggested to provide the major force for INM [18,19]. Furthermore, Syne-2/nesprin-2 has been shown to connect the nucleus to the flowing actin and thus move the nucleus after wounding in tissue culture cells [20]. Thus, it would be worthwhile to investigate the detailed mechanism of how the microtubules and actin filaments are organized in the neuronal progenitors. Which cytoskeletal component is essential for providing the driving force for nuclear migration during G1 and G2 phase? Do noncentrosomal microtubule arrays exist? Do different combinations of motors, such as dynein, kinesin and myosinII, function together to move the nucleus through cytoplasmic obstacles during INM? How does Syne-2/nesprin-2 coordinate its interactions between dynein, kinesin and actin? These questions could be addressed by combining high-resolution imaging techniques and genetic manipulation, as demonstrated in the new work by Fridolfsson and Starr [5].

References

1. Morris, N.R. (2000). Nuclear migration. From fungi to the mammalian brain. J. Cell Biol. *148*, 1097–1101.
2. Wynshaw-Boris, A. (2007). Lissencephaly and LIS1: insights into the molecular mechanisms of neuronal migration and development. Clin. Genet. *72*, 296–304.
3. Ayala, R., Shu, T., and Tsai, L.H. (2007). Trekking across the brain: the journey of neuronal migration. Cell *128*, 29–43.
4. Starr, D.A., and Fridolfsson, H.N. (2010). Interactions between nuclei and the cytoskeleton are mediated by SUN-KASH nuclear-envelope bridges. Annu. Rev. Cell Dev. Biol. *26*, 421–444.
5. Fridolfsson, H.N., and Starr, D.A. (2010). Kinesin-1 and dynein at the nuclear envelope mediate the bidirectional migrations of nuclei. J. Cell Biol. *191*, 115–128.
6. Starr, D.A., and Han, M. (2002). Role of ANC-1 in tethering nuclei to the actin cytoskeleton. Science *298*, 406–409.
7. Zhou, K., and Hanna-Rose, W. (2010). Movers and shakers or anchored: Caenorhabditis elegans nuclei achieve it with KASH/SUN. Dev. Dyn. *239*, 1352–1364.
8. Patterson, K., Molofsky, A.B., Robinson, C., Acosta, S., Cater, C., and Fischer, J.A. (2004). The functions of Klarsicht and nuclear lamin in developmentally regulated nuclear migrations of photoreceptor cells in the Drosophila eye. Mol. Biol. Cell *15*, 600–610.
9. Tsujikawa, M., Omori, Y., Biyanwila, J., and Malicki, J. (2007). Mechanism of positioning the cell nucleus in vertebrate photoreceptors. Proc. Natl. Acad. Sci. USA *104*, 14819–14824.
10. Zhang, X., Lei, K., Yuan, X., Wu, X., Zhuang, Y., Xu, T., Xu, R., and Han, M. (2009). SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. Neuron *64*, 173–187.
11. Malone, C.J., Misner, L., Le Bot, N., Tsai, M.C., Campbell, J.M., Ahringer, J., and White, J.G. (2003). The C. elegans hook protein, ZYG-12, mediates the essential attachment between the centrosome and nucleus. Cell *115*, 825–836.
12. Zhou, K., Rolls, M.M., Hall, D.H., Malone, C.J., and Hanna-Rose, W. (2009). A ZYG-12-dynein interaction at the nuclear envelope defines cytoskeletal architecture in the C. elegans gonad. J. Cell Biol. *186*, 229–241.
13. Meyerzon, M., Fridolfsson, H.N., Ly, N., McNally, F.J., and Starr, D.A. (2009). UNC-83 is a nuclear-specific cargo adaptor for kinesin-1-mediated nuclear migration. Development *136*, 2725–2733.
14. Fridolfsson, H.N., Ly, N., Meyerzon, M., and Starr, D.A. (2010). UNC-83 coordinates kinesin-1 and dynein activities at the nuclear envelope during nuclear migration. Dev. Biol. *338*, 237–250.
15. Williams-Masson, E.M., Heid, P.J., Lavin, C.A., and Hardin, J. (1998). The cellular mechanism of epithelial rearrangement during morphogenesis of the Caenorhabditis elegans dorsal hypodermis. Dev. Biol. *204*, 263–276.
16. Roux, K.J., Crisp, M.L., Liu, Q., Kim, D., Kozlov, S., Stewart, C.L., and Burke, B. (2009). Nesprin 4 is an outer nuclear membrane protein that can induce kinesin-mediated cell polarization. Proc. Natl. Acad. Sci. USA *106*, 2194–2199.
17. Taverna, E., and Huttner, W.B. (2010). Neural progenitor nuclei IN motion. Neuron *67*, 906–914.
18. Norden, C., Young, S., Link, B.A., and Harris, W.A. (2009). Actomyosin is the main driver of interkinetic nuclear migration in the retina. Cell *138*, 1195–1208.
19. Del Bene, F., Wehman, A.M., Link, B.A., and Baier, H. (2008). Regulation of neurogenesis by interkinetic nuclear migration through an apical-basal notch gradient. Cell *134*, 1055–1065.
20. Luxton, G.W., Gomes, E.R., Folker, E.S., Vintinner, E., and Gundersen, G.G. (2010). Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement. Science *329*, 956–959.

[1]Howard Hughes Medical Institute and Department of MCDB, University of Colorado, Boulder, CO 80309, USA. [2]Institute of Developmental Biology and Molecular Medicine, School of Life Science, Fudan University, Shanghai 200433, China.
*E-mail: mhan@colorado.edu

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Asymmetric Cell Division: A New Way to Divide Unequally

It has long been known that cells can divide unequally by shifting the mitotic spindle to one side. Two recent reports identify an alternative way to generate daughter cells of different sizes.

Christopher D. Higgins and Bob Goldstein*

All good cell biologists know that the mitotic spindle determines the plane of cytokinesis. Ray Rappaport, the godfather of cytokinesis [1], showed that experimentally moving a spindle could change the site of cytokinesis [2], and cytokinesis can be prevented by removing the spindle from a cell at least a few minutes before the cytokinetic furrow normally forms [3,4]. Recent work has begun to outline a mechanism for the furrow-inducing activity of the mitotic spindle. Astral microtubules and midzone microtubules affect myosin distribution and actin architecture through local RhoA activation and Rac inactivation at the equatorial cortex, where the actin and myosin will form a contractile ‘purse string’ [5–7]. In nearly all cells, the spatial relationship between the spindle and the actomyosin-rich furrow is consistent with the above causal relationships: the spindle’s position predicts accurately where furrowing will occur.