Mini-Review

Nuclear Migration: From Fungi to the Mammalian Brain

N. Ronald Morris, M.D.

Department of Pharmacology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, New Jersey 08854

Textbooks represent the animal cell nucleus as a sort of cellular Jabba the Hutt, torpidly enthroned in the center of the cell. In fact nothing could be farther from the truth. The nucleus more closely resembles Luke Skywalker, the hero of Star Wars, in its ability to move about in its cellular universe. Instances of nuclear motility are found throughout biology. Indeed, nuclear migration appears to be required for the proper growth and development of essentially all eukaryotes. Some well known examples, i.e., those in textbooks, are the congression of male and female pronuclei during fertilization, the movement of nuclei to the egg cortex during embryogenesis in *Drosophila melanogaster*, and during karyogamy and the migration of the daughter nucleus into the bud in *Saccharomyces cerevisiae*. Innumerable other nuclear motility events have been described in animals, plants, insects, algae, and fungi. However, until relatively recently, little was known about the mechanism of nuclear migration, except that it required microtubules (MTs)[1]. An excellent recent review focuses particularly on how MTs exert forces on nuclei (Reinsch and Gonczy, 1998). The focus of the present review will be on the contribution of genetic systems to our understanding of nuclear migration. The early work on the genetics of nuclear migration came from three "simple" organisms, the yeast *S. cerevisiae*, and two filamentous fungi, *Aspergillus nidulans* and *Neurospora crassa*. Recently, important findings have also come from *Drosophila melanogaster*, *Caenorhabditis elegans*, and possibly man. Nuclear migration has been studied in relation to karyogamy and migration of the daughter nucleus into the bud in budding yeast; in relation to the migration of nuclei through the mycelium in the filamentous fungi; during migration to the cortex in fly development; and during cell specific migrations in worm development. Similarities between the NUDF nuclear migration protein of *A. nidulans* and LIS1, a protein required for neuronal migration in the brain, have led us to suggest that nuclear migration is also a feature of brain development.

Nuclear Migration in Yeast

Our knowledge of nuclear migration in yeast comes from genetic and morphological studies of mating and mitosis in *S. cerevisiae*. Mating yeast respond to each other by forming pear-shaped, stem-end–opposed cells termed shmoos. In the first stage of mating, astral MTs emanating from the spindle pole body (SPB), a microtubule organizing center embedded in the nuclear envelope, are oriented to the shmoo tip. This occurs by a random search and capture mechanism that requires Kar3p kinesin and Kar9p, which is a MT orientation protein whose position at the shmoo tip depends on cell polarization proteins (actin, Bni1p, Spa2p, Pea2p, and Bud6p; Lee et al., 1999; Miller et al., 1999a). Direct observations of nuclear movements during karyogamy show that they closely track the growth and shortening of the shmoo tip MT bundle (Maddox et al., 1999), raising the possibility that MT dynamics provides the motive force that moves the nucleus. As the nuclei move toward the schmoo tips, the tips fuse, and the shmoo tip MT bundles fuse to form an intranuclear bundle, which progressively shortens to mediate nuclear congression (Maddox et al., 1999). These nuclear movements are affected by mutations in Kar3p, which is a microtubule-dependent motor that also depolymerizes MTs, and other proteins that influence astral MT dynamics (Cin1p, Cin2p, and Cin4p; see review of karyogamy by Rose, 1996). Whether Kar3p functions primarily as a motor or as a mediator of MT dynamics (or both) is unclear.

During mitosis a much larger set of proteins moves the nucleus to the bud neck and into the bud, including three kinesins (Kar3p, Kip3p, and Kip2p) and cytoplasmic dynein (CD) plus dynactin (Eshel et al., 1993; Li et al., 1993; Cottingham et al., 1999; Kahana et al., 1998; Miller et al., 1998). There is substantial functional overlap among CD, Kar3p, and Kip3p. Deletion of any one of them has little effect, but deletion of more than one has an increasingly severe, deleterious effect on both nuclear positioning and cell viability. This is not necessarily related to loss of their motor functions because, like Kar3p, CD and Kip3p also affect astral MT stability. Deletion of the CD heavy chain causes an increase in astral MT length that is intensified by deletion of Kar3p and Kip3p. Since their loss increases MT length (i.e., stability), these proteins must normally act to destabilize MTs in vivo. In contrast, deletion of Kip2p increases astral MT length, reverses the MT length abnormalities caused by deletion of the CD heavy chain, Kar3p and Kip3p, and suppresses the effects of these deletions on
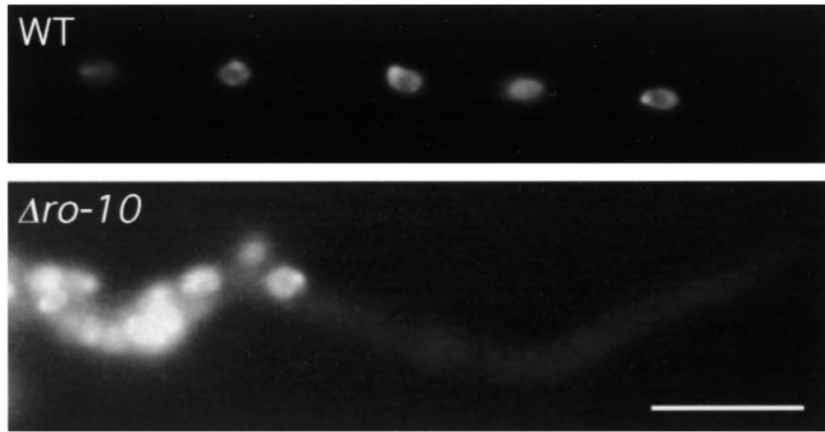
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nuclear positioning. Loss of Bim1p, which also affects MT stability, has similar effects (Schwartz et al., 1997; Tirnauer et al., 1999). These observations and other related pieces of genetic and pharmacological evidence suggest that astral MT dynamics play a significant role in nuclear positioning. Time-lapse fluorescence microscopy studies of GFP-tagged MTs showed that nuclear movements during mitosis, as during karyogamy, mirror the growing and shrinking rate of astral MTs attached to the cell cortex, consistent with the idea that dynamic MTs interacting with the cell cortex mediate nuclear movement (Carminati and Stearns, 1997; Shaw et al., 1997; Maddox et al., 1999). Kar9p, which during mitosis orients astral MTs to the bud tip (Miller et al., 1999a), and Num1p, which is associated with the mother cell cortex, are also required for nuclear positioning, apparently by providing targets for MT capture by the cortex (Farkasovsky and Kuntzel, 1995). All of the motors involved in *S. cerevisiae* nuclear movements are probably now known, but how they are targeted to specific locations in the cell, how their activities are regulated and coordinated, and how they actually generate force are still incompletely understood.

Nuclear Migration in Filamentous Fungi

In comparison to the short range migrations seen in yeast, nuclear migration in the filamentous fungi can be a long-range process, sometimes very long-range, as some fungal colonies are miles in diameter (Smith et al., 1992). As the fungal colony grows, the nuclei migrate through the cytoplasm toward the advancing hyphal tip. Early observers noted that nuclei appeared to be pulled from a point on the nuclear periphery, which is now known to be the SPB. Observations on living fungi show that the nuclei move apart after mitosis, then migrate in the same direction, but at different rates, towards the hyphal tip, resulting in a relatively even distribution along the mycelium (Suelmann et al., 1997). Differential laser ablation of spindle versus astral MTs in *Fusarium solani* and *Nectria haematococca* revealed that a tractive force on the SPB MTs separates the nuclear masses during anaphase B of mitosis (Aist et al., 1991). The pulling force that moves interphase nuclei through the fungal cytoplasm is thought to be a continuation of this process. Laser tweezer experiments showed that nuclei of *N. haematococca* are anchored in place dur-

ing interphase and that this, like the anaphase B force, depends on CD (Inoue et al., 1998). Unlike the situation in yeast, deletion of the CD heavy chain causes a decrease in the number and length of the SPB MTs in *Nectria*. Because the astral MTs are decreased in the absence of CD, one cannot in this case conclude that the anchoring force is related to CD motor activity.

As in yeast, genetic studies have identified many of the proteins required for nuclear migration in the filamentous fungi (Morris, 1975; Plamann et al., 1994; Xiang et al., 1994, 1999; Bruno et al., 1996; Inoue et al., 1998; Minke et al., 1999a). The first nuclear migration mutants were a byproduct of a mitotic mutant search in *A. nidulans* 25 years ago (Morris, 1975). These were termed *nud* (for nuclear distribution) mutations. In *N. crassa* similar mutations were termed ropy (*ro*) because the hyphae resemble intertwined rope strands. Phenotypically, the *nud* and *ro* mutants are characterized by a strikingly uneven distribution of nuclei along the mycelium (Fig. 1). Both grow slowly, branch excessively, and sporulate poorly. The *A. nidulans* apsA (which encodes a protein similar to *Saccharomyces cerevisiae* NUM1p) and apsB mutants, initially identified as sporulation defective, also affect nuclear distribution (Clutterbuck, 1994; Fischer and Timberlake, 1995). Many of the *nud* and *ro* genes encode subunits of CD or of dynactin (Table I), including the heavy, intermediate, and light chains of CD and the p150[glued] and ARP1 subunits of dynactin (Xiang et al., 1994; Plamann et al., 1994; Robb et al., 1995; Tinsley et al., 1996; Beckwith et al., 1998; Xiang et al., 1999; Xiang and Morris, unpublished data). Other *nud* and *ro* genes encode proteins that are not known components of CD or dynactin, but may be required for the integrity, localization (e.g., *ro-10*) or activity of CD or dynactin. Of particular interest is the *nudF* gene of *A. nidulans*, which encodes a protein similar to LIS1, a protein required for human brain development (Xiang et al., 1995a; see below).

Introduction of a temperature-sensitive *nudF* mutation into a strain carrying a CD heavy chain deletion causes no more inhibition of nuclear migration or growth than the CD deletion alone. Therefore, NUDF protein must lie on the same functional pathway as CD. It presumably acts upstream of CD, since the growth inhibition caused by deletion of NUDF can also be suppressed by mutations in the CD heavy chain (Willins et al., 1997), and therefore it may

Table I. Nuclear Migration Proteins in the Dynein Pathway Identified in Fungi

	A. nidulans	N. crassa	S. cerevisiae	Higher eukaryotes
Cytoplasmic dynein components	NUDA	RO1	Dyn1p (Dhc1p)	CD heavy chain
	NUDI	–	Pac11	CD intermediate chain
	NUDG	–	Slc1p	CD 8-kD light chain
Dynactin components	–	RO3	Nip100p (pac13)	p150[glued]
	NUDK	RO4	Act3p (Act5p)	ARP1 (centractin)
	–	–	Jnm1p (Pac3p)	p50
	–	RO2	–	p70
Other dynein pathway components	NUDF	–	Pac1p	LIS1 (PAFAH1b)
	NUDC	–	Not found*	NUDC[‡]
	NUDE	RO11	Not found	Coiled coil region homologues
	–	RO10	Not found	–

*A NUDC homologue is present in the *Schizosaccharomyces pombe* genome.
[‡]NUDC homologs from higher eukaryotes have an added 15 kD of NH_2-terminal.

be an upstream activator of CD function. Physical interactions of the yeast (Pac1p) and human (LIS1) homologues of NUDF with CD have recently been reported in support of this idea (Faulkner, N., and R. Vallee. 1999. American Society for Cell Biology (ASCB). 65. [Abstr.]; Geiser, J., J. Kahana, P. Silver and M. Hoyt. 1999. ASCB. 114. [Abstr.]). As in yeast, however, the effects of CD and NUDF on nuclear migration also involve MTs. The growth inhibition caused by deletion of the CD heavy chain or NUDF can be suppressed by destabilizing MTs, indicating that NUDF and CD normally decrease MT stability in vivo (Willins et al., 1995). Recently, we have purified the NUDF protein and demonstrated that it directly inhibits the polymerization of MAP free tubulin in vitro (Ahn, C., G. Han, and N.R. Morris, unpublished observations). Thus, the in vivo effect of NUDF on MT stability may reflect either a direct effect on MT dynamics or an indirect effect mediated via loss of CD activity, or both. That the growth defect of an *A. nidulans* strain doubly mutant for both CD and NUDF is no more severe than that caused by either parental mutation could be due to the fact that there may be a limit to the extent to which MTs can be stabilized, such that loss of either NUDF or CD function causes maximal hyperstabilization.

Immunostaining showed the CD heavy chain to be concentrated at the hyphal tip in both *A. nidulans* and *N. crassa* (Xiang et al., 1995b; Minke et al., 1999b). This could reflect an abundance of CD-containing vesicles near the tip (see Seiler et al., 1999), but it is also consistent with a model in which tip-anchored CD pulls the nucleus toward the tip by migrating on astral MTs toward the SPB (Xiang et al., 1995b). A modification of this model suggested that CD on SPB MTs links nuclei together in a chain pulled toward the tip as described above (Plamann et al., 1994), and a third model suggested that the CD is anchored to the cortex at intervals along the mycelium (Efimov and Morris, 1998). However, CD has not been detected either on MTs between nuclei or on the lateral cell wall. Observations of GFP-tagged CD and NUDF in living cells shows comet-like structures that migrate toward, and become more concentrated at, the tip (Xiang, X., D. Winkelmann, and N.R. Morris, unpublished data; also, see http://www2.umdnj.edu/rmlabweb/moventer.html#two). The comets appear to be at the ends of advancing MTs. Whether this localization of CD and NUDF at the tips of MTs influences MT stability or is even related to nuclear migration still remains to be determined. Direct observational studies similar to those that have been done in yeast are needed to determine the relationship between CD, NUDF, and MT dynamics and nuclear migration in *Aspergillus* and other filamentous fungi.

Nuclear Migration in Flies and Worms

Studies of nuclear migration in the developing *D. melanogaster* embryo have provided strong evidence that CD and microtubule-dependent forces exerted on the centrosome are responsible for nuclear migration. During early embryogenesis nuclei move to the egg cortex. If nuclear division is inhibited, either by the GNU (giant nucleus) mutation or by inhibition of DNA synthesis (Freeman et al., 1986; Raff and Glover, 1989), the centrosomes continue to replicate, pull free from the nondividing nucleus, and progress to the egg cortex. Thus, a tractive force on the centrosome is responsible for this nuclear migration. Evidence for a tractive force on the spindle poles also comes from a mutation in *Drosophila* KLP3A kinesin, which disrupts the interdigitation of central spindle microtubules in spermatocyte central spindles, but does not affect spindle elongation during anaphase B (Williams et al., 1997). In both *D. melanogaster* and *C. elegans*, interference with CD function causes dislocation of centrosomes from the nucleus (Gonczy et al., 1999; Robinson et al., 1999). It also causes failure of centrosome separation and causes abnormal spindle orientation in both the fertilized single cell worm embryo and the coenocytic fly embryo after nuclear migration to the cortex (Robinson et al., 1999). CD is concentrated at the periphery of the male and female pronuclei in the worm egg, leading to the suggestion that the centrosome attaches to the nucleus by an interaction between the astral MTs of the centrosome and the perinuclear CD. It also has been suggested that migration of centrosomal astral MTs on perinuclear CD is responsible for centrosome separation (Skop and White, 1998; Gonczy et al., 1999). UNC-84, a transmembrane protein required for certain specific nuclear migrations and for nuclear anchor-

ing during development in *C. elegans*, localizes to the nuclear envelope and has been proposed to anchor CD and the centrosome to the nucleus in the worm (Malone et al., 1999). The *klarsicht* gene product (marbles renamed), which is required for nuclear migration in the fly eye, also has a perinuclear distribution and has been suggested to interact with CD (Mosley-Bishop et al., 1999).

Nuclear Migration and Neuronal Migration

We have hypothesized that neuronal migration in the human brain is mediated by a mechanism similar to that responsible for the long range nuclear migration seen in filamentous fungi (Morris et al., 1998a). Dosage insufficiency of LIS1, the human homologue of *A. nidulans* NUDF (and also *S. cerevisiae* Pac1p; Geiser et al., 1997) causes a disease known as lissencephaly (smooth brain), in which neurons become arrested during their migration from the paraventricular replicative zone to the cerebral cortex (Dobyns and Truwit, 1995). This causes the cortex to be underpopulated with neurons. Consequently, the surface of the brain is smooth, rather than folded, as it is in normal individuals. The defective cortical development causes severe mental retardation, epilepsy, and usually death at an early age. LIS1 associates with two enzymatically active subunits to make the enzyme known as platelet activating factor acetyl hydrolase (PAFAH), whose function is to metabolize and inactivate PAF, a potent lipid second messenger. Striking similarities between the *A. nidulans* NUDF nuclear migration protein and LIS1 have led us to propose that neuronal migration and nuclear migration are related (Morris et al., 1998a). NUDF and LIS1 are 42% identical in amino acid sequence (Reiner et al., 1995; Xiang et al., 1995a). LIS1 is a homodimer, NUDF is also a homodimer (Ahn, C., and N.R. Morris, unpublished data), and both contain a short, predicted NH_2-terminal coiled coil (Reiner et al., 1995; Xiang et al., 1995a). *NudF* interacts genetically with two other genes, *nudC* and *nudE* (Xiang et al., 1995a; Efimov, V., and N.R. Morris, unpublished data), the *A. nidulans* homologue of the *ro-11* gene of *N. crassa* (Minke et al., 1999a). Similarly, LIS1 interacts with higher eukaryotic homologues of NUDC protein that are known to be functionally conserved because they complement the nuclear migration defect caused by the *nudC3* mutation of *A. nidulans* (Cunniff et al., 1997; Miller et al., 1999b; Morris et al., 1998b; *S. pombe* genome project; Dawe, A., G. Caldwell, N.R. Morris, and M. Chalfie, unpublished data). Moreover, LIS1 interacts with a mammalian RO-11/NUDE homologue in the yeast two hybrid assay (Hirotsune, S., personal communication). Whether the *A. nidulans* genome encodes a PAFAH catalytic subunit that interacts with NUDF is not yet known, but a catalytic subunit homologue has been described as far down the evolutionary scale as *Drosophila* (GenBank/EMBL/DDBJ accession AAC83820).

The migration of WART lung adenocarcinoma cells in culture provides a model to connect LIS1-mediated neuronal migration with NUDF-mediated nuclear migration. WART cells move by extending a long anterior process through which the cell body translocates (Klominek et al., 1991). The cells then retract the rearward cytoplasmic remnant and move forward by reiterating the process. This type of nuclear-driven cell migration is termed nucleokinesis. Certain neurons in culture also move by nucleokinesis (Book and Morest, 1990; Liesi, 1992), as do early blastomeres of the P cell lineage in *C. elegans* (Gonczy et al., 1999). The hypothesis that the defective neuronal migration seen in lissencephaly may be a failure of nucleokinesis (Morris et al., 1998a) has been tested by an examination of the migratory behavior of cerebellar granule cell explants from a LIS1 knockout mouse (Hirotsune et al., 1998). Wild-type explants send out cytoplasmic processes through which the cell bodies then migrate. Explants from LIS1 knockout mice extend processes similar to those from wild-type mice, but migration of the cell bodies is defective. Thus, the LIS1 knockout mouse experiment supports the hypothesis that a nuclear migration defect underlies the neuronal migration defect of lissencephaly. Like *A. nidulans* NUDF, LIS1 affects MT stability, but whereas NUDF deficiency increases MT stability in vivo (Willins et al., 1995) and purified NUDF inhibits MTs in vitro, purified LIS1 has been reported to stabilize MTs in vitro (Sapir et al., 1997).

Many features are common to nuclear migration in lower and higher eukaryotes. In both, nuclei are pulled around by an attached organelle: in the fungi by the SPB and in higher eukaryotes by the centrosome. In all cases, MTs, CD, and dynactin are involved, but in *S. cerevisiae*, kinesin proteins also play a role. Whether the involvement of the kinesins in nuclear migration is general or specifically related to the peculiarities of yeast bud nucleation remains to be determined. The effects of the motor proteins on MT stability and nuclear movement in the fungi are of great interest because they invoke the question of whether nuclear migration is mediated by motor activity and/or by effects on MT dynamics. Whether NUDF and LIS1 have a conserved mechanism, what that mechanism may be, and whether and how they affect CD, dynactin, and/or MTs, remain as fascinating topics for future investigation.

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