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# Extracellular factors that regulate neuronal migration in the central nervous system

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## Abstract

Neuronal migration is an essential process in the development of the central nervous system (CNS). The movement of neuronal precursors from their birthplaces to their ultimate position in the adult brain is regulated by extrinsic and intrinsic signals. The understanding of the extracellular factors that regulate neuronal migration has increased significantly in the last few years. In this review, we will discuss the latest insights into the roles of the extracellular matrix (ECM), cell adhesion molecules (CAMs), soluble and membrane-bound factors, neurotransmitters and ion channels in the migration of neurons.

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## 1. Introduction

Cell migration is a major step in the development of the vertebrate CNS. Newborn neurons, generated in the germinal layers of the neural tube, move to their final destination in the cortex and other areas of the CNS, where they establish appropriate synaptic connections. These cell movements are critical for normal brain development and function. Neuronal migration in the CNS, which encompasses migration of neuronal progenitors and post-mitotic neurons, occurs primarily by two modes, radial and tangential migration. In radial migration, neurons migrate along radial glial guides that are perpendicular to the germinal layer. This form of migration occurs throughout the brain, including the cerebrum and cerebellum. Tangential migration is the movement of early neurons from their birthplace to their final destination in a direction running parallel to the ventricle (Corbin et al., 2001; Marin and Rubenstein, 2001). In contrast to

radial migration, cells migrating tangentially appear to be attached to one another or to axons, rather than to glial cells, forming chains of migrating neurons (Lois et al., 1996). This observation led to the conclusion that tangential migration occurs independently of glia. However, in the RMS to the olfactory bulb, an area of extensive tangential migration, tubes of astrocytic cells appear to surround the chains of migrating neurons (Doetsch and Alvarez-Buylla, 1996) and there is evidence that glia may play an active role in the regulation of tangential migration (Mason et al., 2001).

Recent studies show that different neuronal populations use different modes of migration (Marin and Rubenstein, 2001; Parnavelas, 2000). For example, in the cerebral cortex, the precursors of excitatory neurons migrate from the cortical germinal zone to the cortical layers primarily by radial migration. In contrast, the precursors of inhibitory interneurons, which are born in the germinal layers of ganglionic eminences, migrate to the cortex by tangential migration. It is likely that the different modes of migration of these neuronal populations reflect the fact that they are born in different regions but need to ultimately mix within the mature cortex. The cortical germinal layer is close and topographically similar to the cortex, allowing glutamatergic neurons to reach the cortex simply by “ascending” from the ventricular wall to the cortical layers aided by radial glia. This results in clonally related excitatory neurons ending close to one another, which may have functional relevance (Rakic, 1988). In contrast, GABAergic neurons, which enter the cortex coming from a distant source and need to disperse into

*Abbreviations:* ApoER, apolipoprotein E receptor; BDNF, brain-derived neurotrophic factor; BLBP, brain lipid-binding protein; CAM, cell adhesion molecule; CNS, central nervous system; Dab, disabled; DCC, deleted in colo-rectal cancer; ECM, extracellular matrix; HSPG, heparan sulfate proteoglycan; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; MIA, migration inducing activity; NCAM, neural cell adhesion molecule; NRG, neuregulin; RMS, rostral migratory stream; SDF-1, stromal-derived factor 1; SVZa, anterior subventricular zone; u-PAR, urokinase plasminogen activator receptor; VLDLR, very low density lipoprotein receptor

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a large area, cannot rely on the restricted migratory paths provided by the radial glial guides.

Neuronal migration, either radial or tangential, consists of several steps that are in many ways similar to migration of other cell types. First, when migration is initiated, the cell has to transition from a stationary state to a motile form. Once motile, the cell must maintain the migratory state and at the same time respond to guidance cues that may aid in its navigation. Finally, at the proper destination, the cell must end its migration and take its final position in order to establish proper connections. Each of these steps depends on extracellular factors that the cell encounters during its migration. These signals contribute to the changes in cell behavior by regulating movement (inducing or inhibiting signals), modulating speed (enhancing or diminishing signals) and influencing the direction of migration (attractants or repellents). These extracellular cues act through intracellular signaling cascades, which in turn regulate the cytoskeleton, the machinery subserving cell locomotion.

Neuronal migration also shares many characteristics with axonal outgrowth and pathfinding processes. Migrating neurons possess a short leading process ending in a growth cone similar to those of growing axons. However, during cell migration the neuronal cell body closely follows the growing process, while during axonal outgrowth the cell body remains stationary as the neurite elongates. Cell migration and axonal outgrowth also share basic molecular mechanisms. Recent studies show that some of the molecules that regulate neurite outgrowth, such as netrin and semaphorin, have similar effects on neuronal movement (Song and Poo, 2001).

During the last few years, significant progress has been made in the understanding of the molecular mechanisms that control neuronal migration. This review will focus on recent discoveries regarding extracellular signals that regulate neuronal migration in the vertebrate CNS and the ways in which they do so. Extracellular molecules that we will consider in this review include ECM components and their receptors, CAMs, secreted and membrane-bound factors and their receptors, neurotransmitters and their receptors and ion channels, all of which have been shown to influence neuronal migration.

## 2. Extracellular matrix molecules

The ECM is a complex network of proteins and polysaccharides that fills the intercellular space. The cells produce all components of the ECM and at the same time are dramatically affected by them. This is particularly clear in the nervous system, where the ECM influences many aspects of development, including differentiation and axonal guidance. Recently, several examples of the importance of the ECM in neuronal migration have been described. ECM molecules involved in neuronal migration include reelin, integrins, HSPGs, laminin, anosmin-1 and possibly fukutin.

The best studied example of an ECM protein involved in neuronal migration is reelin, a large extracellular protein that, when mutated, causes the disruption in neuronal migration observed in reeler mutant mice (D'Arcangelo et al., 1995; Rice and Curran, 2001) and lissencephaly with cerebellar hypoplasia (LCH) in humans (Hong et al., 2000). The brains of reeler mice have multiple neuroanatomical defects, including inverted layering of the cortical layers and abnormal Purkinjee's cell morphology and folia in the cerebellum. In the cerebrum, reelin is expressed by Cajal–Retzius cells, which are located in the outermost layer of the developing cortex and accumulates in the ECM around them. It has been proposed that reelin functions by allowing the migrating cells to detach from the radial glial guide once they reach the outer cortical surface. This would free the radial glia process for younger migrating neurons to move past the older ones, resulting in the inside–out organization of the cortex. In mouse reeler mutants, younger cells cannot pass the older cells, resulting in inverted cortical layering and abnormal cerebellar morphology. Strong genetic and biochemical evidence shows that reelin functions through the ApoER2 and the VLDLR (D'Arcangelo et al., 1995; Hiesberger et al., 1999) and Dab, a phosphoprotein that binds non-receptor tyrosine kinases (Howell et al., 1997). Mice lacking the gene for Dab or lacking the genes for both ApoER2 and VLDLR receptors have phenotypes almost indistinguishable from those of reeler mice. However, the mechanisms by which these molecules contribute to neuronal migration are not yet understood. Another family of proteins proposed to function as reelin receptors is the cadherin-related neuronal receptor (CNR) (Senzaki et al., 1999). It has been shown that CNRs bind reelin and this binding can be blocked by reelin or by CNR functional-blocking antibodies. Moreover, the CNR antibody disrupts both reelin signaling through Dab and the aggregation of dissociated cortical neurons. However, *in vivo* evidence for a role of CNR in cortical lamination is not yet available. In addition, it has been suggested that some aspects of reelin function in neuronal migration may be mediated by interactions with  $\alpha3\beta1$  integrin receptors, since reelin associates strongly with this receptor. Functional experiments showed that exposure to exogenous reelin can disrupt radial migration in wild-type mice, but it fails to do so in  $\alpha3\beta1$  deficient mice suggesting that reelin– $\alpha3\beta1$  integrin interactions are important for migration (Dulabon et al., 2000). Most recently, it has been proposed that reelin functions in migration are mediated by its serine protease activity (Quattrocchi et al., 2001).

Integrins, the major cell surface molecules responsible for interactions of cells with the ECM, appear to be involved in neuronal migration beyond their association with reelin. Using an *in vitro* model of chain migration, Jacques et al. (1998) demonstrated that blockade of integrin  $\alpha6\beta1$  impeded the formation of chains of migrating neuronal precursors and significantly reduced the rate of precursor migration. Furthermore, exposure to a peptide agonist specific for integrin  $\alpha6\beta1$  led to an increase in the formation of chains.

Thus, the interaction between a ligand and the integrin receptor appears to affect migration of neuronal precursors.

HSPGs and laminins are other important components of the ECM that also influence neuronal migration. HSPGs are highly negatively charged molecules that interact with other ECM components and with cell surface and secreted proteins, changing their localization and/or their function. They appear to play a role mediating the effects of Slit-2 (a repulsive/inhibitory signal for migrating neurons, see later) in migration. Hu (2001) showed that removal of HSPG from the surface of olfactory bulb neurons decreases binding of Slit-2 and leads to a reduction in Slit-2 effects. Laminin has been implicated in the migration of cerebellar granule cells, with functional-blocking antibodies inhibiting neuronal migration in vitro (Liesi et al., 1995). Interestingly, laminin can also convert netrin-1 from an attractant to a repulsive signal for axons (Hopker et al., 1999) and could affect neuronal migration in similar fashion.

Certain human diseases involving defects in neuronal migration appear to be caused by defects in other ECM components. For example, Fukuyama congenital muscular dystrophy (FCMD) with type II lissencephaly and myopathy has been mapped to the fukutin gene. Since, this gene is predicted to encode a secreted molecule and FCMD tissues show disruptions in ECM, it has been proposed that this protein might be an ECM component (Kobayashi et al., 1998). The mutation responsible for one form of Kallman syndrome, which is composed of anosmia, hypogonadism and occasionally mental retardation has been mapped to a gene designated *KALI*, which encodes an ECM protein termed anosmin-1 (Soussi-Yanicostas et al., 1998). The hypogonadism in Kallman syndrome is caused by a defect in the migration of the GnRH secreting neurons from the olfactory placode to the pre-optic and hypothalamic areas. However, in this case, the migration defects in this syndrome appear to be secondary to defects in the fasciculation of axonal tracks along which these neurons migrate (Hardelin, 2001).

In summary, the ECM not only contains intrinsic molecules that directly affect neuronal migration, but is also the site of accumulation of soluble molecules that regulate neuronal movement. In this way, the ECM may: (1) contribute to the formation of gradients of attractants or repellents; (2) allow for the combined presentation of some regulatory signals, leading to diverse biological outputs; (3) regulate the formation of brain structures necessary for migration, e.g. axonal tracks; (4) modulate or potentiate the signaling of receptors for guidance or migration modulating cues, as it has been shown to do for basic fibroblast growth factor (Rapraeger et al., 1991; Yayon et al., 1991).

### 3. Cell adhesion molecules and related cell surface proteins

CAMs are cell surface proteins that mediate cell–cell recognition and adhesion. Some proteins that mediate interactions with ECM components are also considered to

function as CAMs. CAMs are critical players in cell–cell binding, tissue patterning and other essential developmental processes. The roles of CAMs in nervous system development, including axon pathfinding and fasciculation, are pivotal. Recent studies have provided evidence that CAMs also play an important part in neuronal migration.

The NCAM is a CAM that functions through homophilic and heterophilic binding to affect adhesiveness of neurons and their processes to other neurons and the ECM. NCAM is produced in three isoforms by alternative splicing from a single gene (NCAM 120, 140, 180, which refer to their molecular weights). The 180 kDa form can be further modified by the addition of polysialic acid (PSA) chains which render the molecule less adhesive (Rutishauser and Landmesser, 1996). The most striking defect in mice lacking the *NCAM* gene is a reduction in the size of the olfactory bulb (Cremer et al., 1994; Ono et al., 1994; Tomasiewicz et al., 1993). This is apparently due to decreased migration of the neuronal precursors, which accumulate along the RMS, never reaching the bulb. This defect is mimicked by deletion of just the 180 kDa form of NCAM or enzymatic removal of PSA from embryonic tissue, suggesting that PSA-NCAM is a critical regulator of this migration. Studies in which  $\beta$ -galactosidase expressing wild-type neuronal precursors were transplanted into wild-type or PSA-NCAM-deficient mice showed the mutant RMS was capable of supporting migration of normal precursors. Thus, in the RMS, expression of PSA-NCAM in a migrating neuronal precursor appears to be necessary for its normal migration. PSA may function by modulating adhesion between the migrating precursor and its immediate surroundings, either other precursors or the surrounding glia, allowing the cell to move. In this way, absence of PSA may result in strong adhesion that would impair migration. Of course, other signals are also involved in regulating migration of RMS cells (see later).

DM-GRASP, also known as SC-1, JC7, BEN, ALCAM and neurolin, is a transmembrane protein containing five extracellular immunoglobulin-like domains, which appears to function in both homophilic and heterophilic binding. This protein has been implicated in cell adhesion, axon growth and fasciculation (Bowen et al., 1995; Burns et al., 1991; Pourquie et al., 1992; Tanaka et al., 1991). Based on its temporal and spatial pattern of expression in chick embryos, Heffron and Golden (2000) suggested that DM-GRASP might play a role in non-radial neuronal migration. Indeed, elegant in vivo experiments showed that a blocking antibody to DM-GRASP specifically inhibits tangential migration in the chick diencephalon but does not affect radial migration or axon outgrowth through this region. This perturbation in tangential migration results in a smaller and morphologically abnormal and disorganized diencephalon, demonstrating the importance of DM-GRASP in brain development. It is possible that DM-GRASP on the surface of tangentially migrating neurons binds to DM-GRASP or other CAMs on the surface of neighboring cells or axons, allowing cells to migrate along tangential pathways.

Astrotactin, a glycoprotein expressed by post-mitotic, migrating neurons, was the first molecule to be shown to mediate interactions between migrating neurons and radial glia (Edmondson et al., 1988). Initial experiments indicated that the migration of cerebellar granule neurons along radial glia fibers could be inhibited by anti-astrotactin (Edmondson et al., 1988) and that these antibodies could also block the adhesion of granule cells to cerebellar glia (Stitt and Hatten, 1990). Expression of astrotactin in fibroblastic cells promotes their adhesion to glial cells (Zheng et al., 1996), suggesting that astrotactin is a key element in neuron–glia adhesive interactions critical for migration. Accordingly, it has been recently reported that neuronal migration is slowed in mice lacking the astrotactin gene (Adams et al., 2002).

#### 4. Soluble and membrane-bound factors and their receptors

Soluble and membrane-bound factors regulate many aspects of vertebrate nervous system development, from the initial steps of neural induction to the maintenance and plasticity of the adult nervous system. These factors lead to many different cellular responses and developmental events, including promotion of cell survival, fate choice and morphological and functional differentiation. In recent years, it has become clear that many of these factors also play critical roles in neuronal migration. By virtue of their ability to diffuse, soluble factors can generate gradients within regions of the developing nervous system, providing positional information that is critical for processes, such as axonal pathfinding and neuronal migration. Topographical information can also be provided by generating gradients in expression levels of membrane bound factors and/or receptors. Many factors and their receptors have pleiotropic effects. They may have distinct biological effects on a particular cell type at different developmental stages or different effects on various cell types at the same developmental stage. Thus, a factor that promotes migration of a particular neuronal cell type early in development may promote its survival after it has migrated and differentiated (e.g. the effect of BDNF on cerebellar granule cells, discussed later). Many factors originally identified as survival, differentiation or mitogenic agents have been shown recently to contribute to different aspects of neuronal migration (e.g. PDGF, see later). The roles of these molecules in migration have been tested in different regions of the CNS. To facilitate discussion, this section will be subdivided by the biological assays and the brain areas on which the studies were performed.

##### 4.1. Radial glia differentiation: neuregulin, RF60, BLBP and Notch

Radial glia are essential for neuronal migration and recently have been reported to serve as neuronal precursors (Noctor et al., 2001). Therefore, understanding the mechanisms that regulate their formation, characteristics

and functions is critical. Early work by Hatten (1985) showed that neuronal contact could induce astroglia to adopt a radial glia phenotype in vitro. More recently, several neuron-derived proteins have been shown to mediate, at least in part, this induction. Embryonic cortical neurons were shown to secrete a protein of an apparent molecular weight 50–60 kDa (RF60) that induces cortical astroglia to adopt a radial shape and to express RC2, a marker for radial glia (Hunter and Hatten, 1995). However, this protein remains uncharacterized. Later, the growth factor NRG (also known as NRG1, since the discovery of three additional *NRG* genes) and its erbB receptor tyrosine kinases were shown to mediate radial glia formation and differentiation in the cerebellum (Rio et al., 1997) and the cortex (Anton et al., 1997). Rio et al. (1997) showed that cerebellar granule neurons expressing NRG activate glial erbB receptors, leading to radial glia formation and that blockade of glial erbB receptors results in blockade of radial glia differentiation. In addition, these experiments demonstrated that blocking erbB receptor signaling in radial glia impaired granule cell migration. This suggests that glial erbB receptor signaling plays a role in neuronal movement itself, possibly by regulating the expression of other glial genes necessary for the support of neuronal migration. Anton et al. (1997) had similar findings using imprints of cortical radial glia and migrating neurons. NRG treatment led to the elongation of radial glia fibers and to an acceleration of neuronal movement while blockade of erbB receptor function with a blocking antibody led to reduction in migration speed. Moreover, they found that NRG treatment of cortical astroglia in vitro induced the expression of BLBP, a radial glia protein that is critical for migration.

BLBP was identified in a screen for developmentally regulated genes in the cerebellum (Feng et al., 1994) and shown to be expressed by radial glia. Neuronal contact regulates BLBP expression in cerebellar astroglia (Feng and Heintz, 1995). BLBP also appears to be necessary for migration, since anti-BLBP antibodies block the radial glia formation induced by neuronal contact and inhibit neuronal movement (Feng et al., 1994). Thus, it seems that BLBP plays a critical role in neuron–glia interactions that regulate migration.

The Notch receptor and its ligands are known for influencing cell fate decisions, particularly for inhibiting neural differentiation. Recently, Gaiano et al. (2000) showed that activation of Notch in neuroepithelial cells in vivo results in the adoption of radial glia fate. Other studies suggest that Notch effects on radial glia formation may be mediated, at least in part, through the regulation of erbB receptor expression. Working with cerebellar cells, Corfas et al. (2001) reported that the induction of radial glia formation by contact with cerebellar granule cells depends both on Notch and erbB receptor signaling. Neuronal contact appears to activate glial Notch receptors, leading to the induction of glial erbB receptor expression. Then, NRG derived from granule cells activates erbB receptors, leading to the completion of the radial glia differentiation program. Interestingly, this study showed that BLBP expression in these glia is regulated by

Notch but not by erbB signaling. It appears that these three pathways (Notch, erbB and BLBP) are intertwined in the events that lead to radial glia formation.

#### 4.2. Radial migration in the cortex: the roles of neurotrophins and epidermal growth factor receptor (EGFR) signaling

BDNF and NT-4, members of the neurotrophin family, have been shown to support the survival of several populations of CNS neurons. Recently it has been found that misexpression of these molecules in the developing brain has dramatic effects on cortical neuronal migration. Brunstrom et al. (1997) demonstrated that infusion of NT-4 or BDNF into the ventricles of embryonic rats or application of these factors onto slices of developing cortex results in heterotopias, which appear to be caused by increased neuronal migration. In a related study, Ringstedt et al. (1998) showed that overexpression of BDNF in the ventricular zone of developing mice leads to a very similar disruption of cortical development. Interestingly, it was found that reelin expression by Cajal–Retzius cells was decreased in the mutant mice, leading the authors to suggest that reelin expression may be regulated by neurotrophins. Thus, the aberrant expression of neurotrophins during cortical development may be responsible for some cortical dysplasias, and this could be mediated by their influence on the expression of reelin or other molecules critical for radial migration.

The EGFR and its ligands, including heparin-binding EGF (HB-EGF) and TGF $\alpha$ , are highly expressed in the germinal layers of the telencephalon and appear to play significant roles in neuronal migration. One line of mice lacking the EGFR shows accumulation of neuronal precursors in telencephalic proliferative zones, suggesting a defect in their migration (Threadgill et al., 1995). More recently Caric et al. (2001), using a replication defective retrovirus, provided evidence that the levels of EGFR expression in cells impacted their ability to migrate, with cells overexpressing EGFR displaying increased radial migration in the cortex and olfactory bulb.

#### 4.3. Cerebellar granule cell migration: chemokines, ephrins, BDNF and their receptors

The developing cerebellum has been a very useful system to study radial migration, providing many insights into the molecular basis of this process. Among these are the findings that chemokines, ephrins, BDNF and their receptors are important for the regulation of granule cell migration, possibly working together to orchestrate the timely migration of these neurons. Originally identified as factors modulating the migration of leukocytes, the chemokines are a family of over 40 proteins that signal through specific seven transmembrane G protein-coupled receptors. The chemokine SDF-1 is expressed in the cerebellar pia and its sole receptor CXCR4 is expressed on the granule cell precursors. Deletion of

either of these genes results in premature invasion of the cerebellar anlage by granule cells (Ma et al., 1998; Zou et al., 1998), suggesting that SDF-1 could provide a signal that prevents precursors from leaving the germinal layer. This is supported by in vitro experiments showing that SDF-1 acts as a chemoattractant for granule cells (Klein et al., 2001). Studies on the signaling mechanism of ephrin B provided further insight into these processes, showing that ephrin B blocks the chemoattractive effects of SDF-1 on granule cells. Thus, the developmentally regulated expression of ephrin B could contribute to the initiation of neuronal migration. The final piece of the puzzle appears to be BDNF. This trophic factor is highly expressed in the developing cerebellum, with the strongest expression in the internal granule layer. Recent studies (Borghesani et al., 2002) show that migration of cerebellar granule cells out of the external granule cell layer is impaired in BDNF<sup>-/-</sup> mice and that granule cells purified from BDNF<sup>-/-</sup> mice show defects in initiation of migration along glial fibers in vitro. Importantly, the defect observed in vitro can be rescued by acute application of exogenous BDNF. Interestingly, BDNF can also act as a chemoattractant for these neurons. Therefore, BDNF is both motogenic and attractant for granule cells. The emerging picture from these studies is that at early stages, SDF-1 produced by the pia keeps granule cell precursors in the proliferative layer, where they are exposed to mitogens, such as sonic hedgehog. At later stages, through the actions of ephrins, the effects of SDF-1 are abolished, leaving the neurons capable of responding to the chemokinetic and chemoattractant effects of BDNF, leading to their migration towards the internal granule cell layer.

#### 4.4. Tangential migration in the rostral migratory stream: Slit, MIA and ephrins

The RMS is the pathway of migration of inhibitory interneurons from the SVZa to the olfactory bulb (Luskin, 1993). These interneurons are generated throughout life and this migration can be observed even in adult animals (Doetsch and Alvarez-Buylla, 1996). This pathway has become a useful model system to study the molecular mechanisms of migration because of its clear anatomical demarcation and the availability of in vitro assay systems that recapitulate this migration and allow for its experimental manipulation. Several molecules that contribute to this migration have been identified recently and their function characterized, including PSA-NCAM (see earlier).

Since astrocytic cells are in close contact with the neurons migrating in the RMS, some groups have explored the possibility that astrocytes regulate this migration. In vivo (Law et al., 1999) and in vitro (Wichterle et al., 1997) studies showed that GFAP-positive astrocytes are not present in the RMS during the early stages of migration. This led to the proposal that astrocytes do not participate in this migration. However, it is possible that immature astrocytes or astrocyte precursors are present and contribute to the migration

in significant ways. Interestingly, [Mason et al. \(2001\)](#) found that astrocytes have dramatic effects on migration of SVZA cells, inducing and enhancing their movement and that this is mediated through a soluble peptide factor called MIA. MIA does not appear to influence the navigation of RMS cells, i.e. it is not an attractant or a repellent.

Slit, a protein identified in *Drosophila* as a repellent for growing axons, has been proposed to also act as a repulsive signal for SVZA cells. In vitro assays using SVZA explants showed that a point source of Slit results in most cells migrating away from the source of this molecule ([Hu, 1999](#); [Wu et al., 1999](#); [Zhu et al., 1999](#)). Application of Slit expressing cells on top of the RMS in brain slices results in complete abolition of migration to the olfactory bulb ([Wu et al., 1999](#)). Since Slit is expressed in the septum, it was proposed that Slit might be instrumental in inducing SVZA cells to move toward the bulb. However, [Mason et al. \(2001\)](#) found that Slit is a very potent inhibitor of SVZA migration and that this inhibition is dose dependent. Rather than supporting the notion that Slit is primarily a repulsive signal, this study suggested that the asymmetric migration generated by a point source of Slit is the result of a gradient of inhibition, with stronger inhibition closer to the Slit source. This study also showed that addition of MIA could convert the inhibitory effects of Slit into true repulsive actions. These results suggest that guidance of migratory cells may be the result of the combined presentation of several regulatory signals in specific spatial configurations ([Mason et al., 2001](#)).

Eph receptor tyrosine kinases and their ligands, the ephrins, have been implicated in axonal pathfinding ([Feldheim et al., 1998](#); [O'Leary and Wilkinson, 1999](#)), synapse formation ([Dalva et al., 2000](#); [Takasu et al., 2002](#)) and neuronal migration in the cerebellum (see earlier). Experiments by Alvarez-Buylla and co-workers suggest that these molecules are also involved in migration in the RMS. It was found that EphB1–3 and EphA4 receptors and ephrins B2/3 ligands are expressed throughout the RMS in mice, the ligands being associated with astrocytes. It was further shown that blockade of Eph signaling results in altered migration ([Conover et al., 2000](#)). Thus, the function of these molecules appears to be important for this type of migration.

#### 4.5. *Tangential migration from the ganglionic eminence: semaphorin, EGF receptor ligands and hepatocyte growth factor/scatter factor (HGF/SF)*

The ganglionic eminences are the sources of a large number of inhibitory neurons that migrate long distances to reach their destinations. It has been proposed that the LGE gives rise not only to olfactory interneurons but also to some cortical interneurons ([Anderson et al., 1997](#)), while the MGE gives rise to the majority of striatal and cortical interneurons ([Anderson et al., 2001](#)). The migration of these neurons is primarily tangential and occurs through specific pathways, the rostral and lateral–cortical migratory streams, respectively.

Like in the RMS, Slit appears to act as repellent for some of these cells. Using an explant assay system, [Zhu et al. \(1999\)](#) showed that neurons from the subventricular zone of the LGE are repelled by explants of the ventricular zone of the LGE, a tissue that expresses Slit. Since similar repulsion of migration from explants was observed with cells secreting Slit and the migration of LGE cells to the cortex in tissue slices was blocked by application of Slit-expressing cells in their pathway, the authors proposed that Slit might provide guidance to neurons migrating from the LGE to the cortex.

Semaphorins constitute a family of secreted and membrane bound molecules shown to be involved in axonal pathfinding, acting through cell membrane receptors called neuropilins and plexins ([Tamagnone and Comoglio, 2000](#)). As with other axonal guidance molecules, semaphorins appear to contribute to the guidance of migrating neurons, as has been shown recently regarding neuronal migration from the MGE. Neurons born in the MGE give rise to two populations of neurons that migrate to distinct areas in the cortex and the striatum. Cells that migrate away from the MGE at early stages avoid the striatum to reach the cortex. [Marin and Rubenstein \(2001\)](#) examined the roles of semaphorins and neuropilins in the navigation of these neurons using knock out mice and slice cultures. These studies showed that the semaphorins are expressed in the developing striatum and the neuropilins by the MGE cells, and that these molecules mediate the avoidance of the striatum by early migrating cells, allowing them to reach the cortex.

While the previous studies highlight the roles of negative signals in migration from the ganglionic eminences, positive signals also appear to play important roles in this migration. One such signal is HGF/SF, a protein shown to induce migration of non-neuronal cells and which acts as a chemoattractant for spinal motor axons. Recently, [Powell et al. \(2001\)](#) found that HGF/SF and its tyrosine kinase receptor, MET, are expressed in the telencephalic ventricular zone early in development. Using slice cultures, they showed that application of exogenous HGF/SF causes increased migration of ventricular zone cells, and that disruption of HGF/SF results in abnormal migration of interneurons. Moreover, they also showed that mice lacking the u-PAR, a protein necessary for cleavage and release of HGF/SF, have a reduced number of calbindin expressing interneurons in the cortex. Based on these results the authors suggested that HGF/SF might induce migration of interneurons through autocrine or paracrine mechanisms. Since interneurons were not totally absent from the cortex of u-PAR<sup>-/-</sup> mice, it is likely that other factors also contribute to the induction of migration from the ganglionic eminence.

#### 4.6. *Tangential migration in the hindbrain: netrin-1 and deleted in colo-rectal cancer (DCC)*

During hindbrain development large numbers of cells born in the rhombic lip use non-radial migration to reach their destinations, including the pre-cerebellar nuclei and the

external granule cell layer of the cerebellum. Recent studies show that netrin-1, an axonal guidance cue, is essential for some of these migrations. Mice lacking either the genes for netrin-1 or its receptor, DCC, lack pontine nuclei (Fazeli et al., 1997; Serafini et al., 1996). Yee et al. (1999) found that netrin-1 is expressed by the floor plate of the hindbrain, and DCC is expressed by neurons in the dorsal neuroepithelium. Using *in vitro* assays they showed that netrin-1, acting as an attractant, influenced the orientation of the leading processes of cells migrating from the dorsal rhombencephalic neuroepithelium. Analysis of the knock out mice showed that in the absence of netrin-1 or its receptor, the processes of these cells fail to reach the ventral midline *in vivo*. They concluded that a gradient of netrin-1 is sufficient to orient these migrating cells. The roles of netrin in the migration of hindbrain cells was further explored by Alcantara et al. (2000). Using similar *in vitro* assays they found that while netrin-1 is an attractant for embryonic inferior rhombic lip cells, it functions as a chemorepulsive signal for migrating granule cells and their processes. Thus, the migration of different rhombic lip derived cells is affected differently by netrin-1.

## 5. Neurotransmitters and ion channels

Migrating neurons are known to express neurotransmitter receptors and ion channels, and the role of these molecules in migration has been explored by some investigators. Komuro and Rakic (1996) studied the roles of calcium channels and glutamate receptors in the migration of cerebellar granule cells using laser-scanning confocal microscopy. These elegant experiments showed that intracellular calcium levels oscillate during granule cell migration, and that the rate of cell movement depends on these fluctuations, with the frequency and amplitude of intracellular  $\text{Ca}^{2+}$  fluctuations positively correlating with rate of movement. Consistent with this, while migration could be increased by increasing extracellular  $\text{Ca}^{2+}$  concentration, movement could not be enhanced by simply increasing the average intracellular  $\text{Ca}^{2+}$  concentration. They also found that blockade of N-type  $\text{Ca}^{2+}$  channels or reduction of extracellular  $\text{Ca}^{2+}$  concentration blocked or reduced granule cell migration (Komuro and Rakic, 1992), suggesting that this type of channel is critical for migration. Interestingly, changes in NMDA receptor activity also had an impact on migration, with blockade of receptors leading to inhibition of migration and NMDA receptor activation resulting in increased motility (Komuro and Rakic, 1993). These results led to the hypothesis that activation of NMDA receptors by glutamate may contribute to the regulation of granule cell migration, and that this may be mediated by the high  $\text{Ca}^{2+}$  permeability of this receptor. However, the ways in which the N-type channels and the NMDA receptors interact during migration are not yet understood.

Another neurotransmitter that appears to regulate aspects of neuronal migration is GABA. Studies on the migration of LHRH neurons from their site of origin in the olfactory pit to

the brain show that activation of GABA<sub>A</sub> receptors by muscimol inhibits and blockade of GABA<sub>A</sub> receptors by antagonists enhances migration of these neurons *in vitro* (Fueshko et al., 1998). Studies on the effects of GABA receptors in cortical migration suggest that GABA may exert complex effects on migratory neurons and that these effects may depend on the receptor subtype involved. Using rat cortical slices Behar et al. (2000) found that blockade of GABA<sub>A</sub> receptors enhances migration to the cortical plate, blockade of GABA<sub>A/C</sub> receptors completely blocks migration, but blockade of GABA<sub>B</sub> results in incomplete migration, with cells reaching only the intermediate zone. These results are in agreement with those obtained using Boyden chambers, which showed that GABA, acting through GABA<sub>B</sub> and GABA<sub>C</sub> receptors, acts as a chemoattractant for cortical neuronal precursors, but as an inhibitor of migration when acting through GABA<sub>A</sub> receptors (Behar et al., 1996).

## 6. Conclusions

Progress in understanding the molecular mechanisms of neuronal migration in the last few years has been extensive. In this review, we have summarized only one aspect of migration control, that by extracellular signals. In similar fashion, extensive progress has been made toward understanding the intracellular signaling cascades and cytoskeletal mechanisms of migration (Song and Poo, 2001). How these different levels of signaling are integrated in order to allow neuronal migration to occur properly is an area of current intense research. One of the most important lessons from the studies described above is that migrating neurons need to integrate complex “environmental” signals in order to accomplish their journey from their birthplaces to their final destinations. It has become clear that many of these signals are also used to regulate the migration of other cell types, as well as for pathfinding by growing axons. However, specific molecular controls for neuronal migration appear to exist and it will be important to define those clearly. It is likely that discoveries of new factors involved in neuronal migration will continue in the next few years that will further unveil the mechanisms of how a vertebrate nervous system is constructed. Abnormal neuronal migration leads to numerous malformations including schizencephaly, lissencephaly, polymicrogyria and heterotopias. These malformations in turn lead to clinical disorders, such as varying degrees of epilepsy, cerebral palsy, mental retardation and psychiatric disturbances (Aicardi, 1998). Therefore, understanding the molecular mechanisms of neuronal migration will provide important insight into the pathogenesis of brain malformations.

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