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Review

Molecular regulation of neuronal migration during neocortical development

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ABSTRACT

Neocortex, a distinct six-layered neural structure, is one of the most exquisite nerve tissues in the human body. Proper assembly of neocortex requires precise regulation of neuronal migration and abnormalities can result in severe neurological diseases. Three major types of neuronal migration have been implicated in corticogenesis: radial migration of excitatory neuron precursors and tangential migration of interneurons as well as Cajal–Retzius cells. In the past several years, significant progress has been made in understanding how these parallel events are regulated and coordinated during corticogenesis. New insights have been gained into regulation of radial neuron migration by the well-known Reelin signal. New pathways have also been identified that regulate radial as well as tangential migration. Equally important, better understandings have been obtained on the cellular and molecular mechanics of cell migration by both projection neurons and interneurons. These findings have not only enhanced our understanding of normal neuron migration but also revealed insights into the etiologies of several neurological diseases where these processes go awry.

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One of the most striking anatomical features of the cerebral neocortex is its exquisite laminar organization. Two major neuronal cell types are found in the mature cortex: excitatory projection neurons that compose the vast majority of cortical neurons and locally projecting inhibitory interneurons. Both neuronal types consist of a large number of subtypes, each of which possesses distinct molecular, morphological, and electrophysiological fingerprints. Nonetheless, despite such cell type heterogeneity, cortical neurons display an extraordinary organization in that they partition their cell bodies into distinct layers along the radial axis of cortex. This orderly organization

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of cortical lamination likely provides key advantages for the processing and storage of neural information in the cortex.

Long-standing interests in the mechanisms of cortical layer formation have in the past led to major breakthroughs in our knowledge in this area. Most notable is the identification of the extracellular protein Reelin (Reln) in regulating radial neuron migration. This has subsequently led to the elucidation of a novel pathway in migrating neurons that mediate Reln signaling. Key questions, however, remain unanswered as to how precise laminar targeting of excitatory neurons is achieved and what precise roles Reln plays in this process. In the first part of this article, I will review recent data that have shed new light on the mechanisms of Reln signaling in radial neuron migration as well as additional pathways that have been implicated in regulating this process. I will also review new insights that have been gained into the cellular and molecular mechanics of radial neuron migration.

Since the discovery of their origin in the ventral forebrain over a decade ago, significant progress has also been made in understanding how interneurons populate the cortex through tangential migration. In the second half of this article, I will review recent progress on this front, focusing in particular on how the migration of interneurons and excitatory neurons is coordinated during cortical laminar assembly. Another major finding in the past few years has been the determination of extracortical origins for the vast majority of Cajal–Retzius (C-R) cells, the transient neuronal population that occupy the developing cortical marginal zone (MZ). I will review recent data that implicate a chemokine signaling pathway in regulating C-R cell migration and localization within the cortex. Lastly, as defective cortical neuron migration is closely associated with several neurological diseases including lissencephaly and epilepsy, I will review how advances in our understanding of the genetic basis of these diseases have enhanced our knowledge of neuronal migration and *vice versa*.

Intercellular signaling and radial neuron migration

Cortical excitatory neurons are born in the ventricular zone (VZ) where their progenitors reside (Fig. 1). Proper cortical lamination thus requires precise guidance of these neurons from the VZ to cortical plate (CP) in order for them to reach appropriate cortical layers (reviewed in Ayala et al. (2007); Rakic (2007). Early autoradiographic studies have established that cortical layers are formed in a unique inside-out manner, with deep layers formed first and followed by superficial layers (Angevine and Sidman, 1961; Rakic, 1974). As such, newborn neurons must migrate past their older siblings to reach their destinations in the CP. Pioneering electron microscopy studies have revealed close alignment of migrating neurons with radial glial fibers in the developing primate cortex (Rakic, 1972), laying the foundation for a critical role of radial glia in guiding cortical lamination as well as contribution of differential cell adhesion to this process. Interestingly, recent evidence indicates that radial glia in developing rodent cortex are themselves progenitors for cortical neurons (Anthony et al., 2004; Malatesta et al., 2000; Noctor et al., 2001), suggesting a multi-faceted function of radial glia in corticogenesis. However, as neocortex expands during evolution in mammals, a distinct non-dividing radial glial lineage may have arisen in primates, which likely facilitates development of the convoluted primate cortex (Rakic, 2007).

Major insights into the molecular mechanisms underlying cortical lamination have come from studies of *reeler* mice (reviewed in Rice and Curran (2001); Tissir and Goffinet (2003). In the *reeler* cortex, the normal inside-out pattern is replaced by a roughly inverted pattern of cortical lamination where newborn neurons fail to migrate past older ones and end up occupying deeper layers of the cortex (Caviness and Sidman, 1973). *reeler* affects the *reln* gene (D'Arcangelo et al., 1995; Ogawa et al., 1995), which encodes a large extracellular matrix glycoprotein highly expressed in C-R cells (Alcantara et al., 1998). Reln signal is received in migrating neurons by two redundant cell surface receptors, Very Low Density Lipoprotein Receptor (Vldlr) and Apolipoprotein E Receptor 2 (ApoER2), and double mutation of *Vldlr* and *ApoER2* results in cortical lamination defects similar to *reeler* mutants (D'Arcangelo et al., 1999; Hiesberger et al., 1999; Howell et al., 1999; Trommsdorff et al., 1999; but see also Dulabon et al. (2000); Senzaki et al. (1999). Downstream of Vldlr and ApoER2, the adaptor protein Disabled-1 (Dab-1) is required for mediating Reln signaling and Dab-1 mutant mice also display *reeler*-like cortical lamination phenotypes (Howell et al., 1997; Sheldon et al., 1997). Thus, Reln signaling to cortical neurons is essential for proper radial neuron migration and cortical layer formation.

What precise step(s), then, does Reln regulate during radial neuron migration? Recent analysis of Reln receptor single mutants has revealed new insights into this question (Hack et al., 2007). By using layer specific markers, Hack et al. (2007) found that in *Vldlr* single mutants, large numbers of layers II–IV neurons over-migrate and occupy the MZ, whereas positioning of layer V neurons in the deeper cortex is largely unaffected. By contrast, in *ApoER2* single mutants, only a small fraction of layers II–IV neurons reach their normal destination in the upper CP while the vast majority are mis-localized beneath the now upwardly displaced layers V and VI. These results suggest that Vldlr and ApoER2 may play distinct roles in regulating cortical neuron migration: Vldlr may mediate a stop signal for migrating neurons whereas ApoER2 promotes the migration of late born cortical neurons. However, since Vldlr and ApoER2 belong to the same receptor protein family, this raises the question of how they may mediate such different effects. Interestingly, recent biochemical evidence suggests that Vldlr and ApoER2 may bind to different sets of cytoplasmic proteins. For example, Pafah1b2 and Pafah1b3, two catalytic subunits of the platelet activating factor acetylhydrolase 1b (Pafah1b) complex, a complex best known for the role of its third subunit Pafah1b1 (better known as Lis1) in regulating neuronal migration, bind specifically to the cytoplasmic domain of Vldlr but not ApoER2 receptor (Zhang et al., 2007). It is thus conceivable that these and additional differences may explain the distinct functions of Vldlr and ApoER2 and Reln may regulate different steps of radial neuron migration through activating these distinct pathways.

An alternative, though not mutually exclusive, possibility was suggested by observations made by Cooper and colleagues, who focused on the mechanism of Reln signaling downregulation during corticogenesis (Feng et al., 2007). Like most signaling pathways, Reln signaling is known to trigger negative feedback loops that terminate pathway activity, which in this case include Dab-1 protein degradation. Indeed, previous results have found that Dab-1 is upregulated in *reeler* cortex. In their recent paper, Cooper and colleagues determined that the E3 ubiquitin ligase component Cullin 5 (Cul5), in a complex with Suppressors of Cytokine Signaling (SOCS), is responsible for binding to Dab-1 and targeting it for degradation. Most strikingly, when Cul5 was knocked down in migrating neurons, which resulted in cell-autonomous buildup of Dab-1, cortical neurons over-migrated and accumulated at the top of CP. Some of these neurons even invaded the MZ occupied by C-R cells. The failure of these neurons to stop properly also seems to prevent younger neurons from migrating past them, an effect curiously reminiscent of aspects of *reeler* phenotype. These results thus reinforce the interpretation that Reln may play roles not only in promoting, but also in terminating neuron migration. In support of this notion, Reln was previously found to act as a detachment signal for chain-migrating interneuron precursors in the olfactory bulb (Hack et al., 2002). Therefore, it is conceivable that, through precisely controlling the timing of signaling activation and termination, Reln may orchestrate the entire process of neuronal migration from beginning to end.

How may Reln signaling promote neuronal migration? Downstream of Vldlr and ApoER2 receptors, Reln signaling requires Src family tyrosine kinases Src and Fyn in activating adaptor protein Dab-1 during cortical lamination (Arnaud et al., 2003; Bock and Herz,