COMMENTARY

A balancing Akt: How to fine-tune neuronal migration speed

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ABSTRACT

In the developing mammalian neocortex, newborn neurons produced deep in the brain from neural stem/progenitor cells set out for a long journey to reach their final destination at the brain surface. This process called radial neuronal migration is prerequisite for the formation of appropriate layers and networks in the cortex, and its dysregulation has been implicated in cortical malformation and neurological diseases. Considering a fine correlation between temporal order of cortical neuronal cell types and their spatial distribution, migration speed needs to be tightly controlled to achieve correct neocortical layering, although the underlying molecular mechanisms remain not fully understood. Recently, we discovered that the kinase Akt and its activator PDK1 regulate the migration speed of mouse neocortical neurons through the cortical plate. We further found that the PDK1-Akt pathway controls coordinated movement of the nucleus and the centrosome during migration. Our data also suggested that control of neuronal migration by the PDK1-Akt pathway is mediated at the level of microtubules, possibly through regulation of the cytoplasmic dynein/dynactin complex. Our findings thus identified a signaling pathway controlling neuronal migration speed as well as a novel link between Akt signaling and cytoplasmic dynein/dynactin complex.

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Mammalian neocortex plays important roles in higher order functions in the brain such as sensory perception, voluntary movement, and cognition. It exhibits well-organized layered structure of orderly aligned neurons of various kinds, which provides a basis for the establishment of functional neuronal connectivity. The construction of this layered structure is achieved by appropriate migration and subsequent deposition of neurons during neocortical development.^{20,42} A neuron undergoes different migration modes from its initiation to termination: first, a newborn neuron that is derived and delaminates from a pseudostratified epithelial layer of neural stem/progenitor cells in the ventricular zone (VZ) has a bipolar shape; it switches to a multipolar shape as it migrates through the subventricular zone (SVZ) and the intermediate zone (IZ); eventually it regains bipolar morphology as it reaches the cortical plate (CP); it then travels toward brain surface by locomotion along a radial glial fiber(s) of neural stem/progenitor cells; and it finishes its journey on reaching the pia and by detaching from the radial glial fiber. Previous studies have revealed molecules and mechanisms controlling contiguous steps of

neuronal migration as well as diseases associated with their impairment.^{8,14,19,25,28,38} Importantly, there is a precise relation between the temporal order in which the various neuronal cell types are generated and their spatial distribution in the neocortex.^{2,4,43,48} Also, cortical neurons utilize multiple modes of migration as described above, and each mode exhibits distinct speed when neurons are migrating through the cortex.^{36,47} Therefore, migration speed needs to be tightly controlled to achieve correct neocortical layering, although the underlying molecular mechanisms remain largely unknown.

Regulation of locomotion speed by the PDK1-Akt pathway

Our work recently identified that the serine/threonine kinase Akt (also known as protein kinase B) and its upstream essential activator phosphoinositide-dependent protein kinase 1 (PDK1) regulate the speed of neuronal migration during bipolar locomotion.²⁴ The PDK1-Akt axis acts downstream of phosphoinositide 3-kinase (PI3K), which in turn is activated by various

extracellular stimuli, and plays key roles in many biological processes including microtubule stabilization, cell polarization and cell migration.^{5,50} PI3K activity is required for normal radial migration in the neocortex,^{6,29} but the contribution of the PDK1-Akt pathway to neuronal locomotion has remained elusive, in part because of functional redundancy among the 3 Akt family members and the early lethality of Akt and PDK1 mutant mice.^{12,17,31} To circumvent these limitations, we conditionally knocked out PDK1 either in the central nervous system or in postmitotic cortical neurons.²⁴ Both mutant brains showed disorganized layer structure in the neocortex, implying migration defects. BrdU birthdating analysis and live-imaging of neuronal migration in organotypic brain slice culture revealed that PDK1 deletion slows down locomotion within the CP in both mutant brains, demonstrating that PDK1 is required for an appropriate speed of bipolar locomotion. We then manipulated Akt activity by overexpressing either wild-type Akt1 or a kinase inactive mutant Akt1 in neural stem/progenitor cells and their progeny, and found that activation of Akt1 accelerates locomotion, while inactivation of Akt1 decelerates it. These results were recapitulated when Akt activity was manipulated specifically in postmitotic cortical neurons, establishing that neuronal Akt activity controls neuronal migration speed.

Inhibition or activation of the PDK1-Akt pathway changed the locomotion speed by 20 to 30%,²⁴ but did not abrogate migration altogether. It is assumed that changing the speed of neuronal migration in entire neuronal population will not affect layer structure. Also, a recent study showed the evidence of a positioning-dependent layer identity acquisition,³⁹ suggesting that minor change in migration speed could potentially be accommodated by the post-migratory environment. However, while deep-layer neurons were positioned normally, upper-layer neurons showed layering defect in PDK1 mutant mouse brains,²⁴ strongly arguing that precise regulation of migration speed is indeed indispensable for the construction of appropriate layer structure. Upper-layer specific defect also implies that neurons migrating longer distances are more vulnerable to changes in migration speed. Regulation of the speed of neuronal migration is therefore likely to be of greater relevance in more superficial layers and in thicker cortical regions, such as the frontal cortex, as well as in organisms with larger brains, such as humans. While the mature CP in human cortex is merely twice thicker than that in mouse cortex,⁹

developing primate cortex has much thicker intermediate layers in between the CP and SVZ/VZ compared to mouse cortex,^{10,42} and cortical neurons undergo locomotion along radial glia before entering the CP,⁴² indicating that the locomotion distance in higher mammals is expected to be at least several times greater than that in mice. It is also plausible that a slow neuronal migration may result in premature cessation of locomotion as a consequence of disappearance of the glial scaffold due to terminal differentiation of radial glia into neurons or astrocytes. This scenario would most affect the latest-born neurons that are destined to superficial layers. Interestingly, it has been described that deficits in interhemispheric connectivity mediated by upper layer callosal neurons are associated with multiple human neurodevelopmental disorders, including autism spectrum disorders.^{15,16} Subtle layering defects during development might increase predisposition to these disorders later in life, and altered migration speed might be responsible, at least in part, for some of their pathology.

Besides incorrect neuronal placement and disorganized layer formation, change in migration speed can affect circuit wiring and development in a different way. Axonal specification of cortical neurons takes place as neurons are undergoing multipolar migration through the IZ,³⁷ while dendrite development starts post migration in the CP.³ Thus, shortening or lengthening the time lag between axonal outgrowth and dendritogenesis by accelerated or decelerated migration, respectively, could affect input vs output balance of neural activity during circuit wiring, whose alteration has been shown to impair axonal targeting and connectivity.^{34,35,46} Thus, altered migration speed can potentially affect circuit formation independently of incorrect neuronal placement in the cortex. Further research is necessary to fully and precisely understand how alteration in migration speed affects neural connectivity and circuit function.

The PDK1-Akt pathway controls coordinated movement of the nucleus and centrosome

Locomotion is a unique mode of neuronal migration in which cells first stabilize and elongate their leading process. The centrosome then moves forward from the perinuclear region into the dilation/swelling of the leading process, followed by movement of the nucleus toward the centrosome and retraction of the cell rear. The cell then repeats this series of steps and move forward in a

saltatory manner.^{7,14,32} Given that centrosome-nucleus coupling is regulated by several genes that are mutated in human neurological diseases, the underlying molecular mechanisms have been studied extensively. For example, *Lis1*, the product of a gene mutated in lissencephaly, and its associated proteins regulate forward movement of the centrosome away from the nucleus as well as pulling of the nucleus toward the centrosome by cytoplasmic dynein, a motor protein that directs transport toward the minus end of microtubules.^{7,14,32,49} However, the molecular mechanism underlying centrosome-nucleus coupling is not fully understood.

Our study found that the PDK1-Akt pathway controls coordinated movement of the nucleus and centrosome.²⁴ Inhibition of this pathway shortened the distance between the nucleus and centrosome, while activation of Akt weakly elongated it. Furthermore, live imaging of the centrosome in migrating neurons showed that Akt inhibition decreases the maximum distance between the nucleus and centrosome as well as the frequency of centrosomal forward movement. I thus speculate that Akt activation triggers centrosomal forward movement, rather than it suppresses nuclear forward movement, to initiate a saltatory migration cycle and that higher Akt activity enables neurons to take a bigger step in each cycle. Akt activation by growth factor stimulation is known to be transient depending on the stimulus and cell type.^{22,33} Therefore, neurons might trigger centrosomal forward movement when they encounter extracellular ligand(s) that leads to Akt activation. Our preliminary immunohistochemical data suggest that Akt is mainly activated in the leading process of migrating neurons (Y.I., unpublished data). However, we currently do not know what the ligand is and when and where in a migrating neuron Akt is activated. It would be extremely interesting to monitor spatio-temporal dynamics of Akt kinase activity in migrating neurons³³ together with centrosomal visualization to understand the spatial and temporal regulation of Akt activation during the centrosome-nucleus coupling.

The PDK1-Akt pathway regulates cytoplasmic dynein/dynactin complex

The dynamic remodeling of microtubules is important for neuronal migration and coordinated movement of the nucleus and centrosome.^{45,49} We found that PDK1

ablation reduces the amount of polymerized microtubules in the developing brain, supporting the idea that the PDK1-Akt pathway regulates locomotion at the level of microtubules.²⁴ Given that microtubule dynamics is regulated by microtubule-associated proteins that either stabilize or destabilize microtubules,^{1,11} we sought to understand the molecular mechanisms that link Akt activation and microtubule regulation by focusing on microtubule-associated proteins. We then identified cytoplasmic dynein/dynactin complex as a potential mediator of Akt regulation of locomotion.²⁴

Cytoplasmic dynein is involved in a wide variety of functions including radial neuronal migration and nucleus-centrosome coupling.^{27,40,44} PDK1 ablation in the developing cortex reduced the expression of cytoplasmic dynein intermediate and light intermediate chain proteins and the amount of polymerized microtubule-associated p150^{glued}, a subunit of dynactin that increases dynein processivity.²⁷ Consistent with this finding, inhibition of the PDK1-Akt pathway in primary culture reduced the amount of soma-localized p150^{glued}, which would reflect impaired dynein motor activity.²⁴ These findings are consistent with the notion that Akt regulation of locomotion is mediated by cytoplasmic dynein/dynactin complex. Cytoplasmic dynein, however, is enriched in the dilation/swelling and in the soma, which is proposed to independently operate centrosomal and nuclear translocation, respectively.⁴⁹ Currently it is unclear how Akt specifically controls centrosomal translocation. Importantly, cell cortex-localized cytoplasmic dynein has been shown to mediate microtubule capture and tethering to generate pulling forces.^{21,30} Since our preliminary data suggest that Akt is mainly activated in the leading process of migrating neurons (Y.I., unpublished data), I speculate that Akt primarily activates cortically anchored cytoplasmic dynein/dynactin complex in the dilation/swelling to generate pulling forces that stabilize microtubules and trigger centrosomal forward movement (Fig. 1). Another non-mutually exclusive possibility is that Akt activity is regulating homeostatic expression levels of cytoplasmic dynein subunits. In this scenario, reduced Akt activity is expected to cause impaired expression levels of cytoplasmic dynein/dynactin complex throughout the cell. The complex in the dilation/swelling could be more vulnerable to the reduced expression of

Figure 1. Schematic models showing the regulation of cytoplasmic dynein/dynactin complex during centrosomal forward movement. In control, membrane-anchored cytoplasmic dynein/dynactin complex at the dilation/swelling tethers microtubules, thereby generating forces to pull the centrosome forward and stimulating saltatory neuronal migration. Inhibition of the PDK1-Akt pathway reduces the expression of cytoplasmic dynein intermediate and light intermediate chains as well as the amount of polymerized microtubules.²⁴ Since cytoplasmic dynein heavy chain interacts with dynactin via cytoplasmic dynein intermediate chain, inhibition of the PDK1-Akt pathway is predicted to cause impaired dynein processivity at the dilation/swelling and reduced pulling forces of the centrosome, which would lead to slower neuronal migration.

cytoplasmic dynein subunits compared to that in the soma.

The molecular mechanism how the PDK1-Akt pathway regulates cytoplasmic dynein/dynactin complex remains an open question. Our data suggested that PDK1 regulates the expression of cytoplasmic dynein subunits at a post-transcriptional level.²⁴ As far as we are aware, mechanisms controlling the levels of cytoplasmic dynein subunits in mammalian cells are not well understood, with the exception that NudC-like protein contributes to stabilization of dynein intermediate chain.⁵² Interestingly, recent work has implicated that cytoplasmic dynein heavy chain and p150^{glued} could be phosphorylated directly by Akt.^{23,26} Thus, it is possible that Akt might phosphorylate component(s) of cytoplasmic dynein/dynactin complex to regulate its expression level, assembly, and/or function. Identifying Akt phosphorylation target(s) involved in cytoplasmic dynein regulation during neuronal migration would help us better understand how extracellular signal is transduced

intracellularly to control cytoplasmic dynein activity and to exert physical forces in locomoting neurons.

Concluding remarks

Our recent work has provided evidence that the PDK1-Akt pathway controls locomotion speed as well as cytoplasmic dynein/dynactin complex during mouse neocortical development. Dysregulated Akt signaling has been associated with neurological conditions such as autism spectrum disorders and focal cortical dysplasia,^{41,51} and *AKT1* is a candidate susceptibility gene for schizophrenia.¹³ An altered speed of radial neuronal migration and consequent impaired circuit formation may contribute, at least in part, to the pathogenesis of these psychiatric disorders. Our work focused on locomotion in the lissencephalic mouse cortex, but higher mammals including humans have a gyrencephalic cortex, which might require additional migration mechanisms.¹⁸ Further research is required to elucidate the exact mechanism of Akt function during neuronal migration and how a

neuron behaves and migrates in the cortex of higher mammalian species, as well as molecular mechanisms underlying such higher mammals-specific mode(s) of migration.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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