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Cyclin-Dependent Kinase 5 Permits Efficient Cytoskeletal Remodeling—a Hypothesis on Neuronal Migration

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Migration of neurons to their proper position underlies mammalian brain development. To remain on the proper path, a migrating neuron needs to detect various external signals and respond by efficiently remodeling its cytoskeleton. Cyclin-dependent kinase 5 (Cdk5), a member of the cyclin-dependent kinase family, regulates neuronal migration by phosphorylating a number of intracellular substrates. Deficiencies in Cdk5 preferentially cause impairments in radial glia–guided migration, a process that involves complex remodeling of the cytoskeleton, particularly the microtubules. Furthermore, the defined substrates of Cdk5 that are important for migration generally link Cdk5 to the cytoskeleton. Interestingly, none of these phosphorylation events seem to directly control the activity of the substrates. Taken together, these findings support a model in which Cdk5 does not directly control the detection of any specific external signals but instead regulates efficient remodeling of the cytoskeleton through phosphorylation of multiple substrates.

Keywords: cyclin-dependent kinase 5, migration, microtubules

Neuronal Migration during Neocortical Development

Formation of the highly structured mammalian neocortex requires carefully choreographed migration of neurons during development (Fig. 1). The principal types of neurons that compose the neocortex are pyramidal neurons and interneurons. The pyramidal neurons, which are generated in the dorsal ventricular zone, migrate to their final cortical position via a radial path. The interneurons, which are produced in the ventral telencephalon, migrate to the dorsal cortex tangentially and then to their final cortical lamina radially. The first distinct event of neocortical histogenesis is the formation of a preplate above the ventricular zone by the earliest born cortical neurons. The preplate is subsequently split into the marginal zone and the subplate by cohorts of radially migrating neurons that form a cortical plate in between. The assembly of the cortical plate follows an "inside out" order, in which earlier born neurons reside in deeper layers, whereas later born neurons migrate past them to settle in more superficial layers.

Recent studies have revealed that movement along the radial path of migration is more diverse than previously thought. In the early stages, most neurons generated at the dorsal ventricular zone inherit the process of the mother radial glia. These neurons migrate by somal translocation, that is, long-range movement of the nucleus or cell soma to their cortical position near the pia (Miyata and others 2001; Nadarajah and others 2001) (Fig. 1). In later stages, somal translocation is rare. Instead, most neurons move in a complicated fashion, undergoing 4 distinct phases of migration (Noctor and others 2004) (Fig. 1). First, they use a pia-directed leading process to move to the subventricular zone. Second, they pause at the subventricular zone and become multipolar. Third, they form a ventricle-directed leading process and move back to the ventricular zone. Finally, they reverse polarity and use a pia-directed leading process to move along the radial glia toward the destined cortical position. This final phase corresponds to a migration mode called locomotion (Nadarajah and others 2001). Ventricle-directed migration and changes in cellular morphology have also been observed in interneurons after they migrate to the dorsal cortex via the tangential path (Nadarajah and others 2002, 2003).

The complex modes of migration suggest that different neurons detect distinct external signals along the migration path and that in response to these signals, neurons must dynamically reorganize their cytoskeleton to alter cellular morphology and achieve specific modes of migration. In the following sections, we discuss an essential role of cyclin-dependent kinase 5 (Cdk5) in regulating neuronal migration through dynamic reorganization of the cytoskeleton.

Neuronal Migration Defects in Cdk5 Mutant Embryos

Cdk5 is a member of the cyclin-dependent kinase (Cdk) family that is activated by p35 and p39. However, unlike other Cdks, expression of the Cdk5 activators and associated kinase activity is predominant in postmitotic neurons (Dhavan and Tsai 2001). Mouse embryos lacking Cdk5 or both activators display severe neuronal migration defects throughout the brain, including the neocortex, hippocampus, cerebellum, olfactory bulb, thalamus, and brain stem (Ohshima and others 1996; Chae and others 1997; Gilmore and others 1998; Ko and others 2001). Detailed analysis of the neocortex suggests that Cdk5-associated migration defects are restricted to distinct populations of neurons. In Cdk5-deficient mouse embryos, the preplate is formed normally, and the earliest wave of pyramidal neurons destined to the cortical plate can migrate into and split the preplate (Ohshima and others 1996; Chae and others 1997; Gilmore and others 1998; Ko and others 2001). The following cohorts of pyramidal neurons, however, are unable to migrate past earlier born neurons but instead accumulate underneath, resulting in an "inverted cortex" (Ohshima and others 1996; Chae and others 1997; Gilmore and others 1998; Ko and others 2001). Interestingly, migration of interneurons, which also follow an inside out order in the formation of the cortical plate (Valcanis and Tan 2003), is unaffected by Cdk5 deficiency (Gilmore and Herrup 2001; Hammond and others 2004).

The restriction of Cdk5-associated migration defects to specific neuronal populations suggests that the need for Cdk5 varies among neurons undergoing different modes of migration. Therefore, to understand how Cdk5 functions to regulate migration, it is important to understand how the phenotype of Cdk5 deficiency compares with other mouse models that have impaired neuronal migration.

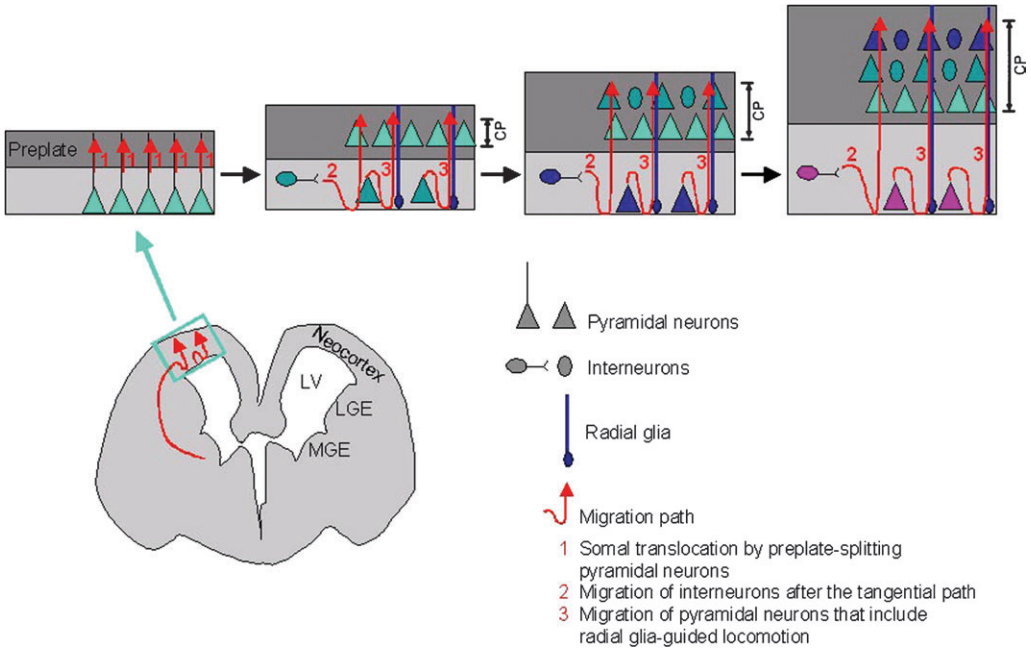

Figure 1. Neuronal migration during neocortical development. Bottom panel: schematic drawing of a coronal section of an embryonic mouse brain and the migration paths of the pyramidal neurons and interneurons. Top panels: schematic drawing of the developing neocortex (panels from left to right represent early to late stages of the neocortex). At early stages, a wave of pyramidal neurons migrates into the preplate by somal translocation to form a CP. At later stages, the CP is expanded in an inside out order by cohorts of neurons, which include both pyramidal neurons born at the dorsal ventricular zone and interneurons born at the basal telencephalon. The migration of both pyramidal neurons and interneurons involves a ventricle-directed phase and switch of the cell polarity prior to the change of migration direction. The final phase of the migration of pyramidal neurons, but not interneurons, uses the radial glia as a guide. Cdk5 deficiency preferentially impairs the migration of pyramidal neurons that undergo distinct phases, including glia-guided locomotion (indicated as migration path 3 in the schematic). CP, cortical plate; LV, lateral ventricle; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence.

Cdk5 and the Reelin pathway

Reelin is an extracellular molecule that regulates migration and positioning of neurons (Tissir and Goffinet 2003; Bielas and others 2004), Therefore, reelin likely serves as an extracellular signal that migrating neurons respond to rather than as a direct regulator of cytoskeleton dynamics. The migration defects in the neocortex, hippocampus, and cerebellum in Cdk5-deficient embryos (Ohshima and others 1996; Chae and others 1997; Gilmore and others 1998; Ko and others 2001) are strikingly similar, although not identical, to that in the corresponding regions of reelin pathway mutants (D'Arcangelo and others 1995; Howell and others 1997; Sheldon and others 1997; Ware and others 1997; Trommsdorff and others 1999). However, in contrast to Cdk5-deficient mice, the earliest wave of pyramidal neurons in reelin pathway mutants is unable to split the preplate. This distinction is important because this first cohort of pyramidal neurons migrate mainly by somal translocation. Somal translocation requires only a single step of nuclear translocation and shortening of the leading process. The later cohorts of pyramidal neurons migrate by distinct phases that involve multiple switches in polarity and repeated cycles of locomotion. The later born neurons, therefore, require a much higher degree of cytoskeletal rearrangement than the first wave. Because the effects of Cdk5 deficiency are only manifested in later born neurons, it is logical to hypothesize that Cdk5 is necessary for organizing complex cytoskeletal dynamics in response to migration signals such as reelin.

This hypothesis is consistent with the genetic interaction between the reelin pathway and the Cdk5 pathway (Ohshima and others 2001, 2002; Beffert and others 2004). The pyramidal neurons with compromised Cdk5 activity may still be able to reorganize their cytoskeleton in response to reelin at an efficiency that is sufficient to support migration. However, when reelin signaling is also decreased, neurons not only have a reduced ability to reorganize their cytoskeleton but also have a reduced signal to do so. Thus, the Cdk5 pathway and the reelin pathway should show synergistic effects on the regulation of neuronal migration.

Hypothesis: Cdk5 Permits Efficient Remodeling of the Microtubule Cytoskeleton

Based on the comparison with reeler mice, we hypothesize that Cdk5 does not directly control the detection of external migration signals but generally permits efficient remodeling of the cytoskeleton required for specific modes of migration. According to this hypothesis, Cdk5-deficient neurons can detect and propagate migration signals normally. However, normal levels of signaling do not lead to efficient cytoskeletal reorganization in these neurons. Thus, the migration modes that require complex cytoskeletal rearrangement, such as radial glia–guided locomotion, are selectively impaired. Two further lines of evidence suggest that Cdk5 more directly regulates the microtubule cytoskeleton. First, migration of interneurons is normal in Cdk5-deficient mice. Whereas pyramidal neurons are thought to require microtubules for nucleokinesis (Tsai and Gleeson 2005), interneurons rely more on myosin and the actin cytoskeleton (Bellion and others 2005). Therefore, the migration modes involving radial glia guides and complex remodeling of the microtubule cytoskeleton are particularly dependent on Cdk5. Second, Cdk5-dependent phosphorylation events that may be important for neuronal migration are more associated with microtubules rather than actin (see below).

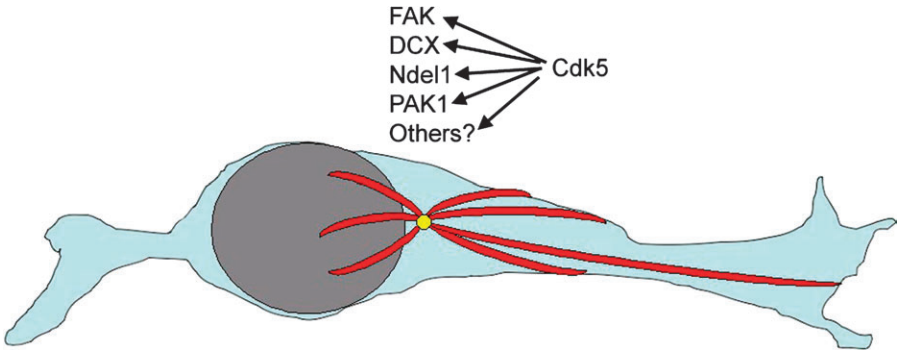

Figure 2. Cdk5 regulates microtubules through phosphorylation of multiple substrates in a migrating neuron. Cdk5 phosphorylation of FAK, DCX, Ndel1, PAK, and perhaps other substrates regulates organization of microtubules (depicted in red) emanating from the centrosome (yellow). These microtubules link the centrosome to the nucleus (gray) and the cell cortex.

Cytoskeletal Defects in Cdk5-Compromised Neurons

Previous studies have provided direct evidence that Cdk5 deficiency causes cytoskeletal defects. The morphology of migrating p35–/– neurons has been analyzed in vivo (Gupta and others 2003). Strikingly, these neurons did not display a typical leading process that aligns with the radial glia. Instead, they extend a branched leading process that is unable to efficiently attach to the radial glia (Gupta and others 2003). According to our hypothesis, this phenotype may reflect the impaired ability of p35–/– neurons to reorganize their microtubule cytoskeleton for radial glial attachment in response to external signals on or around the radial glial process. These signals likely include other molecules in addition to reelin because branched leading processes are rare in reelin pathway mutant mice (Gupta and others 2003).

Molecular Mechanisms of Cdk5 Function in Migrating Neurons

To understand the mechanisms by which Cdk5 regulates the microtubule cytoskeleton in a migrating neuron, it is important to also take a closer look at how microtubules drive neurons to move. In a simplified model (Fig. 2) mainly based on in vitro experiments, a migrating neuron extends a prominent leading process from the cell soma, which is mainly occupied by the nucleus. The centrosome is placed in the leading process ahead of the nucleus and is linked to the leading edge and the nucleus by microtubules. The microtubules control the movement of the nucleus toward the centrosome, a process termed nucleokinesis. Repeated cycles of leading process outgrowth and nucleokinesis result in continued migration of the neuron.

Cdk5 is important for the proper organization of microtubules that link the nucleus and the centrosome. This role was discovered in the study of Cdk5 phosphorylation of focal adhesion kinase (FAK). Cdk5 phosphorylates FAK at S732 both in vitro and in the developing brain (Xie and others 2003). In Cdk5–/– neurons and neurons expressing the non-phosphorylatable mutant FAK-S732A, the microtubules between the nucleus and the centrosome were disorganized (Xie and others 2003). The disorganization of these microtubules likely contributes to a nuclear movement defect in Cdk5-deficient neurons (Xie and others 2003). Therefore, at least partially by phosphorylating FAK, Cdk5 enables neurons to properly organize the microtubules that control nucleokinesis. It will be important to further clarify the role of FAK in neuronal migration using loss-of-function experiments. Existing models are not yet ideal because FAK-deficient mice are early embryonic lethal and, in a more recent study (Beggs and others 2003), the highly stable FAK protein is likely still present in migrating neurons of conditional knockout mice. Furthermore, it will be important to determine whether pyk2, a close homolog of FAK (Xiong and Mei 2003), can compensate for FAK deficiency in neuronal migration.

Another substrate of Cdk5 that is likely important for regulation of microtubules in migrating neurons is doublecortin (DCX) (Graham and others 2004; Tanaka and others 2004). DCX exhibits the properties of a classical microtubule-associated protein (MAP) and contains 2 evolutionarily conserved tubulin-binding repeats (Reiner and Coquelle 2005). Mutations in DCX lead to type I lissencephaly in humans, and silencing of DCX expression by RNAi results in neuronal migration defects in rats (des Portes and others 1998; Gleeson and others 1998; Bai and others 2003). Furthermore, DCX has been suggested to regulate the distance of nuclear–centrosome coupling, most likely through mediation of the microtubule networks involved in nucleokinesis (Tanaka and others 2004). Cdk5 phosphorylates DCX at S297, and this event regulates the interaction between DCX and microtubules (Tanaka and others 2004). Mutation of S297 blocks the effects of DCX in a migration-dependent cellular reaggregation assay in a fashion similar to pharmacological inhibition of Cdk5 activity (Tanaka and others 2004).

In addition to DCX, other MAPs, such as MAP1B, may be involved in Cdk5-dependent neuronal migration. MAP1B plays an important role in cortical neuronal migration (Takei and others 2000; Teng and others 2001; Gonzalez-Billault and others 2005). In dissociated cortical neurons, reelin or netrin treatment induced phosphorylation of MAP1B in a glycogen synthase kinase (GSK) 3- and Cdk5-dependent manner (Del Rio and others 2004; Gonzalez-Billault and others 2005). In nonstimulated brain slices, however, Cdk5 did not appear to phosphorylate MAP1B (Kawauchi and others 2005). Therefore, Cdk5 may phosphorylate MAP1B to facilitate microtubule reorganization when neurons are exposed to external signals such as reelin and netrin. Cdk5 also phosphorylates tau (Dhavan and Tsai 2001). However, phosphorylation of tau has been shown to be independent of Cdk5 in embryonic brains (Ko and others 2001) and thus may not participate in Cdk5-dependent neuronal migration.

Cdk5 may also regulate microtubules by phosphorylating Ndel1, a mouse homolog of the fungal nuclear distribution protein NudE (Morris 2003). Ndel1 is required for efficient neuronal migration during brain development (Shu and others 2004; Sasaki and others 2005). Cdk5 phosphorylates Ndel1 in vitro and in vivo at multiple sites (Niethammer and others 2000;

Sasaki and others 2000; Ko and others 2001). These phosphorylation events may enable Ndel1 to bind 14-3-3ε and strengthen its interaction with katanin (Toyo-oka and others 2005). Because Ndel1 interacts with the microtubule motor dynein and katanin is a microtubule-severing protein, it is likely that phosphorylation of Ndel1 partially mediates the function of Cdk5 in microtubule regulation and neuronal migration.

P21-activated kinase (PAK) may also participate in Cdk5-dependent microtubule remodeling. PAK1 is a small guanosine triphosphate hydrolase (GTPase) effector that regulates both actin and microtubules (Hofmann and others 2004). Cdk5 phosphorylates PAK1 at T212 (Rashid and others 2001). T212-phosphorylated PAK1 is present at high levels in embryonic and early postnatal, but not adult, brains (Zhong and others 2003), suggesting that this phosphorylation may be involved in neuronal migration. Expression of the nonphosphorylatable mutant PAK1-T212A in cultured cortical neurons severely affects neuritic patterning (Rashid and others 2001). Because T212 phosphorylation by the Cdk5 homolog Cdc2 in mitotic cells regulates astral microtubules (Banerjee and others 2002), the altered neuritic patterning in cortical neurons may result from a defect in microtubule organization.

Recent studies have revealed collapsin response–mediating protein-2 (CRMP-2) as another link between Cdk5 and microtubules. CRMP-2 is a microtubule-regulating protein essential for proper establishment of neuronal polarity (Arimura and others 2004). Cdk5 together with GSK-3β phosphorylates CRMP-2 to inhibit its association with microtubules (Uchida and others 2005; Yoshimura and others 2005). Immunoblotting experiments using a phosphospecific antibody suggest that CRMP-2 is a physiological substrate of Cdk5 during brain development (Uchida and others 2005). Thus, it will be interesting to determine whether CRMP-2 and its phosphorylation by Cdk5 regulate neuronal migration.

Cdk5-Dependent Phosphorylation Does Not Directly Control Substrate Activity

It is important to note that Cdk5-catalyzed phosphorylation events during neuronal migration do not seem to directly control the activity of the substrates. First, phosphorylation of FAK at S732 by Cdk5 does not directly alter tyrosine phosphorylation of FAK (Xie and others 2003; our unpublished data). Second, phosphorylation of PAK1 at T212 by Cdk5 does not directly affect the kinase activity of PAK1 (Rashid and others 2001). Third, phosphorylation of Dab1 at S491 by Cdk5 does not regulate the tyrosine phosphorylation of Dab1 (Keshvara and others 2002). Lastly, Cdk5-dependent phosphorylation of DCX (Tanaka and others 2004), Ndel1 (Toyo-oka and others 2003, 2005), and CRMP-2 (Uchida and others 2005; Yoshimura and others 2005) seems to regulate protein–protein or protein–microtubule interactions.

Summary

Here we propose a hypothesis that Cdk5 generally permits efficient microtubule remodeling in migrating neurons in response to external signals (Fig. 2). This hypothesis is consistent with the histological and cellular phenotypes associated with Cdk5 deficiency, the similarities and differences between the Cdk5 pathway and the reelin pathway, and the lack of direct effect of Cdk5 on substrate activity. Nonetheless, there are still unanswered questions. Our hypothesis predicts that, similar to the reelin pathway, other signaling pathways important for neuronal migration may also genetically interact with the Cdk5 pathway. Furthermore, it is unclear how Cdk5-mediated phosphorylation events render microtubules more susceptible to remodeling. One possibility is that Cdk5 phosphorylates various microtubule-regulating proteins to locally stabilize or destabilize microtubules. To test this possibility, future studies need to analyze the dynamic behavior of the microtubules as well as the substrates at high precision in migrating neurons. The studies to date have not addressed whether the drastic polarity changes between different phases of radial migration depend on Cdk5 activity. However, these studies suggest that, at least during locomotion, Cdk5 is required for organizing the cytoskeleton into a state that is fully competent for migration. This state includes an uncompromised leading process that efficiently attaches to the radial glia and a well-organized microtubule structure that effectively controls the nuclear movement.

Notes

Conflict of Interest: None declared.

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