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Structural and Chemical Influences on Neuronal Migration in the Adult Rostral Migratory Stream

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Abstract

Neurogenesis, the birth of new neurons, occurs throughout life in the sub ventricular zone (SVZ) lining the lateral ventricles. New neurons in the adult SVZ can undergo tangential migration through the rostral migratory stream (RMS) to the olfactory bulb (OB). This migration is facilitated by other neurons via homophilic migration whereby chains of neurons support saltatory migration through the RMS. Additionally, astrocyte end feet surround the RMS preventing significant extravasation and influencing migration. Finally, blood vessels are oriented parallel within the RMS where they profoundly affect neuronal migration by secreting protective molecular factors, and serving as a physical scaffold for migrating neuroblasts thereby providing a path-of-least-resistance for neuronal migration. Among the many factors influencing neuronal migration are GABA, VEGF, BDNF, PSA-NCAM and L1 CAMs, β1 integrins, netrins, slits, ephrins, semaphorins, matrix metalloproteinases and extracellular matrix components. Understanding influences on adult neurogenesis and neuronal migration is important because these self-repair mechanisms are induced following many CNS injuries. Although this endogenous regeneration is insufficient for meaningful repair in most cases, therapies could potentially enhance these processes to improve clinical outcome.

Neurogenesis

Neurogenesis, the birth of new neurons, occurs throughout adult life in the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ) lining the lateral ventricles [1-5]. Neurogenesis is quite robust in these regions and originates from glial fibrillary acidic protein (GFAP)-expressing stem cells which form transit amplifying cells capable of generating neuroblasts [6,7]. Endothelial cells are critical components for neurogenesis as they secrete soluble factors that enhance CNS neural stem cell proliferation and maintain their self-renewal and neurogenic potential [8]. Indeed, there is much crosstalk between endothelial cells and neurons as the processes of angiogenesis and neurogenesis are strongly linked in both the SGZ and SVZ germinal zones of the adult brain. In these regions, blood vessels are closely associated with neural progenitors forming a so called neurovascular niche [9-11]. Additionally, nearby astrocytes may influence the proliferation and differentiation of neuronal precursors, although these mechanisms are not fully understood [12].

Among many factors under study, vascular endothelial growth factor (VEGF), which was identified based on its vascular effects (primarily hyperpermeability and the promotion of angiogenesis) and later recognized as an important signaling molecule, appears to be an important driver of angiogenesis-neurogenesis coupling [13,14]. Additionally, several other growth and neurotrophic factors have been implicated in neural precursor proliferation and neurogenesis within the adult rodent SGZ and SVZ such as basic fibroblast growth factor (bFGF), insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), and epidermal growth factor (EGF) [15-19]. For example, in response to angiogenesis, endothelial cells of the vasculature secrete BDNF that in turn increases neurogenesis and VEGF secretion, which in turn enhances both processes [20]. Interestingly, recent evidence suggests that cannabinoids (exogenous and endocannabinoids) promote neurogenesis in as much as agonists stimulate and antagonists inhibit SGZ and SVZ neuronal cell proliferation via cannabinoid receptors CB1 [21-23] and CB2 [24,25].

During development, newly born neurons migrate upon a scaffold of radial glia processes to reach the cortical mantle in an inside-out fashion such that later migrating neurons migrate further than earlier migrating neurons to ultimately form a six-layered cortex [26,27]. In this "gliophilic migration", glial cells support and promote the migration of new neurons to their destination. However, the radial glia present in development disappear in the early postnatal period and are absent in adulthood. In the adult, new neurons born in the SGZ are largely destined to remain in the hippocampus whereas new neurons born in the SVZ enter into the rostral migratory stream (RMS) where they undergo tangential migration toward the olfactory bulb. Once the new neurons reach the olfactory bulb, they undergo radial migration into the granule cell layer or the glomerular layer where they are destined to become granule or periglomerular cells, respectively [28,29].

Neuronal Migration in the Rostral Migratory Stream (RMS)

The RMS is a long, relatively restricted pathway through which immature SVZ neurons tangentially migrate in the caudal-to-rostral direction to the olfactory bulb [2,30]. Figure 1 displays a cartoon depiction of the RMS showing many structural, molecular, and other characteristics of neuronal migration discussed in this review. The RMS is extremely cell dense, consisting of over 1.7 million cells/mm^3 and 1.2 million neuroblasts/mm^3, with four times as many neural cells

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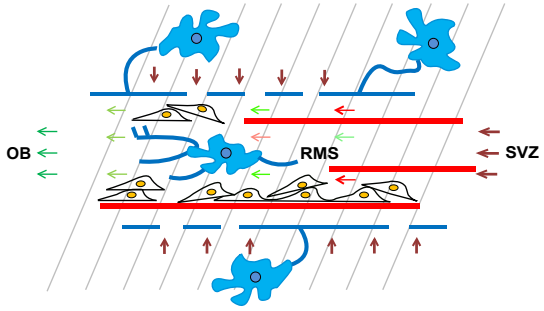

Figure 1: Neuronal Migration in the Rostral Migratory Stream. Neuroblasts (black cells with nuclei shown in yellow) born in the adult subventricular zone (SVZ) migrate in chains through the rostral migratory stream (RMS) to the olfactory bulbs (OB). The RMS contains blood vessels (red bars) oriented parallel with the path of migration which neuroblasts can use as a scaffold to enhance migration. Also, astrocytes (blue) have been found within the RMS where they exhibit a polar morphology with processes oriented parallel to the path of migration. The RMS is also surrounded by astrocyte endfeet (blue bars) which create a mostly enclosed tube around neuroblasts as they migrate through extracellular matrix (diagonal light grey bars). Additionally, cell-bound and soluble factors influence migration efficacy including chemorepulsive cues that repel neuroblasts from the SVZ and from areas surrounding the RMS (red arrows) and chemoattractive cues that promote migration towards the OB (green arrows), many of which exist in gradients across the RMS (color intensity changes).

as astrocytic cells [29,31]. These proliferating and migrating immature neurons emerge from the SVZ and can be identified within the RMS by characteristic immature neuronal markers such as the polysialylated form of neural cell adhesion molecule (PSA-NCAM) and doublecortin (DCX) [3,32,33]. Importantly, this migration process is not merely natural drift of neuroblasts, but involves many complex mechanisms that tightly regulate neuroblast migration direction and efficacy. While neurons can be found moving "backward" toward the SVZ or orthogonally from the axis of the RMS, these are a minority of the population due to regulatory mechanisms [34].

Within the RMS, migrating neuroblasts can form long chain-like structures and act as a self-formed substrate which is sufficient for and enhances their own migration efficacy via cell-cell interactions in a process known as "homophilic migration" or "chain migration" [30,35,36]. Around mouse postnatal day 15 neuroblasts begin to organize into these chains and GFAP-positive astrocytes surround the pathway of tangential migration, thereby beginning to form the RMS that will last throughout adulthood [37]. Mechanistically, evidence suggests that integrin adhesive interactions, especially the β1 integrin-laminin system and matrix metalloproteinases, may be important mediators of neuroblast chain migration in the RMS [11,38,39]. Interestingly, in homophilic migration, some neurons appear to act as "bridge cells" that cease their own migration within the RMS to foster the movement of other neurons and also produce new cells within the RMS itself. Additionally, bridge cells appear to suddenly translocate upon cell-cell contact with the leading edge of a migrating cell and then return to its station when the migrating cell has passed [34]. Once the chain of migrating neuroblasts arrives at the OB, the chain dissociates in response to various factors including extracellular matrix members reelin (via an ERK-dependent pathway) and tenascin-R [40-42].

Human Neurogenesis and Neuroblast Migration

Evidence of neurogenesis and an active RMS in adult uninjured humans emerged years following the rodent and its existence still remains controversial. Indeed, an astrocyte "ribbon" lining the lateral ventricles in the human brain was found to contain neural stem cells capable of neurogenesis throughout adult life [43]. Although confirming the astrocyte ribbon in the SVZ, it has been proposed that a continuous extension of the ventricle exists forming a ventriculo-olfactory neurogenic system (VONS) consisting of the SVZ, RMS, olfactory tract, and OB [44]. Conversely, other groups have not seen evidence of such a ventricle extension and report that although chains of migrating neurons are found extensively in the early postnatal period, these diminish substantially after 18 months and are nearly absent in adult humans [45]. Despite the lack of chain migration, however, neuroblast migration has been found in the anterior ventral SVZ and RMS throughout adult life as evidenced by expression of DCX, PSA-NCAM, and βIII-Tubulin migrating neuroblast markers. Additionally complicating the scenario, none of these migrating neuroblasts are found in the olfactory bulb [46]. Interestingly, however, an additional pathway has been found in 4-6 month humans where neuroblasts branch off from the proximal limb of the RMS, travel through a medial migratory stream (MMS) and target the ventromedial prefrontal cortex [45]. One hypothesis for these findings is that adult SVZ human neurogenesis and migration may exist at relatively low baseline levels, as demand for new neurons may be relatively low, but remain active so that following injury they can be rapidly induced for an endogenous attempt at self-repair/regeneration. Thus, while evidence suggests that neurogenesis and neuronal migration occur in adult uninjured humans, translation from rodent models is not simple and more research is needed to determine species differences.

Structural Factors Influencing Migration in the RMS

Another source of regulation of RMS neuronal migration comes from astrocytes that appear to play a strong structural role in influencing migration. Indeed, an arrangement of GFAP-positive astrocytes surrounds chains of migrating neuroblasts creating glial "tubes" [3,30,31,35,37,47,48]. Although these astrocyte tubes were originally hypothesized to create a physical barrier encasing the RMS in a sheath and preventing neuroblast extravasation entirely, recent evidence suggests the role of astrocytes in the RMS may not be so simple. While astrocytic processes have been found throughout the length of the RMS, they are not completely continuous suggesting that astrocytes may act as a physical guide for the RMS rather than a completely restricting "sheath" or "tube". Interestingly, however, astrocytes have recently been found inside the migration path of the RMS where they extend processes that interdigitate with the migrating neuroblasts. Furthermore, astrocytes within the RMS do not display the typical stellate morphology of an astrocyte but orient narrow processes parallel to the RMS and migrating chains, without radial processes, exhibiting a polar morphology [29]. These specialized arrangements of astrocytes and their processes may actively be influenced by migrating neuroblasts. Indeed, this neuroblast to astrocyte structural influence appears to be mediated by diffusible Slit proteins and their Robo receptors (Slit influence on neuroblasts will be discussed later). In Slit1 knockout mice astrocytic processes were not organized parallel to the path of migration, but were highly irregular with processes frequently oriented orthogonal and directly in the path of migrating neuroblasts. Furthermore, membranes of astrocyte cell bodies were found to form invaginations to accommodate contact with chains of neuroblasts, but to a significantly lesser extent in astrocytes expressing a dominant negative form of Robo [49]. In short, astrocytes of the RMS exhibit specialized structures and localization which are dynamically influenced by migrating neuroblasts. These findings lead to questioning whether neuroblasts redirected to a separate area, such as a site of cortical ischemic injury, would begin to create a new glial

tube to facilitate directed migration, and whether activated astrocytes following such an injury would still be capable of accommodating such formations.

In addition to astrocytes, the vasculature also plays a profound structural role in influencing migration in the RMS. Blood vessels are clearly organized and oriented parallel to the axis of migration (caudal-rostral) within the RMS. Furthermore, there is a significantly higher density of blood vessels within the RMS compared to surrounding areas [29]. Interestingly, nearly all migrating cells within the RMS are aligned along these blood vessels [50]. This association between the vasculature and migrating neuroblasts can be identified by both immunostaining as well as electron micrographs in which direct endothelial cell-neuroblast contact is observed [29]. In fact, neuroblasts can use blood vessels as a physical scaffold providing a path-of-least-resistance that greatly increases migration efficacy in a process termed "vasophilic migration" [51]. Blood vessel scaffolding of neuroblast migration in the RMS can be clearly seen in the staining of Snapyan et al. [50] in 2009 and in the OB in the *in vivo* time-lapse imaging studies of Bovetti et al. [51] in 2007. While along blood vessel tracks, neuroblasts migrate in a saltatory manner alternating fast leading edge progression and cell translocation with slow resting speeds of migration [50,51]. Interestingly, blood vessels extend the entire length of the RMS so neuroblasts can get on blood vessel "tracks" within the SVZ and migrate along them until reaching the olfactory bulb. This vascular scaffolding result in nearly 80% of vessel length in the RMS directly associated with neuroblasts [29]. In addition to serving as a physical substrate and guide, it has been hypothesized that RMS vasculature may be involved in cell survival of the migrating neuroblasts as well [37,48].

Lastly, in addition to astrocytes and the vasculature, chains of migrating neuroblasts in the RMS may be influenced by the structure of the extracellular matrix (ECM). Indeed, extracellular matrix molecules play structural as well as signaling roles affecting migration in the RMS, for example via integrin interactions with cells or degradation by matrix metalloproteinases (MMPs). Taken together, the structural makeup within and around the RMS, displayed well by Whitman et al. [28,29] demonstrates that the RMS has a complex yet organized architecture that tightly regulates neuroblast migration.

Molecular Factors Influencing Migration through the RMS

A broad array of membrane-bound and secreted molecules from each of the structural components of the RMS has been implicated in the regulation of neuroblast migration. While individual studies may examine the role of one or a few of these influences, it is important to consider that within the *in vivo* microenvironment of the RMS many of these influences are likely acting concurrently on neuroblast migration. For example, these influences may act cooperatively, possess additive or synergistic effects, exert opposing effects, interact directly, or have other actions of indirect significance to migration. Therefore, it is the structural and chemical factors that regulate direction and efficacy of migration. Another consideration is that neuroblasts may be differentiating as they migrate toward the olfactory bulb suggesting cross-talk between migration and differentiation pathways with important implications [52]. With these considerations in mind, the following influences have been implicated in some aspects of neuroblast migration through the RMS, and are summarized in Table 1.

Chemoattractive	Chemorepellent	Inhibitory	Chain Formation and Organization	Chain Dissociation at OB
• **BDNF**: Chemoattractive and promigratory via TrkBR [55,56], Promigratory via p75NTRs [50] • **PSA-NCAM**: Disrupted migration in KO animals resulting in decreased OB size [57-59,64] • **β1 Integrins**: Chemoattractive toward laminin via α6β1 [67], Decreased migration with anti-β1 integrin antibodies [38] • **Netrins**: via DCC and neogenin receptors [38] • **Semaphorins**: 3C and 3F attract axon growth via Neuropilin receptors in cortical and olfactory bulb tissues, respectively (reviewed in [80]) • **MMPs**: MMP2 and MMP9 enhance migration via PI3K/Akt and ERK1/2 [82], ADAM21 is present throughout the RMS and may be promigratory and chemoattractive [48] • **VEGF**: Promigratory and chemoattractive with IQGAP1 as an effector molecule [83], Promigratory and chemoattractant via VEGFR2 and dependent on FGF2 [84,85] • **GDNF**: Chemoattractive in the RMS via Cdk5 and dependent upon NCAM [86] • **HGF**: Chemoattractant and Promigratory via the Met receptor and the Ras/MAPK pathway [87] • **ErbB4**: Loss from neurons results in disrupted migration [88] • **Prokineticin 2**: Chemoattractant via its G-protein coupled PKRs [90] • **Cannabinoids**: via CB1 and CB2 receptors [91]	• **Netrins**: Repel from SVZ via DCCR [68], Repel axon growth via Unc 5-DCC complex receptor [69] • **Slits**: Chemorepellent from SVZ via RoboR [70,71], dependent on astrocyte cues [72], Expressed in Septum, Choroid Plexus, and neuroblasts which lose chemorepellent activity in Slit KO animals [74] • **Ephrins**: Contact mediated EphB/EphrinB, [77] • **Semaphorins**: 3A, 3B, 3C, 3F repel axon growth via Neuropilin receptors in most neural tissuees (reviewed in [80], 3F repels migrating neuroblasts via Neuropilin 2 to confine them along normal migration paths [80]	• **GABA**: Inhibits migration efficacy via $GABA_AR$ [53] • **Slits**: [72,73]	• **PSA-NCAM**: Disrupted chain formation without PSA [60,61] • **β1 Integrins**: Disrupted chain formation in α6β1 KO animals [66] • **Ephrins**: Inhibition disrupts chain formation [77] • **ErbB4**: Loss from neurons results in disrupted chain organization [88] • **ROCK**: Inhibition with Y27632 inhibits chain formation [89]	• **Reelin**: [40,42] • **Tenascin-R**: [41] • **Prokineticin 2**: Chain dissociation cue at the OB via its G-protein coupled PKRs [90]

Table 1: Summary of Molecular Factors Influencing Migration through the RMS.

GABA and BDNF

Interestingly, migrating neuroblasts have been found to secrete the neurotransmitter GABA (gamma-aminobutyric acid) that induces signaling pathways which ultimately inhibit the neuroblasts' own migration. Indeed, application of the $GABA_AR$ antagonist bicuculline actually enhances neuroblast migration rates implying an inhibitory role of endogenous GABA, whereas application of GABA decreases neuroblast migration in a $GABA_AR$-dependent manner [53]. This influence of GABA is tightly regulated by neighboring astrocytes which express the GABA transporters (GATs) as well as functional $GABA_ARs$ thereby altering the amount of GABA accessible to migrating neuroblasts. Interestingly, GFAP positive stem cells in the SVZ respond to tonic GABA currents by decreasing their proliferation, suggesting a negative feedback mechanism regulating neurogenesis within the SVZ [54]. Furthermore, neuroblast-derived GABA also triggers the Ca^{2+}-dependent insertion of high affinity BDNF receptors (TrkB receptors, TrkBR) onto astrocyte membranes. Endothelial cell secreted BDNF is promigratory and acts as a chemo attractant influencing the motility and direction of neuroblast migration via TrkBRs as well as p75NTR on PI3K/MAPK signaling in neuroblasts [50,55,56]. However, it has been hypothesized that GABA-induced astrocyte TrkBR bind and trap BDNF from migrating neuroblasts causing them to enter into a stationary period [50]. Thus, GABA would facilitate its own anti-migratory function by upregulating TrkB receptors to inhibit BDNF's pro-migratory function. This is just one example, conceptually schematized in Figure 2, of how different molecules and different cell pathways may interact with one another to influence neuroblast migration in the RMS.

PSA-NCAM and L1 CAMs

Another molecule which appears to play a profound role in neuronal migration through the RMS is the polysialylated form of neural cell adhesion molecule (PSA-NCAM) expressed on neuroblasts. N-CAMs belong to the immunoglobulin superfamily, possess Ig-like and fibronectin type II repeats, and mediate both homo- and heterophilic cell-cell interactions. Genetic knockout of N-CAM causes an accumulation of OB precursor cells in the inner SVZ as well as a dramatic decrease in olfactory bulb weight [57,58]. Interestingly, specific enzymatic removal of the PSA moiety from N-CAM with endoneuraminidase (EndoN) completely recapitulates the phenotype of the N-CAM knockouts and inhibits the formation of neural growth cones specifically for tangential migration and not migration within the OB suggesting that PSA is a critical component for neuronal migration in the RMS [59]. Additionally, PSA is important in maintaining the proper strength of neuroblast-neuroblast interactions, and when lost disrupts chain formation [60,61]. The role of PSA in maintaining the chain arrangement may be somewhat double-edged in that adhesive interactions are beneficial to keep chains together, but need to be loose enough that individual cells can translocate. Interestingly, knockout mice also display a reduction of the astrocytic tube and many astrocytes are observed within the RMS engaging in cell-cell interactions with neuroblasts [62]. Finally, PSA has been found to encourage the migration of neural progenitors out of neurogenic zones, and PSA removal (by EndoN) promotes neuroblast dispersion out of the RMS into the striatum and cortex with some cells differentiating [63,64], which would presumably inhibit migration. Thus, PSA is involved in the regulation of both migration and differentiation of neuroblasts, which as mentioned above, may be overlapping processes.

Additionally, L1-CAMs and NCAM have been found to interact

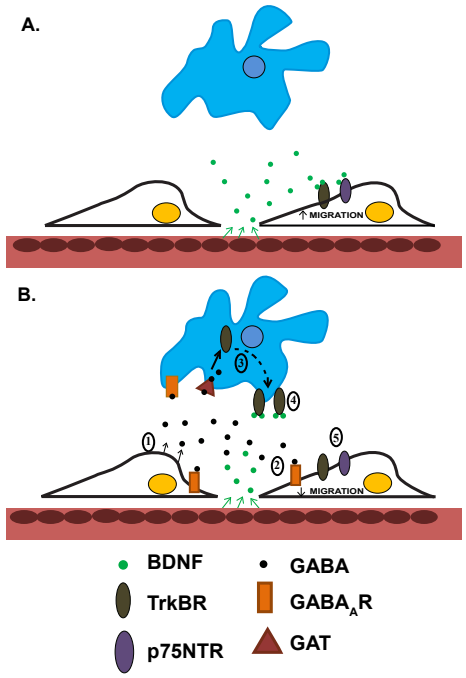

Figure 2: BDNF and GABA Effects and Interactions on Neuroblasts in the RMS. (A) BDNF is promigratory and chemoattractive via TrkB and p75NTR receptors expressed on migrating neuroblasts. **(B)** (1) Secreted GABA (2) inhibits neuronal migration efficacy (3) in addition to being taken up by astrocytes via GATs resulting in the insertion of TrkBRs on astrocytic membranes that (4) Bind and trap BDNF from interacting with TrkBRs and p75NTRs on neuroblasts, thereby decreasing migration by 2 mechanisms – increased GABA and decreased BDNF. For full explanation and references, see the text (Molecular Factors Influencing Migration through the RMS: *GABA and BDNF*).

functionally with integrins, specifically β1 integrins, as co-receptors and to converge on pathways leading to MEK, ERK, and CREB to influence migration at both adhesive and transcriptional levels. Indeed, for optimal cell migration, a specific level of adhesive interactions with the ECM, neither too strong nor too weak, is needed [65].

β1 Integrins and Netrins

β1 integrins have been found to play roles in both neuroblast proliferation and migration. Specifically, blockade of the α6β1 integrin was able to inhibit homophilic neuroblast chain migration in a neurosphere expansion assay [66]. Also, disruption of either α6β1 integrin or its ligand laminin disrupted migration whereas infusion of a piece of laminin redirected migration toward the infusion site, suggesting a homing property [67]. Furthermore, the proliferation of neuroblasts grown as neurospheres was inhibited by blocking the α5β1 and αvβ1integrins [66]. Mechanistically, β1 integrin interactions with chain-localized laminin in the RMS have been found to promote the formation of neuroblast chains. Additionally, β1 integrins appear critical for the maintenance of the glial "tube" surrounding the RMS and β1 integrin knockout leads to the extravasation of migrating neuroblasts out of the RMS [39].

It has been proposed by Murase and Horwitz that within the RMS integrins and laminins give "traction" to enhance the migration of neuroblasts while they are attracted toward netrins produced in the olfactory bulbs. This attraction is mediated by neuroblast netrin receptors Deleted in Colorectal Carcinoma (DCC) and neogenin, whereas slit proteins expressed outside the RMS exert repulsive

forces on the migrating neuroblasts helping to restrict them within the RMS [38]. Interestingly, netrin-1 expressed in the SVZ has also been shown to repel migrating neuroblasts, thereby pushing them through the RMS away from their origin [68]. An explanation for these seemingly paradoxical effects may be provided by the finding that attraction of netrin receptors toward netrin is converted to repulsion upon the expression of UNC5 protein, which associates with DCC to form a receptor complex [69]. Although this finding was made in axonal growth cone extension, it is possible that these properties could translate to neuroblast migration as well. It is also possible that migrating neuroblasts in the RMS exhibiting a polar morphology may selectively express netrin chemorepulsive receptors on their caudal trailing edge and netrin chemoattractive receptors on their rostral leading edge thereby providing both pushing (from the SVZ) and pulling (toward the OB) forces to facilitate migration.

Slit Signaling

In addition to the repulsive forces of netrins in the SVZ, slit proteins in the SVZ and areas surrounding the RMS have been found to repel migrating neurons through their Roundabout (Robo) receptors. Explant assays have shown that GABAergic neuronal migration is repelled from the SVZ by slit proteins. Slit's diffusible chemorepellent activity is concentration gradient-dependent and can be blocked by administration of the extracellular portion of Robo (RoboN), which binds slit without transducing intracellular signaling [70,71]. Interestingly, slit has also been found to inhibit migration rate from SVZ explants [72] and is capable of independently inhibiting and/or repelling migrating neuroblasts [73], which may have interactions with astrocyte cues [72]. In addition to the SVZ, slits are also expressed in the septum and choroid plexus. SVZ explants cultured with septum or choroid plexus explants from Slit1/Slit2 knockout mice show no chemorepellent activity from these regions, resulting in severely disrupted migration of SVZ cells. Interestingly, migrating Robo-expressing neuroblasts themselves appear to secrete slits, which has been hypothesized to act in paracrine and autocrine fashion as a means to coordinate and maintain neuroblast chains as well as to create a slit gradient throughout the RMS [74]. Thus, a caudal-to-rostral decrease in slit concentration would encourage neuroblast caudal-to-rostral migration down the gradient. Further complicating this scenario, slits have also been found to bind directly to netrin-1 with high affinity and have been hypothesized to be targets of reelin, providing another example of interactions between different types of migration cues [74,75]. Some of the effects and interactions of β1 integrins, netrins, and slits (this and previous section) are conceptually schematized in Figure 3.

Ephrins and Semaphorins

Ephrins are transmembrane ligands that associate with receptor tyrosine kinase Eph receptors [76]. EphB1-3 and EphA4 receptors as well as ephrins-B2/3 are expressed in the adult SVZ and RMS where they may play a role in both cell proliferation and migration of neuroblasts. It has been hypothesized that ephrinB ligands on astrocytes around the RMS may help restrict neuroblast migration to the RMS. Interestingly, similar to netrins, Eph/ephrin signaling has been hypothesized to be involved in both cell attraction and repulsion; however, the EphB/ephrinB interactions associated with repulsion are more firmly established. Following the *in vivo* disruption of eph/ephrin signaling by lateral ventricle infusion of the truncated ectodomain of either Eph-B2 or EphrinB-2, neuroblast chain migration from the SVZ was disorganized as evidenced by PSA-NCAM staining for neuroblasts,

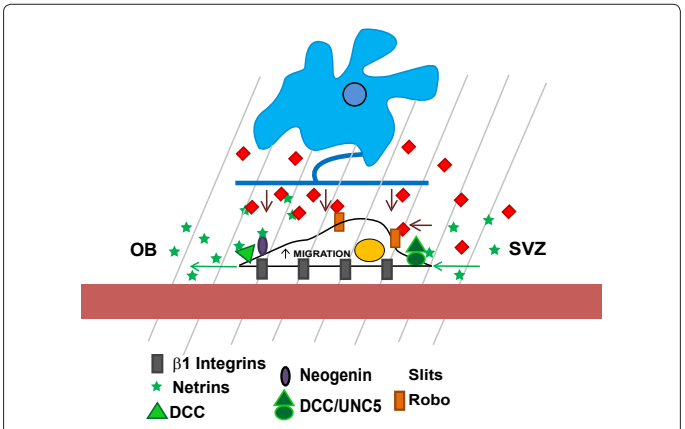

Figure 3: Summary of Some Effects and Interactions of β1 Integrins, Netrins, and Slits. β1 integrins on migrating neuroblasts associate with extracellular matrix molecules (diagonal light grey bars) to provide "traction" and to enhance migration. Netrins secreted by the OB are promigratory and chemoattractive via DCC and Neogenin receptors expressed on migrating neuroblasts. Netrins also have a chemorepulsive effect from the SVZ, which may be explained by the finding that a DCC/UNC5 receptor complex repels neurons from netrins. It is possible that netrins may selectively express netrin attractive receptors on their leading edge and repulsive receptors on their trailing edge providing pulling and pushing forces, respectively, enhancing migration. Slit repels neurons from the SVZ and from areas outside the RMS. Additionally, Slits have been found to bind directly to Netrins. For full explanation and references, see the text (Molecular Factors Influencing Migration through the RMS: *β1 Integrins and Netrins*, and *Slit Signaling*).

but increased proliferation was observed in the SVZ as evidenced by BrdU staining [77]. Additionally, EphB receptors have been found to interact with NMDA receptors and EphrinB stimulation increases the density of NMDAR clusters whereas blockage of EphB receptors reduces the number of postsynaptic specializations. Thus, in addition to proliferation and migration processes, Eph/ephrin signaling may play a role in the next steps of differentiating neuroblast maturation including synapse formation, maintenance, and/or neuronal function [78,79].

Semaphorins are a class of molecules with diverse functions ranging from development to immune system function. Class 3 semaphorins play roles in axon guidance as well as neuroblast migration and, along with their receptors, the neuropilins, are expressed throughout postnatal life in the RMS [52]. Semaphorins may be either membrane spanning or secreted proteins that remain tightly localized on or near their origin cell resulting in relatively local action. While associated with repulsion of axons in most neural tissues, semaphorin 3C and 3F have been found to attract cortical and olfactory bulb tissue axons, respectively [80]. Additionally, Semaphorin 3F has been found to repel migrating neuroblasts, via its neuropilin-2 receptor, to confine neuroblasts along normal migration paths [81]. However, as seen with other molecules, the role of semaphorins in influencing RMS neuroblast migration is more complex than simple repulsion and includes signaling pathways and interactions with other molecules. For example, semaphorins released by endothelial cells have been found to regulate the activity of matrix metalloproteinases (MMPs), also secreted from endothelial cells. Furthermore, endothelial cells also express neuropilin-1 receptors, which in addition to binding semaphorins can be bound by the angiogenic and hyperpermeabilizing vascular endothelial growth factor (VEGF) and potentially transduce some of VEGF's promigratory effects. Therefore, in addition to repulsion, semaphorins may play a profound role in remodeling the vascular and ECM architecture in and around the RMS, thereby indirectly influencing neuroblast migration [52].

Matrix Metalloproteinases (MMPs) and Vascular Endothelial Growth Factor (VEGF)

A Disintegrin and Metalloproteinase (ADAM) proteins can cleave and activate ECM proteins and also bind integrins, which are important for RMS neuroblast migration. Specifically, ADAM21 is expressed in the SVZ where it may regulate proliferation and throughout the inside of the RMS where it localizes to long thin processes from subependymal cells of the SVZ and terminates at the OB. ADAM21 has been found to closely associate with neuroblast α6β1 integrin (discussed above), suggesting binding that would presumably enhance migration. Interestingly, Tissue Inhibitors of Metalloproteases (TIMPs) were found immediately outside the SVZ and prior the OB, suggesting that ADAM21 and other MMPs are spatially regulated to act specifically within the RMS to facilitate migration [48]. Therefore, exogenously administering MMP inhibitors inhibits migration. Other MMPs implicated in neuroblast migration include MMP2 and MMP9, for example, which are secreted by activated endothelial cells and have been found to enhance neuroblast migration in a neurosphere expansion assay via the PI3K/Akt and ERK1/2 signaling pathways and are blockable by MMP or pathway inhibitors [82].

Astrocytes of both the SVZ and RMS have been shown to express VEGF, which stimulates, perhaps via the IQGAP1 scaffolding protein, neural progenitor migration and differentiation, further implicating the coupling of these processes [83]. Importantly, VEGFR2 has been found to be expressed in migrating neuroblasts, through which response to VEGF is transduced. Mechanisms by which VEGF promotes migration include acting as a chemoattractant and guidance cue. Interestingly, evidence suggests that both the expression of VEGFRs and the chemoattraction property of VEGF on neuroblasts is fibroblast growth factor 2-dependent [84,85]. Additionally, VEGF also plays a key role in neuroblast migration following injury such as ischemic stroke.

Other Influences on RMS Migration

In addition to the molecules and factors above described in detail, a variety of other influences have been implicated in neuroblast migration through the RMS. For example, the growth factors glial cell line-derived neurotrophic factor (GDNF) [86] and hepatocyte growth factor (HGF) [87] appear to influence migration whereas insulin-like growth factor 1 (IGF-1) seems to stimulate neuroblast exit from the SVZ (and also later positioning in the OB) [19]. Additionally, signaling via the receptor tyrosine kinase ErbB4 expressed on migrating neuroblasts and ErbB4 ligands the neuregulins (present in the SVZ and RMS) have been associated with organization of chains and differentiation of OB precursors [88]. The Rho kinase pathway also appears to play a role in neuroblast migration as inhibition of Rho-dependent kinase (ROCK) with Y27632 has been found to promote neuroblast elongation, process extension, and migration, but to inhibit formation of chains from neurospheres or SVZ explants [89]. Furthermore, prokineticin 2 acts as a secreted OB chemoattractant and may serve as a detachment signal once migrating chains arrive at the OB by acting on its G-protein coupled receptor. Prokineticin 2-deficient mice display abnormal architecture and reduced size of the OB in addition to neuroblast accumulation in the RMS, thus demonstrating the importance of prokineticin 2 [90]. Interestingly, in addition to their pro-neurogenic effects (discussed in the *Neurogenesis* section above), endocannabinoids appear to promote neuroblast migration via both CB1 and CB2 receptor mediated pathways. Endocannabinoids were further shown not only to promote migration efficacy, but also to promote the morphology of neuroblasts into the more polarized form conducive to migration, specifically via extension of a single dominant leading process [91]. Similarly, disruption of MAP/microtubule affinity-regulating kinase 2/polarity kinase 1 (MARK2/Par-1) interferes with proper positioning of the leading process of neuroblasts, resulting in multipolarity with no preference for migration direction and less neurons in the OB, without affecting mean migration speed [92,93]. Lastly, cytokines and chemokines are known to be involved in neuroblast migration although their role is much more significant during or following pathological conditions or insults such as ischemic stroke.

While this list of influences on neuroblast migration is large, it is not all-inclusive and more influences will likely be identified in the future. For example, the olfactory bulb, specifically the glomerular layer, still possesses chemoattraction independently of netrins, semaphorins, ephrins, slits, and chemokines [94]. However, it is important to be cognizant of each of these factors implicated in neuroblast migration, because, as mentioned at the beginning of this section, many of these factors can influence the expression of one another, can influence one another by binding to each other, and may exert similar, opposite, or independent effects from one another. Thus, if one of these influences is altered or missing, one would have an idea of what other molecules to investigate and what consequences to predict for migration. Conversely, if one notes a particular abnormality in neuroblast migration they might have an idea what influences to investigate. Finally, adult neurogenesis and neuroblast migration processes and influences are important to understand because these processes are increased following CNS insults such as ischemic stroke. This activation may be an endogenous attempt at brain self-repair and could be a promising therapeutic target.

Summary

Adult neurogenesis occurs in the subventricular zone and the subgranular zone and is coupled with angiogenesis. Newborn neurons from the subventricular zone migrate into the rostral migratory stream where they associate in chains facilitating tangential migration to the olfactory bulb. Migrating chains have been found to use blood vessels as tracks to enhance migration and are relatively restricted from extravasation out of the RMS by astrocytic end feet. In addition to these structural influences, neuroblasts are subject to a variety of molecular influences that can be chemoattractive, chemorepulsive, promigratory, or inhibitory to migration and often exist in gradients within the RMS to regulate neuroblast migration. However, many questions remain unanswered in the field, especially regarding how well animal studies can translate to humans where there may be more influences on migration, more complex interactions between influences, and much greater migration distances. Understanding neurogenesis and neuroblast migration mechanisms is particularly important as these processes are enhanced following CNS injury such as ischemic stroke in an endogenous attempt at self-repair. Therefore, armed with the knowledge of neurogenesis and migration influences, it may be possible to capitalize on these processes for therapies.

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