REVIEW

Neuronal migration and molecular conservation with leukocyte chemotaxis

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Cell migration is essential in species ranging from bacteria to humans (for recent reviews, see Lauffenburger and Horwitz 1996; Mitchison and Cramer 1996; Montell 1999). In the amoebae *Dictyostelium discoideum*, cell migration is involved in chemotaxis toward food sources and in aggregation (for review, see Devreotes and Zigmond 1988; Parent and Devreotes 1999; Chung et al. 2001). In higher vertebrates, cell migration plays crucial roles in multiple physiological and pathological processes. During embryonic and neonatal development, cell migration is crucial in morphogenetic processes such as gastrulation, cardiogenesis, and the formation of the nervous system (for review, see Hatten and Mason 1990; Rakic 1990; Hatten and Heintz 1998; Bentivoglio and Mazzarello 1999). In adult animals, cell migration is required for leukocyte trafficking and inflammatory responses (for review, see McCutcheon 1946; Harris 1954; Devreotes and Zigmond 1988). In tumoriogenesis, tumor-induced angiogenesis and tumor metastasis both involve cell migration. Although it is well known that cell migration is necessary for all these processes, our understanding of mechanisms controlling cell migration is still limited. Here we briefly review the significance of neuronal migration and focus on recent studies on the directional guidance of neuronal migration, discussing the possibility that guidance mechanisms for neurons are conserved with those for other somatic cells.

Ontogenetic and phylogenetic significance of neuronal migration

Although the idea of neuronal migration was proposed in the late 1800s through the observations of Kolliker, His, Vignal, and Ramon y Cajal (Bentivoglio and Mazzarello 1999), there was a long-standing debate as to whether there is active neuronal migration or only passive neuronal displacement (e.g., Tilney 1933). A large amount of work based on histology, autoradiography, retroviral tracing, dye labeling, and modern imaging have now established that the majority of, if not all, neurons actively migrate in the developing CNS (Angevine and Sidman 1961; Rakic 1971a,b, 1972; Nowakowski and Rakic 1979; Hatten and Liem 1981; Mason et al. 1988; Gray et al. 1990; Walsh and Cepko 1990; Hatten and Heintz 1998).

Neuronal migration is essential for the formation and normal functioning of the nervous system. Many human diseases are caused by defects in neuronal positioning (e.g., Volpe 1987; Reiner et al. 1993; Norman et al. 1995; Flint and Kriegstein 1997). Although some diseases such as lissencephaly (smooth brain) are easily explained by developmental abnormalities, others, such as epilepsy and autism, are not immediately obvious and are most likely indirect consequences of abnormal neuronal positioning. In addition, migration is also important for metastasis or invasion of neuroblastoma and glioma (e.g., Giese and Westphal 1996). Genetic studies of defects affecting neuronal positioning in humans and mice have helped further our understanding of neuronal migration (for recent reviews, see Dhavan and Tsai 2001; Rice and Curran 2001; Ross and Walsh 2001). For example, an interesting pathway that has emerged from these studies consists of the secreted protein Reelin, the ApoE receptor, the very low density lipoprotein (VLDL) receptor, and the cytoplasmic protein Disabled (Dbl), and has been revealed to play a role in neuronal positioning, a topic that has been recently reviewed by Rice and Curran (2001).

In addition to playing a critical role in early development and disease, neuronal migration is also important for changes in the adult brain. In birds, neuronal migration is required for postnatal behavior changes (Nottebohm 1981; Goldman and Nottebohm 1983; for review, see Alvarez-Buylla and Kirn 1997; Goldman and Luskin 1998; Nottebohm 2002). Findings of neurogenesis and adult neural stem cells suggest that neuronal migration is also important in the brains of adult mammals, including humans (Altman 1962; Reynolds and Weiss 1992; for review, see Gage 2000; Alvarez-Buylla and García-Verdugo 2002; Gould and Gross 2002; Rakic 2002). Because neuronal stem cells give rise to neurons during neural plasticity (Greenough et al. 1978; Kempermann 2002), neuronal migration can be essential for neural plasticity, although it is unknown whether neuronal migration is regulated in neural plasticity.

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An additional role for neuronal migration in brain evolution has been proposed by Rakic and colleagues (Letinic and Rakic 2001). Comparative studies of neuronal migration between humans and monkeys have led to the suggestion that establishment of new routes of neuronal migration might contribute to the evolution of the human brain (Ogren and Rakic 1981; Letinic and Rakic 2001; Rao and Wu 2001; Letinic et al. 2002). Regions connected to each other anatomically and functionally are thought to coevolve during the evolution of the mammalian brain (Barton and Harvey 2000). The establishment of a new migratory pathway between two functionally connected regions may contribute to the coevolution of the frontal cortex and the thalamic nuclei (Letinic and Rakic 2001).

Radial and tangential modes of migration

According to the direction of neuronal migration relative to the surface of the CNS, neuronal migration can be classified into radial and tangential modes. A cellular model for radial migration based on reconstruction of sections examined by electron microscopy proposes that neurons migrate along radially aligned glial fibers (Rakic 1971a,b, 1972, 1978, 1990; Levitt and Rakic 1980). This model is supported by later observations using retroviral tracing, immunohistochemistry (Misson et al. 1991), and in vitro studies of live granule cells from the cerebellum (Hatten and Liem 1981; Edmondson et al. 1988; Gregory et al. 1988; Mason et al. 1988; Hatten and Mason 1990). Further in vitro studies have shown that granule cells can also migrate along glass fibers coated with extracellular matrix proteins such as laminin or fibronectin (Fishell et al. 1993), suggesting that extracellular matrix proteins could provide substrate along which neurons can migrate.

Recent studies have indicated that there are two modes of radial migration (Nadarajah et al. 2001; Nadarajah and Parnavelas 2002): somal translocation and locomotion (Fig. 1). Locomotion is the classical radial glia-dependent neuronal migration involving the migration of an entire cell, including its processes and the cell body. Somal translocation involves a neuron whose process is attached to the pia (a part of the meninges) and its cell body translocates as the process becomes shorter. The same neuron can have both modes of migration, first moving by locomotion and later by somal translocation once its leading process touches the pia (Nadarajah et al. 2001; Nadarajah and Parnavelas 2002).

Tangential migration of neurons occurs along pathways parallel to the surface of the CNS. Although tangential migration was observed in the 1960s (Altman and Das 1966; Hicks and D'Amato 1968; Hinds 1968; Altman 1969; Rakic and Sidman 1969), its importance is better appreciated after findings of tangential migration in multiple regions of the CNS including the telencephalon, the cerebellum, and the spinal cord (Table 1; for review, see Parnavelas 2000; Corbin et al. 2001; Marin and Rubenstein 2001).

Unlike radial migration, tangential migration does not rely on glial fibers. In some structures such as the pontine nuclei, migration depends on interactions with axonal pathways (Rakic 1990). In other structures, such as the adult rostral migratory stream (RMS), tangential migration relies on astrocytes, which have been implicated in forming tubular structures through which chains of neurons migrate (Lois et al. 1996; Alvarez-Buylla and García-Verdugo 2002). In vitro, tangential migration of some cell types is independent of other cells. For example, neuronal precursor cells from the medial ganglionic eminence (SVZa) in the postnatal forebrain or the embryonic lateral ganglionic eminence (LGE) and the medial ganglionic eminence (MGE) can migrate individually in a three-dimensional collagen matrix without relying on other cells (Wu et al. 1999; Zhu et al. 1999; Wong et al. 2001). Thus, the roles of axonal or glial fibers in tangential migration are not clear.

Some cells can undergo both tangential and radial migration. For example, cells in the external germinal layer (EGL) of the cerebellum migrate tangentially before they change the migration mode to that of classic radial mi-

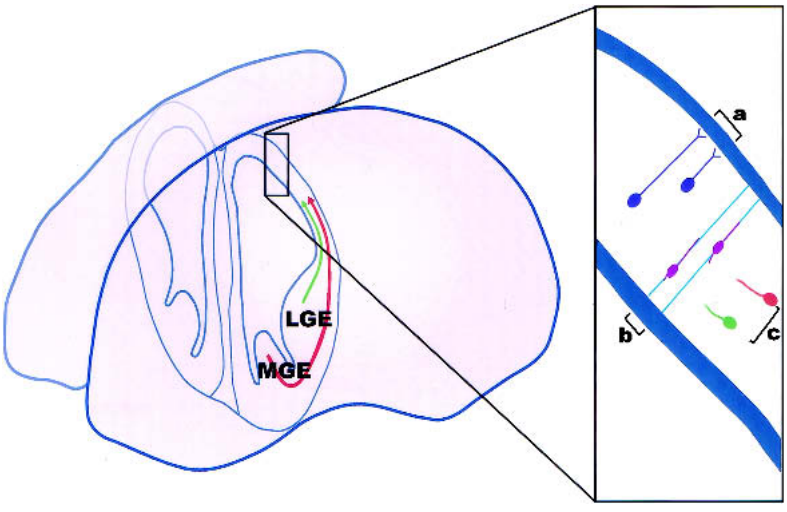

Figure 1. Routes of neuronal migration. A diagram of an embryonic rodent brain is shown on the *left*. Two examples of tangential migration are colored in red and green. MGE, medial ganglionic eminence; LGE, lateral ganglionic eminence. A diagram of the coronal section of the neocortex is shown on the *right*. There are two modes of radial migration: somal translocation and locomotion. Neurons migrating by somal translocation is shown in *a*, neurons migrating by glial-dependent locomotion is shown in *b*, and neurons migrating tangentially is shown in *c*.

Table 1. *Examples of tangential migratory pathways in the brain*

Origin	Destination	References
URL	Cerebellar EGL	Alder et al. 1996; Altman and Bayer 1997; Wingate and Hatten 1999; Wingate 2001
URL	Midhindbrain boundary	Koster and Fraser 2001
LGE	OB and neocortex	Anderson et al. 1997; Zhu et al. 1999; Wichterle et al. 2001; Nadarajah et al. 2002
SVZa	OB	Altman and Das 1966; Altman 1969; Luskin 1993; Lois and Alvarez-Buylla 1994; Hu et al. 1996; Wichterle et al 1997; Wu et al. 1999
MGE	Striatum and neocortex	Van Eden et al. 1989; Yan et al. 1992; DeDiego et al. 1994; De Carlos et al. 1996; Anderson et al. 1997; Tamamaki et al. 1997; Lavdas et al. 1999; Zhu et al. 1999; Marin et al. 2000; Wichterle et al. 2001; Nadarajah et al. 2002

URL, upper rhombic lip; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; OB, olfactory bulb; SVZa, subventricular zone in the anterior forebrain; EGL, external germinal layer.

gration (Komuro et al. 2001). After EGL cells radially migrate into the internal granular layer, these new granule cells can detach from the radial glial cells (Bergmann glia) and migrate farther in a radial direction but in a manner independent of the Bergmann glial fibers (Komuro and Rakic 1998). It is unclear what determines the migratory mode taken by a neuronal precursor cell or the transition between different modes of migration.

Cell adhesion and neuronal migration

Cell adhesion is important for both radial and tangential migration. Antibody perturbation studies have suggested roles for several cell adhesion molecules in radial migration. For example, antibodies against the cell adhesion molecules astrotactin, tenascin, and thrombospondin, or those against $\alpha_3\beta_1$ integrin can inhibit the migration of glial cells (Edmondson et al. 1988; O'Shea et al. 1990; Husmann et al. 1992; DeFreitas et al. 1995). Antibodies against astrotactin and $\alpha_3\beta_1$ integrin inhibit neuronal association with glial fibers (Stitt and Hatten 1990; Fishell and Hatten 1991; Cameron and Rakic 1994; Anton et al. 1996, 1999; Zheng et al. 1996), suggesting that the migratory defects may be a result of reduced association with glial fibers.

Adhesion molecules have also been shown to be important in tangential migration. For example, the polysialylated form of the neural cell adhesion molecule (N-CAM), the cell adhesion molecule TAG-1, and the Ng-CAM binding protein DM-GRASP have been implicated to play important roles in the tangential migration of different cell types (Tomsiewicz et al. 1993; Ono et al. 1994; Hu et al. 1996; Chazal et al. 2000; Heffron and Golden 2000; Denaxa et al. 2001; Kyriakopoulou et al. 2002).

Although gene targeting studies have confirmed the importance of astrotactin in granule cell association with glial fibers (Adams et al. 2002), it has been observed that mice lacking the β_1 integrin gene do not show defects in cortical migration (Graus-Porta et al. 2001). Thus, additional studies will be needed to determine the biological roles of the different adhesion molecules in neuronal migration. It will also be interesting to investigate the relationship between cell adhesion and directional guidance.

Directional guidance of neuronal migration: slit as a guidance cue

Although the previously mentioned adhesion molecules, glial fibers, and neuronal axons are important for neuronal migration and may limit the dimension in which neurons can move, they do not provide sufficient information to guide the direction of neuronal migration. Instead, secreted molecular cues have been shown to play important roles in guiding neuronal migration. A general principle from recent studies is that guidance cues for neuronal migration are shared with those for axon projection. There are four families of axon guidance cues known. We will use the Slit family as a primary example, before discussing other axonal guidance cues and their roles in neuronal migration.

The Slit gene was first discovered in a genetic screen for defects in embryonic pattern formation in *Drosophila* (Nusslein-Volhard et al. 1984). Slit genes have now been found in a wide range of species from *Caenorhabditis elegans* to humans (for review, see Wong et al. 2002). The *Drosophila* Slit protein contains an N-terminal signal peptide, four leucine-rich repeats (LRRs), seven EGF repeats, a laminin G domain, and a C-terminal cysteine-rich motif (or cysteine knot; Rothberg et al. 1988, 1990; Rothberg and Artavanis-Tsakonas 1992). Vertebrate Slit proteins are similar to *Drosophila* Slit except that they contain nine EGF repeats.

Initial characterizations of *Drosophila slit* mutants led to the conclusion that Slit was involved in midline cell differentiation, whereas its phenotype of the apparent fusion of longitudinal axons was thought to be secondary to cell differentiation defects (Rothberg et al. 1988, 1990). In 1999, work by three labs on *Drosophila* and vertebrates independently demonstrated that Slit was a diffusible chemorepellent for axons in *Drosophila* (Kidd et al. 1999) and mammals (Brose et al. 1999; Li et al. 1999). Thus, Slit acts directly on axons to direct their projection. Since then, Slit proteins have been shown to be potent repellents for axons in a variety of regions (for review, see Wong et al. 2002).

In addition to its role in axonal guidance, Slit plays a role in the directional guidance of neuronal migration. Such a role for Slit was first demonstrated in the RMS from the SVZa to the olfactory bulb (Wu et al. 1999), which relays information from the olfactory epithelium

to the olfactory cortex. Coculture experiments indicated that the septum at the midline of the telencephalon was repulsive to the SVZa neurons (Hu and Rutishauser 1996; Wu et al. 1999). Two of the three mammalian Slit genes are expressed in the septum (Wu et al. 1999). When SVZa explants are cocultured in vitro with an aggregate of Slit-expressing cells (Wu et al. 1999) or with purified Slit proteins (Hu 1999), Slit is able to repel SVZa neurons. Thus, these data suggest that the repulsive activity in the septum is due to the expression of the Slit genes.

Slit also repels other cell types, including GABAergic neurons containing that migrate tangentially from the ganglionic eminence to the neocortex in the embryo (Zhu et al. 1999; Fig. 2) and cells that migrate radially from the ventricular zone of the neocortex (Hu 1999).

The concentration gradient of Slit is important for its function as a repellent in vitro (Wu et al. 1999). When SVZa explants are cocultured with the septum in the presence of the extracellular domain of the Slit receptor Roundabout (Robo), the repulsive effect of the septum on SVZa neurons is reduced (Wu et al. 1999), suggesting that that Slit contributes to the repulsive activity in the septum. Although these results indicate that Slit can repel SVZa neurons, it should be noted that the role of endogenous Slits (or the septum) in SVZa migration has not been demonstrated, and, although Slit can repel neurons within the radius of 1 mm in vitro, the effective distance of endogenous Slit is unknown.

The idea that the same molecule can function in neuronal migration and axon guidance is supported not only by the roles of Slit on both axon guidance and neuronal migration (Wu et al. 1999), but also by the finding that the same motifs in the Slit protein are involved in both activities (Battye et al. 2001; Chen et al. 2001; Nguyen-Ba-Charvet et al. 2001b). The N-terminal LRRs of Slit are sufficient to repel both projecting axons and migrating neurons (Chen et al. 2001).

A recent paper reports that Slit functions only as an inhibitor to reduce the speed of neuronal migration but not as a repellent to change the direction of neuronal migration, and that Slit acts as a repellent only in the presence of a glial-derived migration-inducing activity (Mason et al. 2001). Further work is needed to determine whether Slit functions as a repellent or an inhibitor.

Multiple molecular cues guide neuronal migration

Four families of axon guidance cues are known: netrins (Colamarino and Tessier-Lavigne 1995), semaphorins (Semas; Kolodkin 1996; Raper 2000), ephrins (Flanagan and Vanderhaeghen 1998), and Slits. Netrins usually function as attractants, whereas the others are often repellents. Ephrins are membrane bound, whereas the others are diffusible. They all function by binding to their transmembrane receptors. There is now evidence that they are not only involved in axon guidance, but all four families are also involved in neuronal migration.

Neurons from the dorsal rhombencephlic neuroepithelium migrate ventrally and rostrally, eventually residing in several nuclei including the basilar pontine nuclei and the inferior olivary nuclei. Neurons in the pontine migratory stream end up in the basilar pons, which are located near the ventral midline (the floor plate). Netrin is expressed in the floor plate, whereas the migrating neurons express their receptor Deleted-in-Colorectal-Cancer (DCC; Yee et al. 1999). Netrin attracts neurons migrating toward the basilar pons (Yee et al. 1999; Alcantara et al. 2000). Netrin may also serve as a stop signal for neurons migrating circumferentially from the dorsal rhomb-

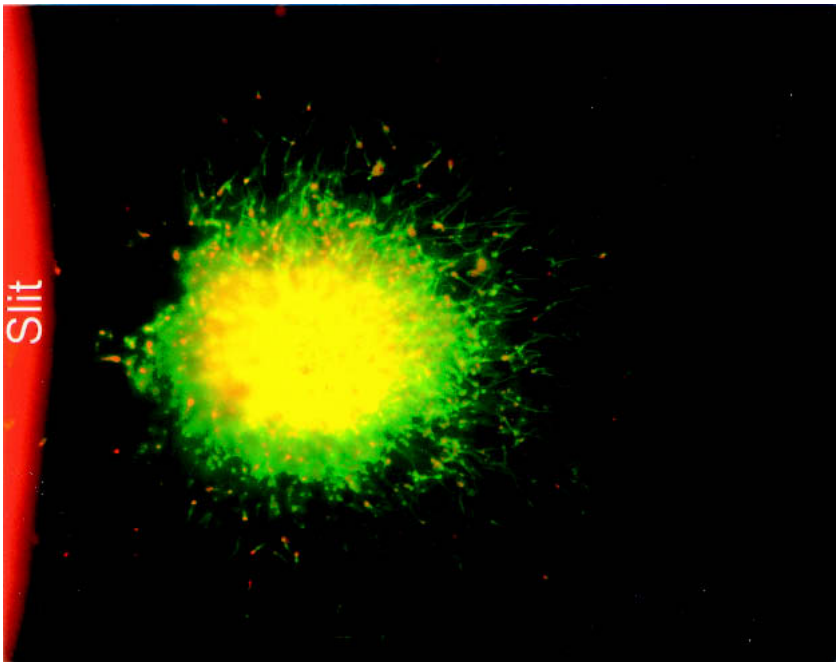

Figure 2. Directional guidance of neuronal migration by slit. This image shows how lateral ganglionic eminence (LGE) neurons behave in the presence of the repellent molecule Slit. An aggregate of human embryonic kidney (HEK) cells transfected with Slit cDNA was placed on the *left* side. An explant of LGE was placed on the *right*. The cells were cocultured in a three-dimensional gel matrix overnight. TUJ1 staining for neuronal specific tubulin is shown in green and anti-GABA staining in red (to show that these neurons contain the neurotransmitter GABA). Normally, cells migrating out of an LGE explant would be distributed symmetrically around its circumference. In the presence of Slit supplied from a point source, however, there are more cells in the quadrant distal to the Slit source than in the proximal quadrant. This result suggests that Slit is a repellent for LGE cells.

encephlic neuroepithelium to the inferior olivary nucleus (Bloch-Gallego et al. 1999; de Diego et al. 2002).

Netrins may also play a role in establishing or maintaining the rostral boundary of the cerebellum (Przyborski et al. 1998). Netrin-1 is expressed in the pontine area and it has been demonstrated that a loss of function mutation in its receptor, Unc5h3, causes the embryonic EGL cells and Purkinje cell precursors to migrate across the normal rostral boundary into the midbrain (Ackerman et al. 1997; Przyborski et al. 1998). Although netrin-1 repels cerebellar precursor cells postnatally (Alcantara et al. 2000), direct tests of netrin-1 did not show any effect of netrin-1 on EGL cells of the appropriate embryonic stages, suggesting that perhaps other netrins may function through Unc5h3 (Alcantara et al. 2000). In addition to its roles in the cerebellum, netrin repels cells in the MGE and LGE of the telencephalon (Hamasaki et al. 2001).

Precursor cells from the MGE can migrate either into the striatum or the neocortex to become interneurons. Repulsion by Semas is important for directing some interneurons into the neocortex and others into the striatum (Marin et al. 2001). Sema 3A and Sema 3F are expressed in the striatum, whereas its neuropilin receptors are expressed in interneurons migrating from the MGE to the neocortex, but not in interneurons migrating into the striatum (Marin et al. 2001). Sema 3A and its receptor neuropilin-1 may function in repelling or inhibiting the migration of neural crest cells from the trunk and hindbrain (Eickholt et al. 1999; Kawasaki et al. 2002). Sema 3C may promote the migration of neural crest cells into the proximal cardiac outflow tract (Feiner et al. 2001).

Ephrins and their Eph receptors are involved in delineating the migratory pathway of neural crest cells in the peripheral nervous system (PNS) (O'Leary and Wilkinson 1999; Klein 2001; Wilkinson 2001; Knoll and Drescher 2002). Because ephrins are not diffusible, they function by creating regions that are nonpermissive to migrating neural crest cells. In the CNS, ephrins and Eph are expressed in the SVZa and the RMS (Conover et al. 2000). Injection of extracellular domains of Eph receptors can disrupt SVZa migration (Conover et al. 2000), although the precise roles of ephrins in the RMS remain to be defined.

Conservation of guidance cues for neurons and leukocytes

Since its discovery in the late 1800s, migration has been well known to be a basic feature of cells ranging from leukocytes in adult animals (for review, see McCutcheon 1946; Harris 1954; Devreotes and Zigmond 1988) to neuronal precursor cells in embryos (for review, see Hatten and Mason 1990; Rakic 1990; Hatten and Heintz 1998; Bentivoglio and Mazzarello 1999). Only recently, however, has it become apparent that mechanisms guiding neuronal migration also seem to be shared with those for leukocytes, suggesting a fundamental conservation of directional control of cell migration among distinct cell types. Leukocyte chemotaxis was first described by Leber in 1888 (McCutcheon 1946; Harris 1954) and is one of the best-characterized models of cell migration in adult mammals (Boyden 1962; Zigmond 1974; Devreotes and Zigmond 1988; Servant et al. 2000). Work in the last 20 years has demonstrated the importance of the chemokine family in leukocyte chemotaxis (Baggiolini et al. 1997; Luster 1998; Cyster 1999; Locati and Murphy 1999). The first chemokine was isolated in 1977 (Duel et al. 1977) and functional studies of the chemokines began in 1987 with the identification of interleukin-8 (Yoshimura et al. 1987). There are presently more than 40 chemokines, which are small and structurally related proteins containing 70–100 amino acid residues that promote leukocyte motility and attract leukocytes.

There are multiple differences between neurons and leukocytes, including: (1) different migratory environments; (2) specialized morphologies (a migrating neuron has a single leading process versus leukocytes, which have multiple short pseudopodia; Fig. 3); (3) the speed of neuronal migration is significantly slower than that of leukocyte chemotaxis; and (4) all guidance cues for neurons function through single transmembrane proteins, whereas all leukocyte chemotactic factors function

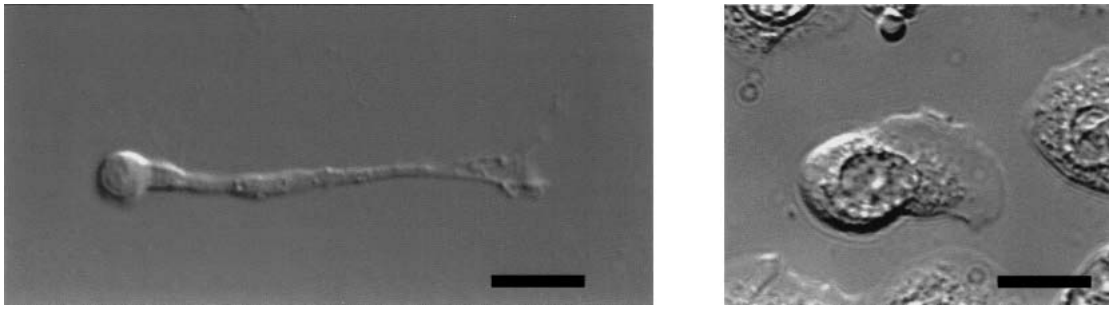

Figure 3. Morphological comparison of a migrating neuron and a chemotactic leukocyte. A neuronal precursor cell from the medial ganglionic eminence is shown on the *left* and a migrating neutrophil is shown on the *right*. Pictures were taken under the same microscope with the same magnification. Bars, 10 μm. Both cells were migrating from the left to the right. In the *left* panel, the cell body is located in the left and the tip of the leading process is at the right. In the *right* panel, the neutrophil was differentiated from a PLB cell. The photograph was taken when the cell was migrating after treatment with the chemotactic factor *N*-formyl peptide f-Met-Leu-Phe (fMLP).

through seven transmembrane proteins coupled to a heterotrimeric G protein. It is thus possible that different mechanisms have evolved to guide the migration of different cell types. However, recent studies indicate that, despite these differences, the guidance cues and receptors for neurons and leukocytes are used in both systems, supporting a conservation of guidance mechanisms for cells of distinct types.

Recently, Slit has been found to control leukocyte chemotaxis (Wu et al. 2001). Two mammalian Slit genes and three Slit receptors (Robos) are expressed in adult tissues outside the nervous system (Wu et al. 2001). Slit could inhibit the migration of monocytes, lymphocytes, and neutrophils induced by multiple types of chemokines and nonchemokine type of chemotactic factors (Wu et al. 2001). The effect of Slit on leukocyte chemotaxis is inhibited by a soluble form of the extracellular domain of Robo (Wu et al. 2001), which was shown earlier to inhibit Slit repulsion of neurons (Wu et al. 1999; Zhu et al. 1999). These results support the idea that the same receptor (and presumably intracellular pathways) is used in both neurons and leukocytes (Wu et al. 1999; Zhu et al. 1999; Wu et al. 2001). In addition to providing evidence for conserved mechanisms of cell migration, these results also suggest a strategy to control unwanted leukocyte chemotaxis. Thus, the inhibitory effect of Slit could be used to attenuate leukocyte infiltration during inflammation (L. Feng, J.Y. Wu, and Y. Rao, unpubl.). Ongoing research indicates that down-regulation of endogenous Slit expression may contribute to inflammation, suggesting that the endogenous Slit and Robo may play roles in leukocyte chemotaxis.

A role for leukocyte guidance cues in neuronal migration has been studied in the case of the chemokine stromal derived factor (SDF)-1. SDF-1 was originally found in the immune system (Tashiro et al. 1993; Nagasawa et al. 1996), where it functions as a chemoattractant for leukocytes through its CXCR4 receptor. When SDF-1 and CXCR4 genes were knocked out, a surprising finding was that cerebellar granule cells were found in the internal layers prematurely in the embryo (Ma et al. 1998; Tachibana et al. 1998; Zou et al. 1998), suggesting that SDF-1 may either directly or indirectly play a role in preventing the EGL cells from premature migration (Ma et al. 1998; Zou et al. 1998). However, the precise role of SDF-1 in EGL migration was not known (Ma et al. 1998; Zou et al. 1998; Asensio and Campbell 1999; Mennicken et al. 1999). Based on the premature neuronal migration phenotype of the SDF-1 knockout mice, one suggestion was that SDF-1 inhibits neuronal differentiation and thus reduces migration (Ma et al. 1998). Another was that SDF-1 increases cell adhesion and thus immobilizes the EGL cells (Zou et al. 1998). Recent work indicates that SDF-1 is expressed in the meninges and can attract cerebellar granule cells (Klein et al. 2001; Lu et al. 2001; Zhu et al. 2002). SDF can attract embryonic but not postnatal EGL cells (Zhu et al. 2002), resulting in the anchoring of embryonic EGL cells. This switch of cellular responsiveness occurs through the inhibition of SDF-CXCR4 signaling by Eph and ephrins, which are expressed in the postnatal EGL cells (Lu et al. 2001). Further studies with the hippocampus also indicate a role for SDF-1 and CXCR4 in the migration of dentate granule cells (Bagri et al. 2002a,b; Lu et al. 2002). Thus, the chemokine SDF-1 and its receptor CXCR4 are used both in leukocytes and in neurons. Similar to neuronal response to guidance cues (Song et al. 1998), the attractive responses of leukocytes to SDF-1 can also be reversed by changes in cyclic nucleotide levels (Poznansky et al. 2000), further supporting the idea that guidance mechanisms are conserved between neurons and leukocytes.

Studies of CD100/Sema4D suggest that a ligand similar to those functioning as guidance cues in the nervous system may be used by a different receptor in leukocytes. CD100/Sema4D is a transmembrane Sema similar to human Sema 3A that can be cleaved into a diffusible form (Furuyama et al. 1996; Hall et al. 1996; Hérold et al. 1996; Elhabazi et al. 2001). Although it has not been shown to guide neuronal migration, CD100 is the first member of the Sema family of neuronal guidance cues detected in the immune system. CD100 has multiple functions in lymphocytes including T-cell adhesion (Hérold et al. 1996), B-cell aggregation and survival (Hall et al. 1996), lymphocyte activation (Kumanogoh et al., 2000; Shi et al. 2000; Watanabe et al. 2001), and monocyte migration (Delaire et al. 2001). Neuropilins and plexins are the Sema receptors in the nervous system. It has been demonstrated that the inhibitory effect of CD100 on monocyte migration is not through either neuropilin-1 or neuropilin-2 (Delaire et al. 2001). Instead, CD100 acts on lymphocytes by binding to CD72, a lectin-related transmembrane receptor (Kumanogoh et al. 2000). Furthermore, the effect of CD100 on monocyte migration is not regulated by intracellular cyclic nucleotide levels (Delaire et al. 2001), whereas neuronal responses to Semas are (Song et al. 1998). Therefore, although CD100/Sema4D regulates lymphocyte function and migration, the underlying mechanisms are different from those used to mediate Sema guidance of axons and neurons (Kumanogoh and Kikutani 2001).

Signal transduction mechanisms guiding neuronal migration

Signaling transduction mechanisms in axon guidance have been reviewed recently (Patel and Van Vactor 2002). We will focus here on the previously mentioned Slit-Robo pathway because it is the only pathway that has been directly studied in neuronal migration. It remains to be investigated whether the same pathway is used in both neurons and leukocytes.

Although Slit was discovered over a decade ago, it was only recently that the receptor for Slit was found to be the transmembrane protein Robo (Kidd et al. 1998; Brose et al. 1999; Li et al. 1999). Robo was first discovered for its role in commissural axon guidance in *Drosophila* (Seeger et al. 1993; Kidd et al. 1998). Studies in *Drosophila* indicate that *slit* and *robo* mutations interact genetically (Kidd et al. 1999). Biochemical studies of

mammalian Slit and Robo proteins provide direct evidences that Slit binds Robo (Brose et al. 1999; Li et al. 1999), and functional studies indicate that the extracellular part of Robo blocks neuronal responses to Slit (Wu et al. 1999; Zhu et al. 1999).

Robo is a single-pass transmembrane protein with five immunoglobulin (Ig) domains and three fibronectin type III (FNIII) repeats in its extracellular part. Biochemical experiments showed that the Ig domains in Robo are sufficient to interact with the LRR in Slit (Battye et al. 2001; Chen et al. 2001; Nguyen-Ba-Charvet et al. 2001b).

The large intracellular region of *Drosophila* Robo and the three mammalian Robos contains four identifiable conserved motifs designated CC0, CC1, CC2, and CC3 (Kidd et al. 1998; Zallen et al. 1998). The cytoplasmic domain of Robo is important in mediating repulsion in response to Slit (Bashaw and Goodman 1999). In transgenic flies, neurons expressing a chimeric receptor containing the ectodomain of Frazzled (Fra), a receptor for netrin, and the cytoplasmic domain of Robo (Fra-Robo) avoided the netrin-expressing midline (Bashaw and Goodman 1999), indicating that the cytoplasmic domain of Robo determines the repulsive response. Deletion of each of the CC motifs leads to a partial *robo* phenotype (Bashaw et al. 2000), suggesting an additive effect of these motifs (Bashaw et al. 2000). The CC2 motif is a consensus binding site for Ena-VASP-homology domain (EVH1) of Enabled (Ena), and in vitro binding experiments suggested that Ena interacted with Robo through CC2 and CC1 (Bashaw et al. 2000). The Abelson kinase (Abl) can phosphorylate Robo in vitro and Abl seems to antagonize the activity of Robo in *Drosophila* (Bashaw et al. 2000). It is unknown whether Slit can regulate the activities of Abl and Ena. In *Drosophila,* genetic interaction between *ena* and *slit* and that between *abl* and *robo* have been detected (Bashaw et al. 2000), suggesting functional roles of Ena and Abl in the Slit-Robo pathway, at least for commissural axon guidance.

Work in *Drosophila* has suggested the involvement of protein tyrosine phosphatases (PTPases) in the Slit-Robo pathway (Sun et al. 2000). Mutations in two receptor PTPase genes, *PTP10D* and *PTP69D,* interact genetically with *slit* and *robo* (Sun et al. 2000). Phenotypic analyses suggest that PTPases increase the sensitivity of commissural axons to Slit (Sun et al. 2000). The roles of Ena, Abl, and PTPases in neuronal migration remain to be determined.

The CC3 motif of Robo1 interacts with srGAPs, a novel subfamily of GTPase-activating proteins (GAPs; Wong et al. 2001). srGAPs 1 and 2 are expressed in regions responsive to Slit and in patterns similar to that of Robo1 (Wong et al. 2001). Extracellular interaction between Slit and Robo increases the intracellular interaction between the CC3 motif of Robo and the SH3 motif of the srGAPs. Slit treatment of either a mammalian cell line or the primary SVZa cells reduces the amount of the active form of the Rho GTPase Cdc42 (Wong et al. 2001). The functional role of Cdc42 in neuronal migration has been demonstrated by the observation that the repulsive effect of Slit on migrating SVZa cells was blocked by a constitutively active mutant of Cdc42 (Wong et al. 2001). Whether and how Slit regulates the activities of the other Rho GTPases (RhoA and Rac1) depends on the cell type (Wong et al. 2001), and the functional significance of RhoA and Rac1 in Slit-Robo signaling is presently unknown.

Because the active form of Cdc42 activates N-WASP, which promotes actin polymerization, a working hypothesis for Slit-mediated repulsion of migrating neurons has been proposed (Wong et al. 2001). This pathway begins with the extracellular interaction of Slit with Robo, and the signal is transduced through the increased intracellular interaction of Robo with srGAPs, resulting in the inactivation of Cdc42. The relatively lower level of Cdc42 activity on the side of the cell proximal to a higher concentration of Slit leads to relatively lower activities of N-WASP and Arp2/3 complex on the proximal side. Eventually, there will be polarized actin polymerization with less actin polymerization on the proximal side and more actin polymerization on the distal side of the cell (Wong et al. 2001). This model remains to be tested biochemically and functionally.

It is unclear whether the Abl, Ena, and the PTPases are intrinsic components of the intracellular pathway for Slit-Robo signaling, or whether some components are only specifically involved in some, but not all, responses. For example, because *Drosophila abl* and *ena* mutants do not have all the phenotypes of *slit* and *robo* mutants, it is possible that Abl and Ena are required for commissural axon guidance in *Drosophila*, but not necessarily for neuronal migration in mammals. It is not known whether Ena and Abl mediate completely different pathways or whether they interact with srGAPs functionally. Similar to other guidance cues, Slit response can be regulated by intracellular concentration of cGMP (Nguyen-Ba-Charvet et al. 2001a). It is unknown whether and how cGMP regulates the hypothetical srGAP-N-WASP-Arp2/3 pathway.

Genetic studies in *Drosophila* suggested that Slit promotes the asymmetric division of neural precursor cells by down-regulating specific proteins (Mehta and Bhat 2001). One tempting possibility is that Slit can regulate the polarized activity or localization of some component(s) that are used both in guiding cell migration and in establishing cell polarity.

Concluding remarks

The importance of neuronal migration is now clearly established, although the full spectrum of functional roles of neuronal migration in evolution, development, and adult life remains to be clarified. Studies of guidance cues that are shared among migrating neurons, projecting axons, and chemotactic leukocytes are advancing our understanding of the spatial control of migration. The potential link between cell adhesion signaling and directional guidance cues remains to be studied at the molecular level. In addition, because the mechanisms involved in polarized neuronal movement are largely unknown and little is known about temporal regulation of

neuronal migration, additional exploration of these areas will be required. Multiple approaches will thus be required to gain a comprehensive understanding of the mechanisms of neuronal migration and fundamentally conserved mechanisms underlying cell motility and its regulation.

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