

Molecular control of neuronal migration

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Summary

Our understanding of neuronal migration has been advanced by multidisciplinary approaches. At the cellular level, tangential and radial modes of neuronal migration contribute to different populations of neurons and have differential dependence on glial cells. At the molecular level, extracellular guidance cues have been identified and intracellular signal transduction pathways are beginning to be revealed. Interestingly, mechanisms guiding axon projection and neuronal migration appear to be conserved with those for chemotactic leukocytes. *BioEssays* 24:821–827, 2002.

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Introduction

The nervous system is populated with natural migrants; the majority of, if not all, neuronal precursors have to migrate from their place of origin to sites of final residence and functioning. The possibility of neuronal migration was raised by Kolliker, His, Magini, Ramon y Cajal, and Vignal in the late part of the 19th century⁽¹⁾ and is now well established as an important process in neural development.^(2,3) The peripheral nervous system (PNS) is largely derived from neural crest cells migrating out of the dorsal part of the neural tube. In the central nervous system (CNS), neuronal precursor cells in the embryonic ventricular zone can move to other layers in the same brain region by radial migration or to other brain regions by tangential migration.⁽²⁾ Neuronal migration is not limited to embryonic development because it is also found in neonatal

and adult brains. Studies of neuronal migration are important not only for revealing basic mechanisms of neural development but also for understanding the etiology of human diseases caused by abnormal neuronal migration.

Two modes of neuronal migration

Initial categorizations of radial migration and tangential migration were based on the relative directions taken by migrating neuronal precursor cells. Radial migration is defined by neuronal migration in a direction perpendicular to the surface of the brain, whereas tangential migration describes neurons migrating in a direction parallel to the surface of the brain. During radial migration, the precursors of pyramidal neurons, the major projection neurons of the cerebral cortex, are thought to move from the ventricular zone to the pia along the fibers of radial glial cells (Fig. 1).^(2,3) The outwardly migrating neurons form the cortical plate, which separates the preplate. This primitive lamination of the neocortex proceeds in an inside-out pattern in that new cells take more superficial positions whereas old cells are positioned in deeper layers of the cortical plates.⁽⁴⁾ During cerebellar development, two different neuronal precursors employ radial migration for their final destination. In the embryonic cerebellum, Purkinje cells, the principal output neurons, migrate along radial glial fibers towards the surface from the neuroepithelium of cerebellar primordium.⁽²⁾ In the postnatal cerebellum of rodents, cells in the external germinal layer (EGL) migrate inwards along the fibers of Bergmann glia to form the internal granular layer (IGL) (Fig. 1).⁽²⁾

Although tangential migration was observed in the 1960s,⁽⁵⁾ its importance is better appreciated in the late 1980s and 1990s (for recent reviews, see Refs. 6, 7). Tangential migration does not require glial fibers and is a major migrating mode for cells originating in the basal telencephalon (or the subpallium), known as the ganglionic eminences (GE). Significant proportions of interneurons such as the GABAergic neurons in the telencephalon are derived from these tangentially migrating neuronal precursor cells (Fig. 1). Ganglionic eminences are small masses of developing cells in the wall of the lateral ventricles of the basal telencephalon, including the lateral GE (LGE), the medial GE (MGE) and the caudal GE (CGE). Neuronal precursor cells from different GEs migrate into different regions of the brain.^(6–8) For example, cells from the MGE migrate dorsally into the neocortex, whereas cells from the LGE migrate anteriorly into the olfactory bulb. Inter-

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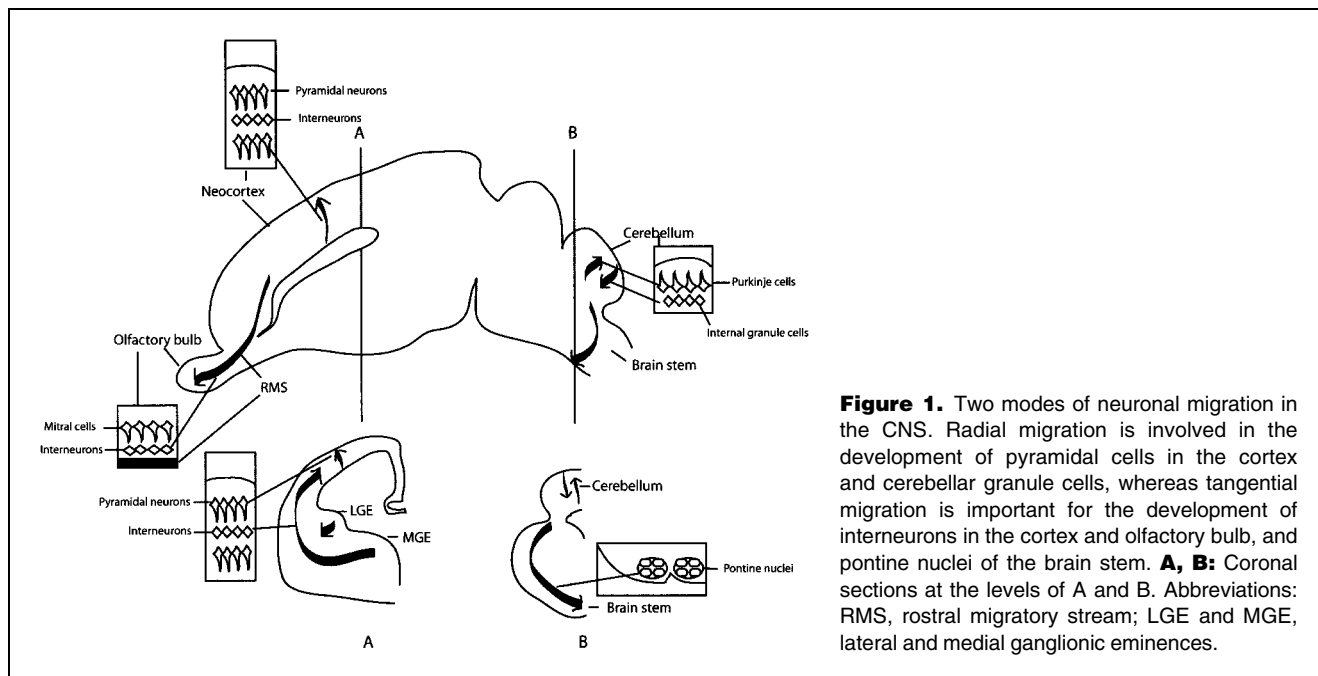


Figure 1. Two modes of neuronal migration in the CNS. Radial migration is involved in the development of pyramidal cells in the cortex and cerebellar granule cells, whereas tangential migration is important for the development of interneurons in the cortex and olfactory bulb, and pontine nuclei of the brain stem. **A, B:** Coronal sections at the levels of A and B. Abbreviations: RMS, rostral migratory stream; LGE and MGE, lateral and medial ganglionic eminences.

estingly, tangential migration persists after birth especially in the subventricular zone (SVZ) of the forebrain, giving rise to more olfactory interneurons during postnatal life (Fig. 1).^(9,10) In the brain stem, precursor cells in the dorsal part of developing hindbrain, the lower rhombic lip, migrate tangentially to the ventral side of the brain stem to form pontine nuclei (Fig. 1).⁽¹¹⁾

Proteins involved in neuronal migration identified by genetic studies

Genetic studies combined with molecular cloning in mice and humans have revealed new molecules that are directly or indirectly involved in neuronal migration. The mouse mutation *reeler* has provided an excellent entry point for studying cortical lamination, starting with genetic and phenotypic studies.⁽¹²⁾ *reeler* mutant mice have abnormal lamination of cerebral and cerebellar cortices. Histological studies of *reeler* mice show that the initiation of neuronal migration from the ventricular zone appears normal, and that the cell number and subtypes of neurons in the cerebral cortex also seem to be normal. However, migrating neurons in the mutant mice do not penetrate the preplate, therefore producing defects in the inside-out pattern.⁽¹³⁾ These results indicate that the *reeler* mice are defective in controlling cell positioning, especially during cortical plate formation. In the cerebellum, *reeler* mice show abnormal lamination of the Purkinje cells.⁽¹⁴⁾ Although hypotheses have been proposed to explain the phenotype of *reeler* mice, such as a defect in a stop signal for the migrating neurons, the precise function of the *reeler* gene remains controversial.

The product of the *reeler* gene is Reelin, a large secreted protein.⁽¹⁵⁾ It is expressed primarily in the Cajal-Retzius (CR) cells in the marginal zone of the neocortex and the cerebellum.⁽¹⁶⁾ Genetic and biochemical studies have demonstrated that the very low-density lipoprotein receptor (VLDLR) and the apolipoprotein E receptor-2 (ApoER2) are the receptors for Reelin.^(17,18) Mice lacking either VLDLR or ApoER2 do not show abnormal phenotype, but mice lacking both genes exhibit anatomical defects almost identical to that in *reeler* mice.⁽¹⁷⁾ The significance of additional Reelin receptors such as the cadherin-related neuronal receptors and integrin $\alpha 3 \beta 1$ remains unclear.^(19,20)

Mice defective in the *scrambler* gene show a phenotype similar to that of *reeler*.⁽²¹⁾ The *scrambler* locus was genetically mapped in the *disabled-1* (*Dab-1*) gene on chromosome 4.⁽²²⁾ Targeted mutation of *Dab-1* revealed a phenotype identical to that of *scrambler*.⁽²³⁾ *Dab-1* is expressed in the Reelin-responsive cortical plate neurons and the Purkinje cells, with a pattern similar to those of VLDLR and ApoER2. *Dab-1* is a tyrosine phosphorylated cytoplasmic protein, which can bind to the intracellular part of VLDLR and ApoER2.⁽¹⁷⁾ Tyrosine phosphorylation of *Dab-1* was increased by extracellular application of Reelin⁽²⁴⁾ and the level of basal tyrosine phosphorylation in *reeler* mice is lower than that in the wild-type mice.⁽²⁴⁾ Mutations in the phosphorylation sites of *Dab-1* cause ataxia and abnormalities in cell positioning in the cerebral and cerebellar cortices.⁽²⁵⁾ There are thus strong biochemical and genetic evidence to support a pathway from the secreted protein Reelin, to the

transmembrane receptors VLDLR and ApoER2, to Dab-1 phosphorylation.

There are other mouse mutants defective in cortical lamination. Mice lacking the cyclin-dependent kinase 5 (Cdk5) show defective migration in the cerebral and cerebellar cortices.⁽²⁶⁾ The defects are different from those in *reeler* mice, and the molecular linkage between Reelin pathway and Cdk5 is uncertain. The migrating cells could split the preplate into the marginal zone and the subplate in *cdk5* mutants, but late-born neurons do not show the inside-out pattern in that they accumulate under the subplate. Cdk5 is a ubiquitously expressed serine-threonine kinase.⁽²⁷⁾ Cdk5 requires p35 and p39 proteins for activation, and mice lacking both p35 and p39 show a cortical phenotype similar to that in *cdk5* mutant mice.⁽²⁸⁾ In vitro studies suggest that Cdk5 regulates cytoskeleton dynamics through the phosphorylation of Pak or microtubule-associated proteins.^(29,30)

Several human developmental disorders have been attributed to defects in neuronal migration. Lissencephaly patients show underdevelopment of the cerebral gyri probably caused by premature termination of neuronal migration.⁽³¹⁾ The Lis-1 gene encodes a regulatory subunit of brain platelet activating factor acetylhydrolase (PAF-AH),⁽³¹⁾ which regulates the metabolism of cellular lipid PAF. PAF-AH is expressed not only in the CR cells but also in the ventricular zone of the developing neocortex.⁽³²⁾ PAF also regulates the migration of cerebellar granule cells.⁽³³⁾ It is still unclear how PAF controls neuronal migration. Zellweger syndrome is characterized by heterotopic neurons in the neocortex, and it is defective in peroxisome biogenesis.⁽³⁴⁾ Patients with mutations in the double cortex or the bicortical lissencephaly genes have two cortical plates separated by the white matter.⁽³⁵⁾ The gene product, Doublecortin, was recently identified and is a microtubule-associated protein expressed in migrating cortical cells.^(35,36)

Directional guidance of neuronal migration

Progress has been made in the last few years on mechanisms guiding the direction of neuronal migration. It is now clear that migrating neurons are guided by molecular cues that also guide the projection of axons (Table 1).

The first molecule directly demonstrated to guide neuronal migration is the secreted protein Slit.⁽³⁷⁾ The *slit* gene was identified in *Drosophila* more than 10 years ago.⁽³⁸⁾ In 1999, three groups discovered that Slit was a repellent for axons projecting from different regions of the nervous system.^(39–41) The role of Slit in neuronal migration was first discovered in the olfactory system.⁽³⁷⁾ Interneurons in the olfactory bulb are derived from precursor cells migrating in the rostral migratory stream (RMS) from the anterior subventricular zone (SVZa) in neonatal rodents.⁽⁴²⁾ Slit can repel SVZa cells, an effect that seems to require the presence of a gradient of the Slit protein.⁽³⁷⁾ Molecular studies also help to further our understanding of cellular interactions that control neuronal migration. Thus, although it was known that GABAergic neurons in the neocortex were derived from the SVZ of GE in the embryo, it was not clear why GABAergic neurons migrated out of the GE. It has now been shown that the ventricular zone in the GE contains a repulsive activity.⁽⁴³⁾ The Slit genes are expressed in the ventricular zone and Slit protein repels the GABAergic neurons.⁽⁴³⁾ Furthermore, the repulsive activity of the ventricular zone is reduced by a fragment containing only the extracellular part of the receptor for Slit, which blocks the interaction of Slit with the endogenous receptor.⁽⁴³⁾ These results suggest both a cellular and a molecular mechanism that may cause GABAergic neurons to migrate away from the GE. Recent genetic studies in *C. elegans* and *Drosophila* provide evidence for the involvement of Slit in cell migrations in vivo. Certain neurons in the head of *C. elegans* embryos migrate posteriorly. Slit appears to repel these neurons because it is expressed in the anterior pole of the embryo and mutant embryos

Table 1. Directional Guidance cues involved in CNS neuronal migration in vivo and in vitro

Ligands	Receptors	Defects in CNS neuronal migration in vivo	Neuronal migration in vitro
Slits	Robo	—	1. Slit repels postnatal SVZa cells ⁽³⁷⁾ 2. Slit repels prenatal SVZ cells of GE ⁽⁴³⁾
Netrins	DCC	1. Abnormal pontine nuclei in DCC and netrin-1 mutants ⁽⁴⁶⁾	1. Netrin-1 attracts pontine nuclei ⁽¹¹⁾
	Unc-5h	2. Abnormal cerebellar development in unc-5h3 ^{(64)*}	2. Netrin-1 repels postnatal cerebellar granule cells and prenatal SVZ cells ^(48,49) 3. Anti-DCC antibody blocks directed migration of postnatal SVZa cells ⁽⁴⁷⁾
Semaphorins	Neuropilin Plexin	1. Abnormal GABAergic interneurons in the striatum in neuropilin-2 mutants ⁽⁵⁰⁾	—
Ephrins	Eph	—	1. Disruption of Eph-B/Ephrin-B system affects the migration of postnatal SVZa cells ⁽⁵¹⁾

*Unc-5h3/RCM mutant mice showed abnormal development of cerebellum. However, it is still unclear that the defect is primarily caused by migration abnormality or other reasons.

lacking Slit showed defects in the posterior migration of these neurons.⁽⁴⁴⁾ In *Drosophila*, the migration of the mesodermal cells that form the ventral muscles is repelled by Slit.⁽⁴⁵⁾

Netrin can either be an attractant or a repellent for axons.^(46,47) The basilar pontine neurons originating from the neuroepithelium of the dorsal hindbrain migrate circumferentially to the ventral midline. Netrin-1 is expressed in the ventral midline and attracts these neurons,⁽¹¹⁾ and netrin-1 mutant mice showed abnormal development of pontine nuclei.⁽⁴⁶⁾ It has recently been suggested that netrin in the olfactory bulb may be involved in the directional migration of SVZa cells and that the function blocking antibody to a netrin receptor, Deleted in Colorectal Cancer (DCC), blocks the directional migration of SVZa cells in RMS.⁽⁴⁸⁾ Netrin-1 also repels some subsets of migrating neurons in vitro. Cells from the external germinal layer of the postnatal cerebellum are repelled by netrin-1 in explant cultures.⁽⁴⁹⁾ Netrin has also been implicated in guiding the migration of cells from the GE into the striatum as a repellent.⁽⁵⁰⁾ Since both Slit and netrin can repel GE cells, it is perhaps not surprising that there was no drastic neuronal migration phenotype in mice lacking netrin.⁽⁴⁶⁾ It should be noted that, although Slit and netrin are repulsive to GE cells, the precise roles of these molecules in vivo are still not known. Do Slit and netrin function redundantly? Or do they act at different steps of neuronal migration from the GE?

Neurons from the GE can migrate into either the striatum or the neocortex. What controls the distinct destinations? A recent study implicates the semaphorins in this process.⁽⁵¹⁾ Semaphorin 3a and 3f are expressed in the developing striatum, whereas their receptors neuropilin 1 and 2 are expressed in those interneurons from the MGE that migrate into the neocortex. MGE cells are repelled by the striatal semaphorins, thereby directing them away from the striatum.⁽⁵¹⁾

Ephrins and their receptors, the Eph tyrosine kinases, have also been implicated in neuronal migration. The B type ephrins are those with a transmembrane whereas the A type ephrins are membrane anchored through glycosylphosphatidylinositol lipid. EphB1-3 and EphA4 and their transmembrane ligands, ephrins-B2/3, are involved in SVZa migration.⁽⁵²⁾ When the extracellular parts of either EphB2 or ephrin-B2 were introduced into the lateral ventricle to inhibit the interaction between endogenous ephrin and Eph, the migration of SVZa cells was disrupted.⁽⁵²⁾

The conclusion that axon guidance and neuronal migration share common mechanisms is supported not only by the findings of similar guidance cues, but also by further dissection of functional domains in the guidance cue Slit. The receptor for Slit is the transmembrane protein Roundabout (Robo).⁽³⁹⁻⁴¹⁾ It mediates Slit responses in both axon guidance^(40,41,53) and neuronal migration.^(37,43,54) Each mammalian Slit contains four leucine-rich repeats (LRRs), nine epidermal growth factor

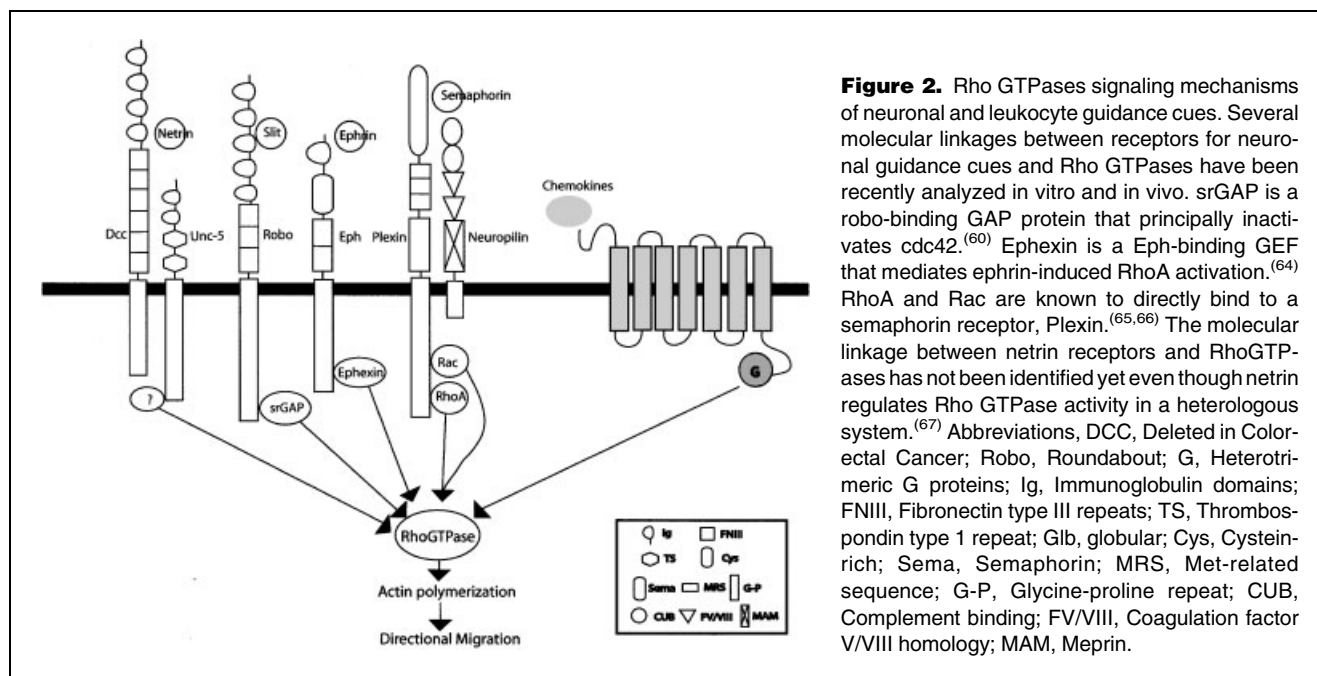
repeats, a laminin G domain and a cysteine-rich C-terminal region. Domain dissection studies have demonstrated that LRRs of Slit bind to Robo, and both the full-length Slit and the N-terminal regions of Slit, which has LRRs repel SVZa cells and olfactory bulb axons.^(54,55) However, only the N terminus of Slit could induce branching of axons from the dorsal root ganglion cells, whereas the full-length Slit functions as a dominant negative manner in axon branching.⁽⁵⁵⁾ These similarities of Slit action in SVZa cell migration and axon repulsion further support the idea that axon guidance and neuronal migration share similar guidance mechanisms.^(37,54)

Intracellular signal transduction pathways involved in neuronal migration

The signal transduction pathways for axon guidance have been recently reviewed, and the Rho family of small GTPases is clearly important (Fig. 2).^(56,57) Interestingly, recent studies on intracellular signal transduction pathways suggest a possible fundamental conservation of molecular mechanisms guiding the neuronal migration and chemotactic leukocytes.⁽⁵⁸⁻⁶⁰⁾ Multiple intracellular components in leukocyte chemotaxis have been identified as downstreams of the chemokine receptors (G-protein coupled seven transmembrane protein), and among these are the small GTPases of the Rho family.^(58,59) Recently, a signal transduction pathway for Slit has been investigated for its role in neuronal migration,⁽⁶⁰⁾ and the Rho GTPase Cdc42 was found to be involved in neuronal migration. Taken together with results from studies of axon projection,^(57,61) it is clear that the Rho GTPases are used in processes ranging from axon guidance to leukocyte chemotaxis (Fig. 2). We will review briefly here the signal transduction mechanism for Slit because it has been studied in the context in neuronal migration.

Robo contains five immunoglobulin (Ig) domains, three fibronectin type III domains, a single transmembrane domain and a cytoplasmic domain with four conserved motifs (CC0, CC1, CC2 and CC3).⁽⁵³⁾ It was previously shown that mutations in any one of the intracellular motifs can reduce, but do not eliminate, the function of Robo in axon guidance in *Drosophila* embryos.⁽⁵³⁾ CC1 is a tyrosine phosphorylation site for the Abelson (Abl) tyrosine kinase whereas CC1 and CC2 serve as a binding site for Enabled (Ena).⁽⁵³⁾ Abl and Ena interact with Robo genetically when analyzed in axon guidance phenotypes.⁽⁵³⁾ While the roles of Abl and Ena have not been determined in mammals or in neuronal migration, recent studies showing the role of mena, mammalian homologue of Ena, in cell migration⁽⁶²⁾ indicate that this molecular link may also play a role in vertebrate Slit-Robo pathways.

Recently, a signal transduction pathway for Slit has been specifically investigated for its role in neuronal migration,⁽⁶⁰⁾ and the identification of proteins binding to the CC3 motif has led to the proposal of a model that explains the repulsion caused by Slit.⁽⁶⁰⁾ The extracellular binding of Slit to Robo



increases the binding of the intracellular CC3 motif of Robo to a new family of GTPase activation proteins named slit-robo GAPs (srGAP). The srGAPs inactivate the small GTPases of the Rho family, which includes Rho, Rac and Cdc42. In several cell types including the SVZa cells, Slit consistently inactivates Cdc42. When a constitutively active mutant form of Cdc42 was introduced into SVZa cells, these cells are no longer repelled by Slit.⁽⁶⁰⁾ This study clearly demonstrates a role for Cdc42 in mediating the repulsive response of SVZa to Slit. Because the Rho GTPases are known to promote actin polymerization,⁽⁶³⁾ the findings of their involvement in neuronal migration and axon guidance also suggest that actin polymerization is likely to be the common output of neuronal motility. The biochemical regulation of Rho and Rac by Slit seems to vary in different cell types and their functional significance in Slit response is unknown, although it is tempting to suggest that differential regulation of Cdc42, Rac and Rho may underlie different functions of Slit including axon repulsion and promotion of axon branching.

Conclusions

There is now compelling evidence for two differential modes of neuronal migration. Radial migration is responsible for the columnar organization in the cortex whereas tangential migration can add cellular complexity for more sophisticated cortical functions. The finding of guidance mechanisms shared among projecting axons, migrating neurons and chemotactic leukocytes suggests a fundamental mechanistic conservation among all somatic cells in the mammals, perhaps extending to free living metazoan cells. There are still many unanswered

questions about neuronal migration. For example, for spatial control of neuronal migration, the functional significance of most of the endogenous guidance cues in neuronal migration has not been established although the effects of exogenous guidance cues are clear and the expression of the endogenous cues is highly suggestive. For temporal control of neuronal migration, mechanisms controlling either the timing or the speed of neuronal migration remain to be studied. At the cellular level, now that some neurons are known to migrate without glial fibers, the precise role of radial glia cells remains to be better understood. Intracellularly, we are only beginning to understand the signal transduction pathways involved in neuronal migration.

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