Mamm Genome (2007) 18:425–430
DOI 10.1007/s00335-007-9034-4

Neuronal migration: unraveling the molecular pathway with humans, mice, and a fungus

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Received: 6 March 2007 / Accepted: 24 April 2007 / Published online: 15 July 2007

Abstract This review highlights the utility of comparative genetics in understanding the molecular mechanisms that underlie neuronal migration. It is apparent from studies in humans, mice, and a fungus that nuclear migration is a key component of neuronal migration and that both are dependent on a dynamic microtubule network. In vertebrates regulation of this network involves a complex pathway that is dependent on extracellular guidance cues, membrane-bound receptors, intracellular signaling molecules, proteins associated with microtubules, and the components of microtubules themselves.

Introduction

It is undeniably exciting the first time, when peering down a microscope, you see the beauty of the cerebral cortex. Its six ordered layers like a medieval army awaiting a cognitive battle. This precise layering and, with it, the ability to entertain higher thought are consequences of neuronal migration. The cortex with its laminar structure is not the only brain region that relies on neuronal migration; the cellular architecture of the cerebellum, hippocampus, and colliculi is the product of a precise neuronal journey. Born in the proliferative ventricular zones, each neuron must migrate to its final destination. But how do they get there? This review focuses on the contribution of humans, mice, and a fungus to the understanding of the molecular mechanisms that underlie neuronal migration. The article begins with an introduction on neuronal migration, followed by assessment of the contribution made by spontaneous and transgenic mutant mice, then human disorders, and finally a look at rather an unlikely contributor, *Aspergillus nidulans*. It does not aim to discuss all genes required for neuronal migration but rather to highlight the value of comparative genetics in the understanding of this biological phenomenon.

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Radial and tangential neuronal migration

Two types of neuronal migration predominate during embryonic stages: radial and tangential. Radial migration describes neurons that migrate in a direction perpendicular to the surface of the brain, guided by a scaffold of radial glial cells. In the cortex, radial glial cells, which are generated prior to neurogenesis, have a cell body in the ventricular zone and a process that reaches the surface of the brain. While initially thought to be static, it has recently been demonstrated that this population of cells undergoes mitosis producing new neurons (Noctor et al. 2001, 2002). Neurons that rely on radial migration are not limited to the cortex and include the pyramidal neurons of the hippocampus, the Purkinje cells in the cerebellum, and the majority of the cells in the superior colliculus. Tangential migration describes neurons that migrate in a direction parallel to the brain surface. Most of these neurons originate from the ganglionic eminences (GE) and are known to include cortical and hippocampal GABAnergic interneurons (Marin and Rubenstein 2001). Unlike radial migration, tangential migration does not rely on radial glia and instead is referred to as neurophilic. Neurons that migrate tangentially are known to employ each other (such as neurons destined for the olfactory bulb), axons, and extracellular

guidance cues. Both radial and tangential migrations involve the extension of a leading neurite, somal translocation of the nucleus into that neurite, and the retraction of the trailing process (Lambert de Rouvroit and Goffinet 2001). The most important question for investigators in the field has been: What are the molecular mechanisms that drive this migration?

Spontaneous mouse mutants: *reeler*, *scrambler*, and *yotari*

The advent of genetic techniques such as positional cloning and exon trapping revolutionized the field of developmental neurobiology, bringing the mouse to the forefront (Rice and Curran 2001). The genes responsible for the neuronal migration phenotypes observed in the spontaneous mouse mutants—*reeler*, *scrambler*, and *yotari*—could now be identified (Rakic and Sidman 1973; Stanfield and Cowan 1979). The first to be cloned was a mutation in reelin, which was responsible for the inverted cortex and the disorganized hippocampus and cerebellum in the *reeler* mouse (D'Arcangelo et al. 1995). The gene *reelin* encodes a large extracellular protein that is expressed primarily in the Cajal-Retzius cells in the marginal zone of the cortex and the cerebellum (Hirotsune et al. 1995). This was the first protein identified in the molecular pathway required for neurons to migrate, and it emphasized the importance of extracellular guidance cues. The cloning of *scrambler* and *yotari* followed shortly afterward. Both of these mice, with similar phenotypes to the *reeler* mouse, have mutations in the disabled gene (*Dab1*), a tyrosine phosphorylated cytoplasmic protein (Sheldon et al. 1997). The similarity of the phenotypes in these mice provided strong evidence that the same pathway was involved.

Transgenics: *Vldlr*, *Apoer2*, and *Cdk5*

The link between reelin and *Dab1* was soon provided by a series of studies conducted by Trommsdorff et al. (1998, 1999). They undertook pull-down experiments that demonstrated an interaction between DAB1 and the cytoplasmic tails of the VLDLR and APOER2 receptors. Generation of *Apoer2* and *Vldlr* knockout mice confirmed the importance of these receptors in neuronal migration. The mice had a loosely packed pyramidal cell layer in the CA1 region of the hippocampus, a less foliated cerebellum, and abnormal cellular distribution in the cortex. They speculated that these receptors interacted with reelin, which was supported by the findings of Howell et al. (1999) who showed that phosphorylation of DAB1 was increased by extracellular application of reelin. The phosphorylation of DAB1 has also shown to be regulated by another important protein, cyclin-dependent kinase 5 (CDK5). Mice lacking *Cdk5* (or its activator *p35*), exhibit lamination defects similar to the *reeler* mouse (Chae et al. 1997; Ohshima et al. 1996). CDK5 phosphorylates DAB1 on serine 491 independent of reelin signaling, suggesting an intersection of pathways. CDK5 is thought to play an important role in the remodeling of the cytoskeleton required for specific modes of migration. Indeed one of the proteins. CDK5 is known to phosphorylate is doublecortin (DCX); a protein that was discovered by studying neuronal migration disorders in humans (Tanaka et al. 2004b; Xie et al. 2006).

The human mutations: *DCX* and *LIS1*

Disorders of neuronal migration are not limited to mice. In humans abnormalities of neuronal migration cause a range of diseases, most notably lissencephaly. Classic lissencephaly, a disorder of both tangential migration and radial migration, is characterized by a cortex that has only four layers and a brain that appears smooth with an absence of gyri and sulci (Dobyns and Truwit 1995) (Fig. 1). Genetic studies have resulted in the identification of several genes that are responsible for abnormal cortical migration in humans.

In two landmark papers, des Portes et al. (1998) and Gleeson et al. (1998) reported that mutations in the X-linked gene doublecortin cause lissencephaly in males and a syndrome known as double-cortex in females. While initially thought to code for a putative signaling protein, it has since been demonstrated that DCX, a protein that is highly expressed in migrating and differentiating neurons, plays a key role in the stabilization of microtubules (Francis et al. 1999; Gleeson et al. 1999). Indeed, the mutations in DCX that cause lissencephaly have been shown to cluster in DCX's two tubulin-binding domains (Sapir et al. 2000; Taylor et al. 2000). The creation of transgenic mice lacking *Dcx* have further demonstrated the importance of this gene for neuronal migration. *Dcx* knockout mice have a fractured pyramidal cell layer in the hippocampus and exhibit defects in tangential migration from the subventricular zone to the olfactory bulbs via the rostral migratory stream (Corbo et al. 2002; Koizumi et al. 2006). It has also been shown that migrating neuron populations derived from the medial ganglionic eminence in *Dcx* knockout mice show abnormalities in migratory dynamics (Kappeler et al. 2006).

Lissencephaly is also known to result from hemizygous deletions in a gene on chromosome 17, known as *LIS1* or *PAFAH1B1* (Reiner et al. 1993). *LIS1* contains WD40 domains and is highly expressed in Cajal-Retzius cells and in the ventricular epithelium in the developing human cortex (Clark et al. 1997). Initially discovered because it

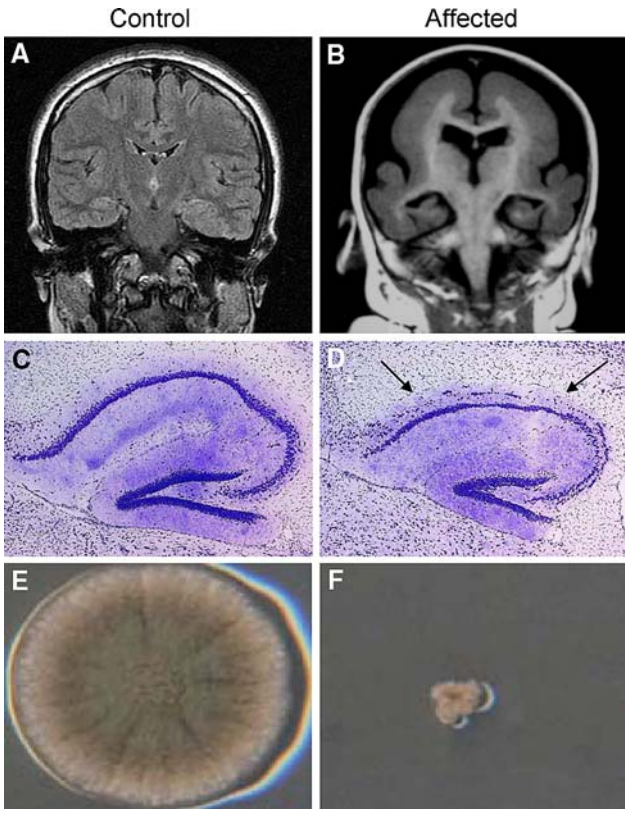

Fig. 1 The consequences of nuclear and neuronal defects in humans, mice and *Aspergillus*. In humans neuronal migration defects can result in lissencephaly. **A–B** Lissencephalic individuals have a smooth cortex lacking the characteristic sulci and gyri observable in controls (**A**). The individual show in panel **B** has a hemizygous deletion of *LIS1*. **C–D** In mice neuronal migration abnormalities manifest themselves as a fractured pyramidal cell layer in the hippocampus (*arrowed*). Panel **D** shows a sagittal section of the hippocampus in the *jenna* mice, which harbour a S140G substitution in TUBA1. **E–F** In *Aspergillus* mutations that affect nuclear migration result in smaller less developed colonies. The colony shown in panel **F**, is a *nudF* mutant

catalyzes the inactivation of platelet-activating factor (Hattori et al. 1994), *LIS1* has been shown to influence microtubule function. Cellular studies have demonstrated that overexpression of *LIS1* increases retrograde movement of cytoplasmic dynein leading to the accumulation of microtubules (Smith et al. 2000). There is also evidence of an interaction between the reelin signaling pathway and LIS1. It has been shown that phosphorylated DAB1 binds to LIS1 and that compound mutant mice with mutations in both reelin and *Lis1* exhibit enhanced layering defects in the cortex and hippocampus (Assadi et al. 2003).

Tubulin and lissencephaly

The importance of microtubules in neuronal migration is further emphasized by our recent discovery that mutations in α-tubulin cause abnormalities in neuronal migration (Keays et al. 2007). Microtubules are formed by the polymerization of heterodimers consisting of α- and β-tubulin. We found that an abnormal radial neuronal migration phenotype in the ENU-induced mouse mutant *jenna* was attributable to a substitution in the GTP binding site of α-tubulin (TUBA1) that affected heterodimerization with β-tubulin. Consequences of impaired neuronal migration in this mouse were notable defects in hippocampal pyramidal cell lamination (Fig. 1) and wavelike perturbations in layers II/III and IV of the cortex. The *jenna* mouse mutant showed striking similarity to the *Lis1* and *Dcx* knockout mice (Corbo et al. 2002; Hirotsune et al. 1998), leading us to speculate that mutations in the human homolog of *Tuba1* might also cause lissencephaly. This was found to be the case, and to date approximately ten *de novo* mutations have been found that result in cortical anomalies in humans (K. Poirier et al., personal communication).

So far we can see that the study of human and mouse mutants has unraveled a pathway that involves extracellular guidance cues, intracellular signaling molecules, and a number of proteins that are associated with cytoskeleton stabilization and modulation (Fig. 2). How do these mutations operate to affect how a neuron actually moves? Insight into the mechanism was to come from an unlikely source: *Aspergillus nidulans*.

Aspergillus nidulans and nuclear migration

Aspergillus nidulans is a filamentous soil fungus. Beginning its existence as a single spore, it undergoes several rounds of nuclear division (resulting in about 4 nuclei), followed by the formation of a projection known as a germ tube. Nuclei then migrate along the germ tube, with each nucleus moving a different distance so the nuclei are separated equally, prior to cellular division (Xiang and Morris 1999) (Fig. 3). Polarized growth of the germ tube then continues, creating an extending tip called a hyphae that undergoes branching and growth. The ability to view this process with a light microscope established *Aspergillus nidulans* as a model organism to study the biology of nuclear migration.

Pioneering experiments with this species were undertaken by Morris. They employed UV radiation to identify a host of nuclear migration mutants, labeling them nuclear distribution (nud) mutants (Morris 1975). These mutants showed normal germination and nuclear division, but the nuclei failed to migrate into the germ tube at restrictive temperatures. The mutants include *nudA*, *nudC*, *nudE*, *nudF*, and *nudG*. They were to be informative in the study of neuronal migration.

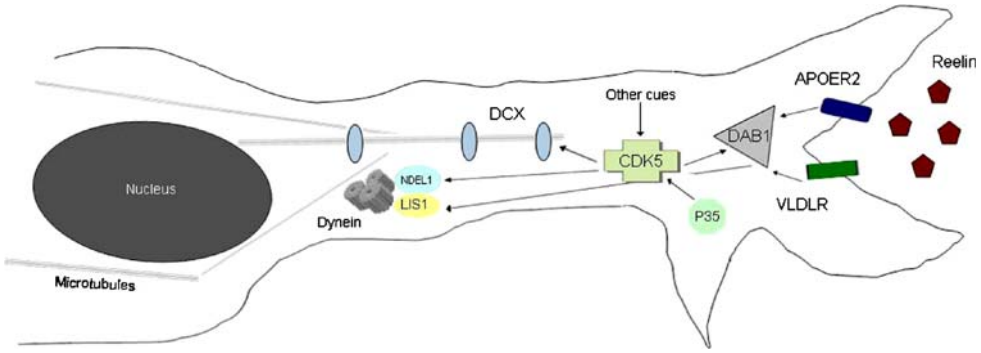

Fig. 2 Molecular pathway associated with neuronal migration. This diagram shows an outline of the molecular pathway required for neuronal migration. Extracellular reelin binds to the membrane-bound receptors APOER2 and VLDLR, which stimulate the intracellular signaling molecule DAB1. Phosphorylated DAB1 interacts with LIS1. CDK5, thought to act via a parallel but intersecting pathway, is activated by P35 and phosphorylates the microtubule stabilizer DCX and NDEL1. NDEL1 complexes with LIS1 and dynein, which act to sustain microtubule bundles and facilitate nuclear migration

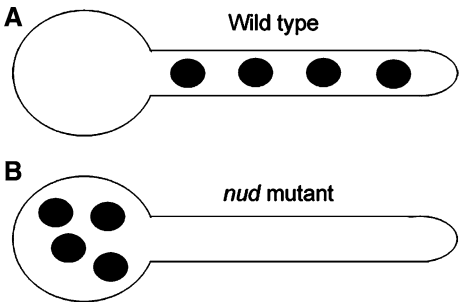

Fig. 3 Nuclear migration in *Aspergillus*. **A** Following several rounds of nuclear division (resulting in about 4 nuclei), each nucleus migrates a different distance along the germ tube prior to cellular division. **B** While nuclear division is normal, nuclear migration fails in the Nud mutants, with the nuclei remaining in the spore

Comparative studies showed that NudF, a WD-repeat protein, is 42% identical in amino acid sequence to *LIS1* (Xiang et al. 1995), the same gene that causes lissencephaly in humans. It was this observation that gave rise to the hypothesis that nuclear migration is required for neuronal migration (Xiang et al. 1995). Other *nud* genes also have mammalian homologs. The homolog of *nudA* is cytoplasmic dynein heavy chain and that of *nudG* is cytoplasmic dynein light chain (Xiang et al. 1994). The dyneins are microtubule-dependent motor proteins that are involved in the motility of a wide variety of organelles. It has been demonstrated that in vertebrates LIS1 colocalizes and interacts with cytoplasmic dynein heavy chain, and both are highly expressed in postmitotic migrating neurons in the cortex (Niethammer et al. 2000; Smith et al. 2000). Mice with ENU-induced mutations in cytoplasmic dynein heavy chain are a model for motor neuron degeneration but also exhibit defects in the migration of facial motor neurons; their cell bodies fail to migrate to their final destination in the hindbrain (Hafezparast et al. 2003). Moreover, disruption of cytoplasmic dynein results in impaired motility in a cellular assay for neuronal migration (Shu et al. 2004; Tanaka et al. 2004a). The dyneins and their role as microtubule motors are clearly important for nuclear and neuronal migration.

nudE, Nde1, and *Ndel1*

There is growing evidence that the interaction between dynein and LIS1 is influenced by another *nud* homolog: *nudE*. *nudE* mutants display impaired nuclear migration and reduced colony growth. They also suppress the more severe phenotype in *nudF* mutants, improving growth and nuclear distribution (Efimov and Morris 2000). In vertebrates there are two *nudE* homologs (with very similar names), *Nde1* and *Nde1* like (*Ndel1*), that are known to interact with LIS1. Each is clearly involved in neuronal migration; however, it seems that *Ndel1* plays a more important role. *Nde1* mice, which exhibit a modest neuronal migration defect, are most noted for their small cerebral cortex and mitotic defects in cortical progenitors (Feng and Walsh 2004). This contrasts with *Ndel1* mutant mice, which display a dosage-dependent neuronal migration phenotype (Sasaki et al. 2005). Functional studies on NDEL1 have shown that it is phosphorylated by CDK5 and forms a complex with LIS1 and dynein that sustains microtubule bundles and facilitates nuclear migration (Niethammer et al. 2000). It is of further interest that RNAi knockdown of *Ndel1* in dissociated mouse cortical neurons results in a disruption of nuclear translocation by uncoupling the centrosome and nucleus (Shu et al. 2004). It is therefore apparent that both nuclear and neuronal migrations require a complex that involves LIS1, NDEL1, and cytoplasmic dynein (Table 1).

Table 1 Nuclear and neuronal migration genes

Gene name	Humans	Mice	*Aspergillus nidulans*
LIS1/nudF	Lissecencephaly, Miller-Dieker syndrome (Reiner et al. 1993)	Cortical, hippocampal, and olfactory bulb disorganization, with an *in vivo* neuronal migration defect (Hirotsune et al. 1998)	Nuclei can divide but they fail to migrate, leading to a cluster of nuclei in the germ tube. Impaired colony growth (Xiang et al. 1995)
α-Tubulin	Lissencephaly and pachygyria	Abnormal cortical and hippocampal architecture, with an *in vivo* neuronal migration defect (Keays et al. 2007)	Suppressor mutation rescues *nudA*, *nudF*, *nudC* and *nudG* mutants
Ndel1/nudE	Not reported	A dosage-dependent neuronal migration phenotype, with increased dispersion of pyramidal cells in the hippocampus. Complete loss of *Ndel1* resulted in perinatal lethality (Sasaki et al. 2005)	Impaired nuclear migration and reduced colony growth. *nudE* mutants suppress the more severe phenotype in *nudF* mutants, improving growth and nuclear distribution (Efimov and Morris 2000)
Cytoplasmic heavy chain dynein/ *nudA*	Not reported	Motor neuron loss and defects in the migration of facial motor neuron cell bodies (Hafezparast et al. 2003)	Nuclei can divide but they fail to migrate, leading to a cluster of nuclei in the germ tube (Xiang et al. 1994)

Tubulins in *Aspergillus*

We have seen that mutations in tubulin result in abnormal neuronal migration phenotypes in mice and humans. The tubulins are similarly important for nuclear migration in *Aspergillus.* Morris showed that nuclear migration was arrested by treatment with benomyl, an inhibitor of microtubule polymerization. Moreover, it was found that a mutant line resistant to benomyl treatment harbored a mutation in β-tubulin (*benA*), leading to the conclusion that nuclear movement was mediated by this protein (Oakley and Morris 1980). A mutation in one of two α-tubulin genes in *Aspergillus* has also been found to suppress the abnormal nuclear migration phenotypes observed in the *nudA*, *nudF*, *nudC*, and *nudG* mutants. This suppressor mutation is thought to act by destabilizing microtubules as it confers sensitivity to cold and benomyl (Willins et al. 1995). It is not known exactly how destabilization of microtubules rescues nuclear migration phenotypes in *Aspergillus*; nonetheless, it again emphasizes the importance of the tubulins in nuclear migration.

Conclusion

It is apparent from studies conducted in *Aspergillus*, mice, and humans that nuclear migration is a key component of neuronal migration and that both are highly dependent on a dynamic microtubule network. In vertebrates regulation of this network involves a complex pathway that is dependent on extracellular guidance cues (reelin), membrane-bound receptors (APOER2, VLDLR), intracellular signaling molecules (DAB1, CDK5, P35), proteins associated with microtubules (DCX, LIS1, NDEL1, dyneins), and the components of microtubules themselves (TUBA). The studies conducted in *Aspergillus* are of particular note. Few would have predicted that studying a simple fungus would help understand the human cerebral cortex, arguably the most complex structure on the planet.

Acknowledgments The author thanks Fiona Francis for her comments on the manuscript. He is also indebted to Nadia Bahi-Buisson and Xin Xiang for the MRI and *Aspergillus* images.

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