Neuron, Vol. 46, 383–388, May 5, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.04.013

Nucleokinesis in Neuronal Migration

Minireview

Li-Huei Tsai[1,*] and Joseph G. Gleeson[2,*]
[1]Department of Pathology
Harvard Medical School
Howard Hughes Medical Institute
77 Avenue Louis Pasteur
Room 858C
Boston, Massachusetts 02115
[2]Neurogenetics Laboratory
Department of Neurosciences
University of California, San Diego
Leichtag 3A16
9500 Gilman Drive
La Jolla, California 92093

Neuronal migration is a critical phase of nervous system development and can be divided into two distinct phases: extension of the leading process and movement of the cell body and nucleus (nucleokinesis). Nucleokinesis appears to require many of the same cytoskeletal and signaling molecules used in cell mitosis. Converging studies suggest it requires cytoplasmic dynein, cell polarity genes, and microtubule-associated proteins that coordinate microtubule remodeling. These coordinate first the positioning of the centrosome (microtubule organizing center) in the leading process in front of the nucleus and then the movement of the nucleus towards the centrosome. The positioning of the centrosome and the dynamic regulation that couples and uncouples the nucleus underlies directed migration of neurons.

Neuronal Migration Is a Key Stage of Brain Development and, When Defective, Leads to Several Diseases

Neuronal migration is a key feature of nervous system development. Throughout the developing and mature neural axis, progenitors are located exclusively along the fluid-filled spaces, where they divide and give rise to postmitotic daughter neurons. These neurons migrate under the influence of chemoattractive and chemorepellent guidance cues to achieve positioning in the maturing nervous system. The distance that a population of neurons migrates may vary tremendously: in the developing retina neurons migrate only 50–100 μM (5–10 cell body distances), whereas in the developing human cerebral cortex, radially migrating neurons are required to migrate approximately 2 cm (hundreds of cell body distances), and tangentially migrating neurons appear to take a circuitous route that may increase this distance several fold.

The molecular basis for neuronal migration has been an area of intense investigation, in part because many human neurological diseases are either directly or indirectly linked to disordered migration. Additionally, many of the genes that have been found to play critical roles in neuronal migration during development also appear to be central to the pathogenesis of neurodegenerative pathways in the adult. For example, defective neuronal migration leads to human classical lissencephaly (smooth brain), a condition in which the cerebral cortex is absent of convolutions. In a related disorder, double cortex, the brain consists of a normal appearing outer cortex as well as a second layer of neurons within the subcortical white matter. These conditions are due to mutations in either the gene *doublecortin*, encoding Dcx (des Portes et al., 1998; Gleeson et al., 1998) or *lissencephaly-1*, encoding Lis1 (Reiner et al., 1993). In other more common conditions such as epilepsy and schizophrenia, there is evidence that disordered neuronal migration may contribute to the pathogenesis, as one of the more frequent neuropathological findings in these conditions is heterotopically located neurons in various positions of the CNS (Falkai et al., 2000; Flint and Kriegstein, 1997; Jakob and Beckmann, 1986; Palmini et al., 1991). Finally, several genes implicated in some forms of neurodegenerative disorders, including tau, amyloid precursor protein, cdk5, and presenilin, show defects in neuronal migration when deleted during embryogenesis (Chae et al., 1997; Hartmann et al., 1999; Herms et al., 2004; Ohshima et al., 1996; Takei et al., 2000), indicating that disordered or reactivation of developmental pathways may underlie some forms of neurodegeneration.

Neuronal Displacement Results from a Repeating of Two Distinct Events: Neurite Outgrowth and Nucleokinesis

Neuronal migration proceeds in a saltatory fashion, with a repeating of two basic events that underlie the movement (Edmondson and Hatten, 1987; Komuro and Rakic, 1995; Wichterle et al., 1997). First there is rapid extension and retraction of the leading neurite, which stabilizes tens of microns ahead of the soma. This is followed by forward displacement of the nucleus and soma into the leading process with concurrent retraction of the trailing process. The periods of leading process extension and periods of the cell somal translocation are not typically synchronized, suggesting that the two events may utilize distinct mechanisms that are somehow loosely linked.

Nucleokinesis: Translocation of the Nucleus into the Growing Neurite

New postmitotic neurons en route to the cortex display a simple monopolar morphology compared with the complex anatomy of adult cortical neurons. The nucleus is by far the largest cargo of the cell, with a volume that is approximately equal to the entire extranuclear volume of the cytoplasmic contents. The overwhelming size of the nucleus compared with other cellular contents, as well as its asynchronous translocation events, suggests that molecular determinants of its movement may be distinct from pathways that direct neurite outgrowth or other phases of neuronal migration.

*Correspondence: li-huei_tsai@hms.harvard.edu (L.-H.T.); jogleeson@ucsd.edu (J.G.G.)

Cytoskeletal Hallmarks during Neuronal Migration: Centrosome Positioning Precedes Nucleokinesis

As neurons migrate, there are major cytoskeletal alterations in the actin and microtubule (MT) cytoskeletons. MTs appear to emanate from a single location just in front of the nucleus and to extend anteriorly into the leading process and posteriorly to envelop the nucleus. The site of MT emanation has been identified as the centrosome (MTOC: microtubule organizing center) of the cell, which remains positioned in front of the nucleus (Gregory et al., 1988; Rakic, 1971; Solecki et al., 2004; Tanaka et al., 2004a). The MTs that project posteriorly toward the nucleus either terminate in the vicinity of the nuclear membrane in the shape of a "fork"-like structure at the anterior edge of the nucleus (Xie et al., 2003), or extend further back to envelop the nucleus in a "cage"-like structure (Rivas and Hatten, 1995). Additionally, an actin cytoskeleton underlying the membrane is evident, especially at the anterior (leading neurite) and posterior (trailing neurite) poles.

Dynamic imaging of the position of the centrosome and nucleus has revealed a spatial relationship that may be critical for nucleokinesis. In migrating neurons, the centrosome maintains a position in front of the nucleus as the cell propels forward (Tanaka et al., 2004a). Time-lapse analysis has indicated a model where first the centrosome advances into the leading process in front of the nucleus, which is followed by nucleokinesis in the direction of the centrosome, in a "two-stroke" fashion (Figure 1) (Solecki et al., 2004). This model suggests two distinct events underlie nucleokinesis: movement of the centrosome into the leading process, then movement of the nucleus toward the centrosome.

Lessons from Nucleokinesis in Lower Organisms

While we are just starting to uncover the regulation of nucleokinesis in neurons, the mechanism of nuclear movement has been well studied in model organisms. For example, in the filamentous fungus *Aspergillus nidulans* during asexual spore production, nuclei migrate toward the growing tip of the hyphae in a fashion that is highly reminiscent of nucleokinesis in migrating neurons. This long distance nuclear movement is MT dependent (Oakley and Morris, 1980; Oakley and Morris, 1981). Mutant screens have identified a series of Nuclear Distribution (NUD) factors that are critical for this movement (Xiang et al., 1994). These include *nudA*, *-G*, and *-K* encoding the mammalian orthologs of cytoplasmic dynein heavy chain, cytoplasmic dynein light chain, and actin-related protein-1 (Arp1), respectively, all components of the cytoplasmic dynein complex. Several novel genes including *nudE* and *nudC* also have strongly conserved mammalian orthologs, and *nudF* encodes a protein with significant homology to Lis1. (Osmani et al., 1990; Xiang et al., 1994; Xiang et al., 1995; Xiang et al., 1999). Studies have indicated the involvement of each of these NUD factors as critical in dynein motor function or as directly associated with the dynein motor complex in mammalian cells (Aumais et al., 2001; Aumais et al., 2003; Dawe et al., 2001; Niethammer et al., 2000; Sasaki et al., 2000; Smith et al., 2000). Together this data suggest that dynein components play critical roles in nucleokinesis.

Knockdown approaches focused on pronuclear migration and the first asymmetric cell division of the one cell stage embryo of *C. elegans* have provided another powerful model for the study of nucleokinesis. In this approach, dsRNA is injected into the female gonad to deplete specific transcripts. Then, following fertilization, a stereotypical series of events occurs: first, migration of the two pronuclei toward the midline; second, centrosome repositioning to opposite sides of the nucleus; and, finally, first mitosis (Doe and Bowerman, 2001; Guo and Kemphues, 1996). In this system, orthologs of dynein heavy chain and Lis1 show strong perinuclear localization. Two proteins that may mediate this microtubule attachment and coupling between the nucleus and centrosome during mitosis are Sun1 and Zyg-12. Zyg-12 binds the dynein complex through direct interaction with dynein light intermediate chain. Sun1 orthologs are components of the nuclear envelope. Therefore, the Sun1/Zyg-12 complex is poised to mediate dynein-based MT capture at the nuclear membrane (Malone et al., 2003). Mutations or depletions in each of these genes (*dhc-1*, *lis-1*, *Sun1*, and *Zyg-12*) show defects in centrosome repositioning, indicating a potential shared function (Cockell et al., 2004; Gönczy et al., 2001; Gönczy et al., 1999). The current model

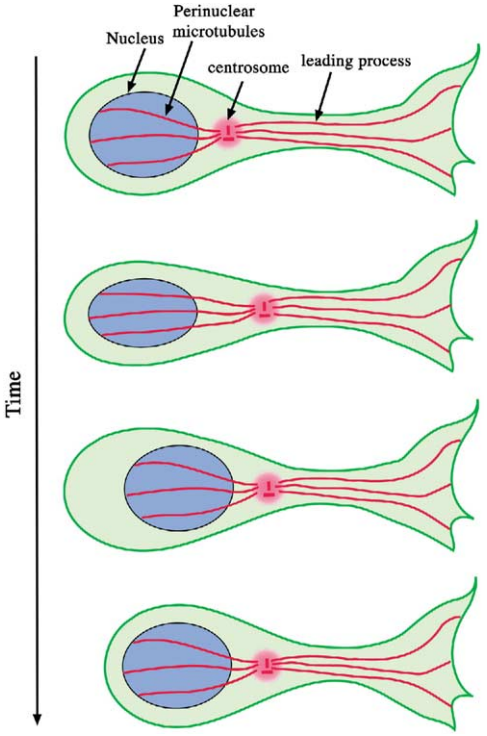

Figure 1. Movement of the Centrosome Precedes Movement of the Nucleus

Neuronal components include the nucleus, perinuclear microtubules, the centrosome, and the leading process microtubules. Time-lapse observations indicate that first the leading process advances in the direction of migration, stabilizing tens of microns in front of the cell. This is followed by advance of the centrosome into the leading process. Subsequently, the nucleus translocates forward in a saltatory fashion, and the trailing process of the neuron undergoes remodeling. Neuronal migration results from repeating of this basic sequence of events.

suggests dynein and Lis1, localized to the nuclear membrane, exert a "pulling" effect on MTs that are anchored to the centrosome to mediate its repositioning. In this model, longer astral MT encounter more motors and, thus, experience a stronger pulling force than shorter ones, reaching equilibrium when the centrosomes are on opposite sides of the nucleus.

Centrosome Positioning and Establishment of Cell Polarity in Neuronal Migration

The establishment of cell polarity, where cellular contents are distributed asymmetrically with reference to the center of the cell, is likely to be involved in nucleokinesis, because the nucleus moves asymmetrically within the confines of the cell membrane. The "*par*titioning-defective" genes (*par*) genes were identified in genetic screens for mutations in *C. elegans* that perturb anterior-posterior polarity in the zygote (Kemphues et al., 1988). During the first cell cycle, certain Par proteins become distributed asymmetrically along the A-P axis of the zygote to prepare for asymmetric cell division; the PDZ-containing proteins Par3 and Par6 become enriched at the anterior cortex, and are required for regulation of the mitotic spindle, thus ensuring that the first cleavage will be asymmetrical (Watts et al., 1996).

The role of the Par pathway in mammalian cell polarity has been established. In cultured hippocampal neurons, polarity is specified by spatially localized Par3/Par6 that involves PI3-kinase phosphorylation of GSK3-β, ensuring the development of a single axon (Shi et al., 2003). In wounded astrocytic monolayer cultures, cell polarity, centrosome reorientation, and wound healing depend on this pathway. Integrin-mediated signaling leads to polarized recruitment and activation of a cytoplasmic mPar6 complex containing the associated kinase PKCζ, in a pathway requiring polarized recruitment of Cdc42 (Etienne-Manneville and Hall, 2001). The mPar6/ PKCζ complex directly regulates GSK3-β through phosphorylation and localized inhibition of kinase activity, to promote polarization of the centrosome in the direction of cell protrusion (Etienne-Manneville and Hall, 2003). This occurs through unknown mechanisms involving spatially restricted association of the adenomatous polyposis coli (APC) molecule to microtubule ends (Etienne-Manneville and Hall, 2003) and likely depends on dynein function (Palazzo et al., 2001).

The role of the Par genes in nucleokinesis during neuronal migration has been explored recently (Solecki et al., 2004). Strikingly, unlike any other system where Par6α has been localized, Par6α is localized to the neuronal centrosome along with PKCζ, the Par6-associated kinase. Disruption of Par6α signaling through overexpression or siRNA-mediated knockdown leads to a dispersion of PKCζ and a perturbed perinuclear MT cytoskeleton (which may be due to the displacement of γ-tubulin from the centrosome) as well as impaired glial-guided migration. The emerging model is that Par6α is essential for nucleokinesis by maintaining the integrity of the microtubule cage and centrosome.

Dynein Motor Protein Component Lis1 and Ndel1 Mutations Result in Defects in Nucleokinesis with Abnormalities in Nuclear-Centrosome Coupling

Disruptions of Lis1 result in a dose-dependent defect in neuronal migration that is probably a result of a defect in nucleokinesis. In these migrating neurons, the neurite outgrowth phase of migration is unaffected, but there is a profound defect in nucleokinesis (Hirotsune et al., 1998; McManus et al., 2004; Shu et al., 2004; Tanaka et al., 2004a). Because mammalian Lis1 plays an important role in dynein function (Smith et al., 2000), the data suggests that dynein is critical for nucleokinesis in neuronal migration.

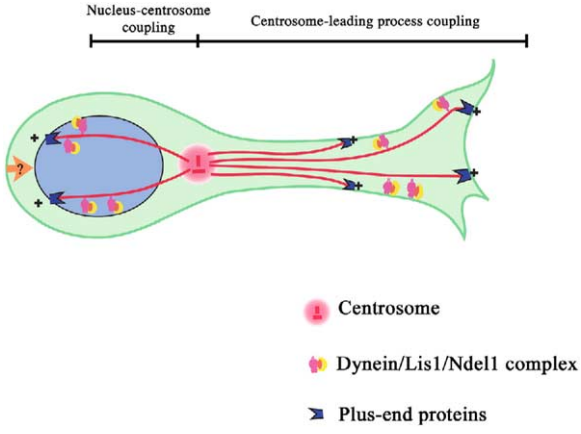

Figure 2. Two Models for Nucleokinesis

In the first, activation of dynein motor activity anchored within the leading process has the effect of "pulling" on microtubules attached to the centrosome and to the nucleus. In this model, defects in dynein activity are predicted to lead to alterations in centrosome-leading process coupling. In the second model, activation of dynein anchored to the nuclear membrane leads to a displacement of the nucleus toward the centrosome. In this model, defects in dynein activity should lead to alterations in nuclear-centrosome coupling. Plus end proteins may serve in the capture of MTs at these respective sites. Additional forces may exist in the rear of the cell to propel the nucleus forward (indicated by arrow).

Two models have been proposed for the role of the dynein complex in neuronal nucleokinesis. In the first model, dynein is anchored to membrane sites in the neuronal leading process. The "minus" end motor activity of dynein then acts on microtubules extending from the centrosome to pull it in the direction of the leading process. Dynein has been localized to membrane sites in epithelial cells, indicating that it is positioned to mediate such an effect (Busson et al., 1998). This model would predict that disruption of dynein function leads to defects in centrosome-leading process coupling (Figure 2). In the second model, the dynein complex is anchored to the nuclear membrane. The motor activity of dynein acting on microtubules extending from the centrosome then pulls the nucleus in the direction of the centrosome. Dynein has been localized to the nuclear membrane (Salina et al., 2002), indicating that it is also positioned to mediate this effect as well. This model would predict that disruption of dynein leads to defects in nucleus-centrosome coupling.

Indeed, data is accumulating that nucleus-centrosome coupling is a critical event in neuronal migration, and many of the factors mentioned above are required for this coupling. Disruption of mouse Lis1, dynein, or Ndel1 (an ortholog of NudE) leads to defective nucleus centrosomal coupling, with the centrosome-nuclear distance increased appreciably following genetic per-

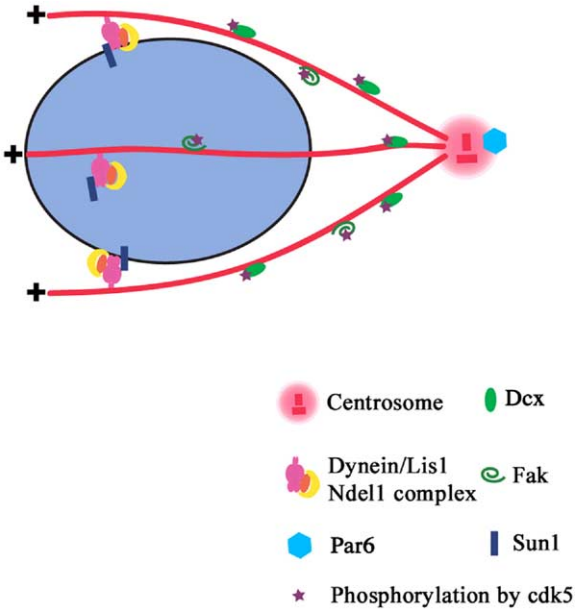

Figure 3. Molecules Likely Involved in Stabilization of Centrosome to Nucleus Bridging MTs and in MT Capture at the Nuclear Envelope

In migrating neurons, Dynein/Lis1 and Ndel1 are localized to the centrosome and the nuclear membrane. Fak and Dcx, both substrates of cdk5 phosphorylation, are localized to perinuclear MTs. Capture of MTs at the nuclear membrane may involve Sun1, a protein linked to dynein function through Zyg-12, or other mechanisms discussed in the text. Dynein activity localized to the nuclear membrane has the effect of translocating the nucleus toward the centrosome. Par6 and other polarity proteins may regulate the position of the centrosome during migration or the initial outgrowth of MTs from the centrosome.

turbation (Shu et al., 2004; Tanaka et al., 2004a). Ndel1, Lis1, or dynein disruptions lead to disruption in microtubules bridging between the centrosome and the nucleus, possibly due to failure of microtubules to be "captured" at the nuclear membrane. These studies relied largely on static measurements of dynamic coupling, so future experiments will require live cell imaging to determine a more detailed view of cellular mechanisms.

Control of Microtubule Stability and Capture at the Nuclear Membrane

The data together suggest a model in which the nucleus is coupled to the centrosome during neuronal migration (Figure 3). Which factors are critical for polymerization and stabilization of these MTs? Dcx may be involved in the stabilization of these MTs, as it localizes to MT bridging between the nucleus and centrosome during migration. Furthermore, overexpression of Dcx in neurons enhances the rate of migration and the degree of nuclear-centrosome coupling. In addition, in utero electroporation of Dcx siRNA results in disruption of radial migration and cortical development, which is reminiscent of the human subcortical band heterotopias (Bai et al., 2003). However, a direct role has not been established for a role of the Dcx family in stabilization of the MTs during neuronal migration.

Another regulator of microtubule stability in migrating neurons is focal adhesion kinase (Fak). Fak plays an important role in stabilizing MTs between the nucleus and centrosome. Fak serves as a substrate for cdk5 phosphorylation at serine 732, and S732-phosphorylated Fak localizes to the pericentrosomal region and MTs in a "fork" structure between the nucleus and centrosome. Furthermore, overexpression of a S732-nonphosphorylatable Fak causes disorganization of the microtubule fork, impaired nucleokinesis, and disrupted neuronal migration. Interestingly, in the absence of S732 phosphorylation of Fak, the distal pole of the nucleus moves in the absence of advancement of the proximal pole. Therefore, phosphorylation of Fak at S732 is important for organization of MTs that may function to pull the proximal region of the nucleus into the leading process, likely in the direction of the centrosome. As both Dcx and Fak are substrates of cdk5 phosphorylation (Tanaka et al., 2004b; Xie et al., 2003), this suggests that cdk5 may play an important role in regulation of microtubule-associated protein function at this key MT structure.

Microtubule Interactions at the Cell Cortex

What are the mechanisms of MT capture by the dynein complex at the nuclear membrane? "Plus" end capping proteins Clip-170, EB1, and APC are dynamically localized to the MT plus ends (Mimori-Kiyosue et al., 2000a; Mimori-Kiyosue et al., 2000b; Perez et al., 1999) and are likely to be critical for capture of these ends at distinct cellular locations such as the nuclear membrane. In non-neuronal cells, the protein IQGAP1, a small GTPase effector protein, interacts with Clip-170 to mediate capture of MT plus ends in response to Rac1 or Cdc42 (Fukata et al., 2002). Another possible mechanism for MT capture is based on the finding that EB1 associates with components of the dynactin complex and cytoplasmic dynein intermediate chain (Berrueta et al., 1999), suggesting that EB1-capped MTs may be captured by nuclear membrane-attached dynein.

Although these pathways have not yet been tested in neuronal migration, they exhibit a high degree of conservation throughout evolution. A similar mechanism of microtubule capture at the cell cortex has been demonstrated by studies of budding in *Saccharomyces cerevisiae.* Genetic studies have shown an important role for dynein and cyclin-dependent kinase (cdk) in nuclear migration during bud formation (Lee et al., 2003). In yeast, nuclear migration and spindle movement occur predominantly in two steps: the first is movement of the nucleus to a position adjacent to the neck. Early in the cell cycle, a cortical attachment site for MT composed of Kar9 and associated proteins forms at the emerging bud tip. If a growing cytoplasmic MT encounters this site, it can be captured (Huisman and Segal, 2005). Subsequent shrinkage of the captured MT pulls the nucleus toward the nascent bud and orients the spindle pole body (centrosome equivalent) along the mother-bud axis. This process is driven by a single cdk (Cdk1p) that probably acts on a range of targets at MT plus ends for MT capture. The second step is movement of the nucleus into the neck. A favored hypothesis is that dynein and Lis1 are anchored in the bud cortex and pull on the microtubules by "walking" in the minus end

direction toward the spindle pole body (Sheeman et al., 2003).

Remaining Questions

How are extracellular guidance cues transmitted to determine positioning of the centrosome? How is process outgrowth linked to centrosome movement and nucleokinesis, and what is the signal that triggers nucleokinesis following centrosomal translocation? Which molecules are required to mediate leading process-centrosome coupling? Are there "pushing" forces exerted on the posterior side of the nucleus to propel it forward? What is the role of actin remodeling in determining dynamic changes in cell morphology around the nucleus or the trailing edge of the cell? These are among the important questions that remain in the field of nucleokinesis. Evolutionarily conserved pathways from yeast, worms, fungi, and flies may help uncover molecular details of this fascinating process.

Acknowledgments

The authors would like to thank Tianzhi Shu for contributing the figures, T. Shu, Benjamin Samuels, Zhigang Xie, Ramses Ayala, Teruyuki Tanaka, Stephanie Bielas, Hiroyuki Koizumi, and Holden Higgenbotham for comments on the manuscript. L.-H.T. is an investigator of the Howard Hughes Medical Institute. The work is supported by NIH grants to L.-H.T. (NS 37007) and to J.G.G. (NS 41537, 42749, and 47101).

Selected Reading

Aumais, J.P., Tunstead, J.R., McNeil, R.S., Schaar, B.T., McConnell, S.K., Lin, S.H., Clark, G.D., and Yu-Lee, L.Y. (2001). J. Neurosci. *21*, RC187.

Aumais, J.P., Williams, S.N., Luo, W., Nishino, M., Caldwell, K.A., Caldwell, G.A., Lin, S.H., and Yu-Lee, L.Y. (2003). J. Cell Sci. *116*, 1991–2003.

Bai, J., Ramos, R.L., Ackman, J.B., Thomas, A.M., Lee, R.V., and LoTurco, J.J. (2003). Nat. Neurosci. *6*, 1277–1283.

Berrueta, L., Tirnauer, J.S., Schuyler, S.C., Pellman, D., and Bierer, B.E. (1999). Curr. Biol. *9*, 425–428.

Busson, S., Dujardin, D., Moreau, A., Dompierre, J., and De Mey, J.R. (1998). Curr. Biol. *8*, 541–544.

Chae, T., Kwon, Y.T., Bronson, R., Dikkes, P., Li, E., and Tsai, L.H. (1997). Neuron *18*, 29–42.

Cockell, M.M., Baumer, K., and Gonczy, P. (2004). J. Cell Sci. *117*, 4571–4582.

Dawe, A.L., Caldwell, K.A., Harris, P.M., Morris, N.R., and Caldwell, G.A. (2001). Dev. Genes Evol. *211*, 434–441.

des Portes, V., Francis, F., Pinard, J.M., Desguerre, I., Moutard, M.L., Snoeck, I., Meiners, L.C., Capron, F., Cusmai, R., Ricci, S., et al. (1998). Hum. Mol. Genet. *7*, 1063–1070.

Doe, C.Q., and Bowerman, B. (2001). Curr. Opin. Cell Biol. *13*, 68–75.

Edmondson, J.C., and Hatten, M.E. (1987). J. Neurosci. *7*, 1928–1934.

Etienne-Manneville, S., and Hall, A. (2001). Cell *106*, 489–498.

Etienne-Manneville, S., and Hall, A. (2003). Nature *421*, 753–756.

Falkai, P., Schneider-Axmann, T., and Honer, W.G. (2000). Biol. Psychiatry *47*, 937–943.

Flint, A.C., and Kriegstein, A.R. (1997). Curr. Opin. Neurol. *10*, 92–97.

Fukata, M., Watanabe, T., Noritake, J., Nakagawa, M., Yamaga, M., Kuroda, S., Matsuura, Y., Iwamatsu, A., Perez, F., and Kaibuchi, K. (2002). Cell *109*, 873–885.

Gleeson, J.G., Allen, K.M., Fox, J.W., Lamperti, E.D., Berkovic, S., Scheffer, I., Cooper, E.C., Dobyns, W.B., Minnerath, S.R., Ross, M.E., and Walsh, C.A. (1998). Cell *92*, 63–72.

Gönczy, P., Pichler, S., Kirkham, M., and Hyman, A.A. (1999). J. Cell Biol. *147*, 135–150.

Gönczy, P., Bellanger, J.-M., Kirkham, M., Pozniakowski, A., Baumer, K., Phillips, J.B., and Hyman, A.A. (2001). Dev. Cell *1*, 363–375.

Gregory, W.A., Edmondson, J.C., Hatten, M.E., and Mason, C.A. (1988). J. Neurosci. *8*, 1728–1738.

Guo, S., and Kemphues, K.J. (1996). Curr. Opin. Genet. Dev. *6*, 408–415.

Hartmann, D., De Strooper, B., and Saftig, P. (1999). Curr. Biol. *9*, 719–727.

Herms, J., Anliker, B., Heber, S., Ring, S., Fuhrmann, M., Kretzschmar, H., Sisodia, S., and Muller, U. (2004). EMBO J. *23*, 4106–4115.

Hirotsune, S., Fleck, M.W., Gambello, M.J., Bix, G.J., Chen, A., Clark, G.D., Ledbetter, D.H., McBain, C.J., and Wynshaw-Boris, A. (1998). Nat. Genet. *19*, 333–339.

Huisman, S.M., and Segal, M. (2005). J. Cell Sci. *118*, 463–471.

Jakob, H., and Beckmann, H. (1986). J. Neural Transm. *65*, 303–326.

Kemphues, K.J., Priess, J.R., Morton, D.G., and Cheng, N.S. (1988). Cell *52*, 311–320.

Komuro, H., and Rakic, P. (1995). J. Neurosci. *15*, 1110–1120.

Lee, W.L., Oberle, J.R., and Cooper, J.A. (2003). J. Cell Biol. *160*, 355–364.

Malone, C.J., Misner, L., Le Bot, N., Tsai, M.C., Campbell, J.M., Ahringer, J., and White, J.G. (2003). Cell *115*, 825–836.

McManus, M.F., Nasrallah, I.M., Pancoast, M.M., Wynshaw-Boris, A., and Golden, J.A. (2004). Am. J. Pathol. *165*, 775–784.

Mimori-Kiyosue, Y., Shiina, N., and Tsukita, S. (2000a). J. Cell Biol. *148*, 505–518.

Mimori-Kiyosue, Y., Shiina, N., and Tsukita, S. (2000b). Curr. Biol. *10*, 865–868.

Niethammer, M., Smith, D.S., Ayala, R., Peng, J., Ko, J., Lee, M.S., Morabito, M., and Tsai, L.H. (2000). Neuron *28*, 697–711.

Oakley, B.R., and Morris, N.R. (1980). Cell *19*, 255–262.

Oakley, B.R., and Morris, N.R. (1981). Cell *24*, 837–845.

Ohshima, T., Ward, J.M., Huh, C.G., Longenecker, G., Pant, H.C., Brady, R.O., Martin, L.J., and Kulkarni, A.B. (1996). Proc. Natl. Acad. Sci. USA *93*, 11173–11178.

Osmani, A.H., Osmani, S.A., and Morris, N.R. (1990). J. Cell Biol. *111*, 543–551.

Palazzo, A.F., Joseph, H.L., Chen, Y.J., Dujardin, D.L., Alberts, A.S., Pfister, K.K., Vallee, R.B., and Gundersen, G.G. (2001). Curr. Biol. *11*, 1536–1541.

Palmini, A., Andermann, F., Olivier, A., Tampieri, D., Robitaille, Y., Andermann, E., and Wright, G. (1991). Ann. Neurol. *30*, 741–749.

Perez, F., Diamantopoulos, G.S., Stalder, R., and Kreis, T.E. (1999). Cell *96*, 517–527.

Rakic, P. (1971). J. Comp. Neurol. *141*, 283–312.

Reiner, O., Carrozzo, R., Shen, Y., Wehnert, M., Faustinella, F., Dobyns, W.B., Caskey, C.T., and Ledbetter, D.H. (1993). Nature *364*, 717–721.

Rivas, R.J., and Hatten, M.E. (1995). J. Neurosci. *15*, 981–989.

Salina, D., Bodoor, K., Eckley, D.M., Schroer, T.A., Rattner, J.B., and Burke, B. (2002). Cell *108*, 97–107.

Sasaki, S., Shionoya, A., Ishida, M., Gambello, M.J., Yingling, J., Wynshaw-Boris, A., and Hirotsue, S. (2000). Neuron *28*, 681–696.

Sheeman, B., Carvalho, P., Sagot, I., Geiser, J., Kho, D., Hoyt, M.A., and Pellman, D. (2003). Curr. Biol. *13*, 364–372.

Shi, S.H., Jan, L.Y., and Jan, Y.N. (2003). Cell *112*, 63–75.

Shu, T., Ayala, R., Nguyen, M.D., Xie, Z., Gleeson, J.G., and Tsai, L.H. (2004). Neuron *44*, 263–277.

Smith, D.S., Niethammer, M., Ayala, R., Zhou, Y., Gambello, M.J., Wynshaw-Boris, A., and Tsai, L.H. (2000). Nat. Cell Biol. *2*, 767–775.

Solecki, D.J., Model, L., Gaetz, J., Kapoor, T.M., and Hatten, M.E. (2004). Nat. Neurosci. *7*, 1195–1203.

Takei, Y., Teng, J., Harada, A., and Hirokawa, N. (2000). J. Cell Biol. *150*, 989–1000.

Tanaka, T., Serneo, F.F., Higgins, C., Gambello, M.J., Wynshaw-Boris, A., and Gleeson, J.G. (2004a). J. Cell Biol. *165*, 709–721.

Tanaka, T., Serneo, F.F., Tseng, H.C., Kulkarni, A.B., Tsai, L.H., and Gleeson, J.G. (2004b). Neuron *41*, 215–227.

Watts, J.L., Etemad-Moghadam, B., Guo, S., Boyd, L., Draper, B.W., Mello, C.C., Priess, J.R., and Kemphues, K.J. (1996). Development *122*, 3133–3140.

Wichterle, H., Garcia-Verdugo, J.M., and Alvarez-Buylla, A. (1997). Neuron *18*, 779–791.

Xiang, X., Beckwith, S.M., and Morris, N.R. (1994). Proc. Natl. Acad. Sci. USA *91*, 2100–2104.

Xiang, X., Osmani, A.H., Osmani, S.A., Xin, M., and Morris, N.R. (1995). Mol. Biol. Cell *6*, 297–310.

Xiang, X., Zuo, W., Efimov, V.P., and Morris, N.R. (1999). Curr. Genet. *35*, 626–630.

Xie, Z., Sanada, K., Samuels, B.A., Shih, H., and Tsai, L.H. (2003). Cell *114*, 469–482.