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Review

The subventricular zone: new molecular and cellular developments

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Abstract. The subventricular zone (SVZ), which lines the lateral walls of the lateral ventricle, persists as a neurogenic zone into adulthood and functions as the largest site of neurogenesis in the adult brain. In recent years, with the acceptance of the concept of postembryonic mammalian neurogenesis, neurogenesis in the adult SVZ has been an area of active research. With the rapid accumulation of new information on the SVZ, some of which is contradictory, summarizing existing knowledge on the SVZ and outlining future research directions in this area become important. In this review, we will cover recent molecular and cellular investigations that characterize the SVZ niche, SVZ neurogenesis, and SVZ cell migration within the adult brain.

Key words. Subventricular zone; neurogenesis; neural stem cell.

The germinal subventricular zone

The complex neural circuitry of the brain is generally thought to be restrictive to the addition of new neurons. Logic dictates that addition of new neurons to a fully integrated, functional system would disrupt existing circuits. Therefore, unsurprisingly the brain has little capacity to generate new neurons. However, recent studies have established that the adult brain maintains discrete regions from which new neurons do emanate. These germinal zones appear to be vestiges of the developmental program that initiates brain formation.

The mammalian brain begins as a layer of cells surrounding a fluid-filled ventricle compartment (fig. 1). Actively dividing stem cells reside along the walls of the ventricle in a cellular layer known as the ventricular zone (VZ) and generate neurons. As development proceeds, a second germinal zone – the subventricular zone (SVZ) – forms beneath the ventricular zone (fig. 1) and gives rise to both neurons and glia. Following postnatal development and into adulthood, these proliferative zones diminish until only a thin SVZ remains (fig. 1). The diminished, although still active, SVZ persists into adulthood and functions as the largest site of neurogenesis in the adult brain [1]. Neurogenesis also continues in the dentate gyrus of the hippocampus, but at a lower rate than in the SVZ [2–4].

Historical perspective

The concept of neurogenesis in the adult brain has only recently gained wide acceptance. However, support had slowly been building over the past century. A review of the literature as far back as the beginning of the 1900s reveals that continued mitotic activity in the SVZ of the adult brain has been known for some time. In 1912 [5], and sub-

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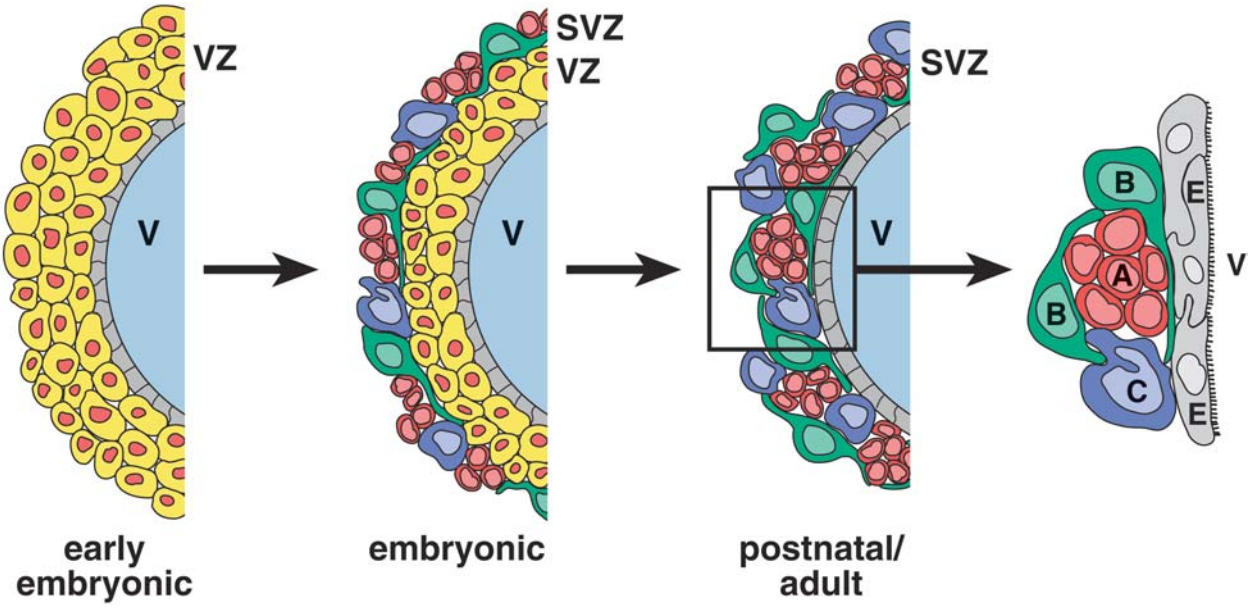

Figure 1. Scheme depicting the proliferative ventricular zone (VZ) and subventricular zone (SVZ) through development and into adulthood. The reduced SVZ in the adult is composed of migrating neuroblasts (A cells), astrocytes (B cells), transitory amplifying progenitor cells (C cells) separated from the ventricle (V) by a monolayer of ependymal cells (E cells) [adapted from ref. 21].

sequently in 1932 [6], 1938 [7], and 1944 [8], investigators reported a 'mitotically active subependymal layer' along the wall of the lateral ventricle of postnatal and adult rodents. With the advent of autoradiography, Smart [9] demonstrated proliferation of SVZ cells in young mice and their transformation into neurons and glia, and Altman, in 1962 [10] and 1963 [11] suggested that neurogenesis may continue in adult rats and cats. However, the fate of these proliferating cells was not always clear; most cells produced in the SVZ during embryonic development were thought to differentiate into neurons, while primarily glial cells were produced in the postnatal and adult mammal [9, 12–16]. The intransigence of the adult brain was revisited in 1983 when Nottebohm and colleagues [17] demonstrated that neuronal replacement occurs in the telencephalon of adult birds. Full acceptance of postembryonic mammalian neurogenesis did not take hold until a decade ago when Marla Luskins [18] described neurogenesis in the anterior portion of the SVZ in postnatal mice and Lois and Alvarez-Buylla [19] demonstrated that adult SVZ cells are capable of proliferation and limited differentiation into both neurons and glia. These findings also suggested the SVZ as the likely source of the neural stem cells identified by Reynolds and Weiss [20].

SVZ niche

Ultrastructural reconstruction of the adult SVZ by electron microscopy (EM) reveals that four major cell types constitute this region [21] (fig. 1). A monolayer of ependymal cells lines the ventricle. Adjacent to the ventricle, and occasionally in contact with it, are astrocytes. Newly generated neuroblasts migrate as tightly apposed chains of cells through the SVZ, eventually congregating in the rostral migratory stream (RMS) that leads to the olfactory bulb. These neuroblast chains are ensheathed by astrocytes (fig. 1). Interspersed among the chains of neuroblasts is an immature cell type best described as a transitory amplifying progenitor (TAP) cell. This TAP cell is the most actively dividing of the SVZ cell types and has an immature phenotype, lacking morphological or immunohistochemical characteristics of either glia or neuroblasts.

Identity of the adult SVZ neural stem cell

Following confirmation of neurogenesis in the adult SVZ, the obvious next step was to identify the stem cell that supports this neurogenesis. The subsequent ensuing search for a self-renewing, multipotent neural stem cell brought conflicting results, due in part to the difficulty identifying a cell that may be quiescent, coupled by a lack of markers to identify neural stem cells. Two claims to the identity of the stem cells that support SVZ neurogenesis have been made. Each identifies a different cell type. Jonas Frisén's laboratory at the Karolinska Institute in Stockholm presented data that suggested the SVZ neural stem cell was an ependymal cell [22], while Arturo Alvarez-Buylla's laboratory at Rockefeller University in New York City identified a cell having characteristics of an SVZ astrocyte as the neural stem cell [23]. Because there are already two excellent reviews on the controversy surrounding the identity

of the SVZ neural stem cell [24, 25], we will only highlight some key differences between the two studies and discuss how discrepancies may have arisen.

As a prelude to identifying the SVZ neural stem cell, Derek van der Kooy's group, using a microdissection technique that separates the ependyma from the SVZ, demonstrated that cells from only the subventricular layer give rise to clonally derived neurospheres capable of self-renewal and multipotency [26]. This report was quickly followed by an opposing report by Frisén's group suggesting that the ependymal cells generate multipotential neurospheres [22]. Two protocols were used by Frisén and colleagues to label and then isolate ependymal cells from the SVZ: (i) injection of the lipophilic fluorescent dye DiI into the lateral ventricle to label ependymal cells lining the ventricle and (ii) cellsorting of ependymal cells based on expression of Notch, a cell fate regulator expressed exclusively by ependymal cells. With both methods, multipotent neurospheres were generated from labelled ependymal cells [22]. At about the same time, Doetsch et al. [23] used the antimitotic agent cytosine-β-D-arabinofuranoside (Ara-C) to temporarily deplete the SVZ of all proliferating cells. Cells positive for glial fibrillary acidic protein (GFAP) and displaying other astrocyte characteristics, as determined by EM, repopulated the SVZ upon withdrawal of the antimitotic agent, suggesting that the progenitors were astrocytes. Also, to show that GFAP-expressing cells in the SVZ function as neuronal precursors, Doetsch et al. [23] used transgenic mice in which the receptor for an avian leukosis virus (Gtva) is expressed under the GFAP promoter [27]. These mice were then infected with an avian leukosis retrovirus (RCAS) expressing alkaline phosphatase. Doetsch et al. [23] could then track SVZ astrocytes infected with the labelled retrovirus in vivo. Again, they found that SVZ astrocytes generated new neurons which could eventually be found in the olfactory bulb.

Subsequently, Laywell et al. [28] examined the potential of ciliated ependymal cells and SVZ astrocytes to form multipotent neurospheres. They found that ciliated ependymal cells are unipotent, giving rise only to glia cells, while SVZ astrocytes grown as monolayers can form neurospheres that produce both neurons and glia, thus supporting the SVZ astrocyte/neural stem cell theory proposed by Alvarez-Buylla and colleagues [23, 29]. Indeed, astrocytes derived from the cerebral cortex, cerebellum, and spinal cord during the first 2 postnatal weeks can all form multipotent neurospheres, while only SVZ astrocytes retain this ability in the adult [28].

Discrepancies in the identity of the neural stem cell most likely arose due to limitations in the ability to properly characterize neural stem cells in vivo and in vitro and to track their differentiation. Detailed reconstruction of the SVZ cytoarchitecture by EM [21] provided the identity of potential neural stem cell candidates and also a cell-cell interactive map of the zone. Based on EM, the Alvarez-Buylla laboratory noted that SVZ astrocytes occasionally make contact with the ventricle surface [23, 30], and pointed out that this may be critical for setting up the neurogenic SVZ astrocyte as a multipotent cell. Without the aid of EM in their studies, the Frisén laboratory may have misidentified this subpopulation of astrocytes with ventricle contact as ependymal cells, as this cell would also become labelled with DiI [22]. Additionally, neither group might be entirely correct, and with the proper markers, the neural stem cell may be identified as a similar, but distinct, subpopulation of astrocyte-like or, possibly, ependyma-like cells.

To date, efforts to characterize neural stem cells have fallen short, due in large part to the lack of specific markers. For example, using flow cytometry, Rietze et al. [31] reported that they had purified neural stem cells from the adult SVZ based on differential binding of the lectin peanut agglutinin (PNA) and heat-stable antigen (HSA, mCD24a). They found a population with low PNA and HSA binding (PNA^{lo}/HSA^{lo}) capable of generating neurospheres. This population lacked cilia and did not express the ependymal marker HSA, but did express nestin, which is expressed by ependymal cells, astrocytes, and migrating neuroblasts in the SVZ [21]. Other differentiated cell markers (beta-tubulin type III, O4, and GFAP) were not expressed by the PNA^{lo}/HSA^{lo} population [31]. However, under conditions promoting differentiation, the progeny of the PNA^{lo}/HSA^{lo} population include neurons (beta-tubulin type III positive), astrocytes (GFAP positive) and oligodendrocytes (O4 positive). If indeed this identifies a separate cell population, neither truly ependyma nor astrocyte, additional markers will be needed to characterize it further.

The suggestion that highly differentiated glial cell populations (either ependymal cells or astrocytes) possess stem cell capacity confounds our definition of stem cell and hints at such mechanisms as 'dedifferentiation' or 'reprogramming'. Does this more 'mature' phenotype also influence differentiation capacity? In vivo, SVZ neural stem cells can generate only astrocytes or small GABAergic inhibitory neurons of the olfactory bulb [23]. However, when labelled adult SVZ neural stem cells were taken out of their niche and placed into mouse preimplantation embryos, labelled cells were detected in tissues and organs of almost all germinal layers [32], assigning a broad capacity or multipotency to adult SVZ stem cells. Caution is necessary in interpreting these results, however, as only embryonic day 11 embryos were analyzed, and full functionality of these integrated neural stem cells was therefore not demonstrated.

Molecular mechanisms that support neurogenesis in the SVZ

Signals must be present to maintain stem cells in an undifferentiated state and to promote the differentiation of

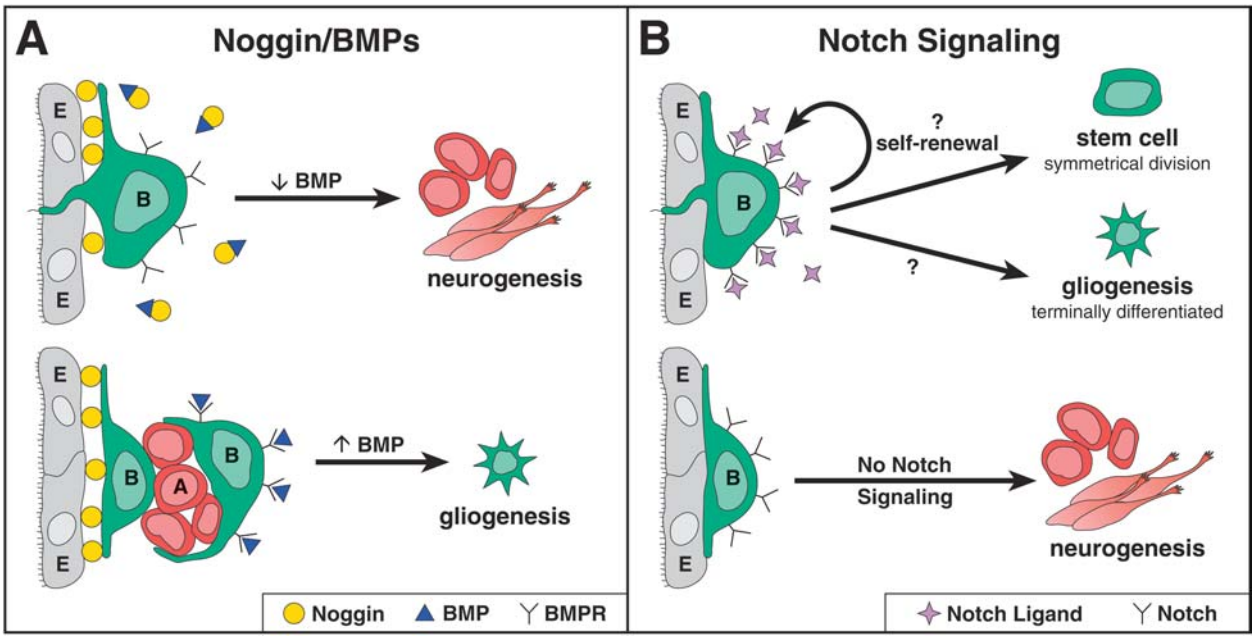

Figure 2. Signalling molecules and their actions within the SVZ. A, neuroblasts; B, astrocytes (putative stem cell); E, ependymal cells. (*A*) In the adult SVZ, ependymal cells express Noggin. Acting as an antagonist, Noggin is thought to block BMP signalling through its receptor, BMPR, promoting neurogenesis instead of gliogenesis. Higher BMP levels or reduced competition of Noggin for BMP results in gliogenesis. (*B*) Notch signalling by neural stem cells is thought either to promote self-renewal or result in gliogenesis. Absence of Notch signalling allows neurogenesis.

their progeny. To date, only two candidates have been attributed with this role, bone morphogenic proteins (BMPs) and Notch ligands. Astrocytes can be found throughout the SVZ; however, those thought to act as stem cells are located immediately adjacent to or within the ependymal wall, with contact to the cerebrospinal fluid (CSF) [23, 30] (fig. 2A, B). Are CSF contact and/or ependyma/SVZ interaction prerequisites for stem cell function? While we do not yet know the answer to these questions, recent findings provide evidence that several molecular mechanisms controlling both proliferation and differentiation are activated through ependyma/SVZ interaction. The BMP-binding protein Noggin, for example, is expressed by ependymal cells, and appears to support neurogenesis by blocking endogenous BMP signals which would otherwise induce gliogenesis [33] (fig. 2A). BMPs and their cognate receptors (BMPRs) are expressed throughout the SVZ, while antagonistic Noggin expression is limited to ependymal cells. Throughout development, BMPs, BMPRs, and Noggin are widely expressed, playing important roles in cell lineage determination. Depending on the context, BMPs can act either as strong instructive neurogenic factors [34, 35] or potent inhibitors of neurogenesis, directing gliogenesis instead [33, 36, 37]. Noggin, similarly, has dual roles in development, acting as both a promotor of neurogenesis [38, 39] and a negative regulator of neuronal differentiation [40]. In adulthood, however, Noggin, BMPR, and BMP expression are retained in limited areas of the brain [33], two of which, the SVZ and the hippocampal dentate gyrus, maintain germinal status and the potential to generate new neurons.

Notch1 receptor signalling is another potential regulatory factor controlling neural stem cell fate decisions in the SVZ. Activation of the Notch receptor has been shown to inhibit neurogenesis [reviewed by refs. 41–44]. One suggested mechanism is that Notch signalling maintains neural stem cells in their undifferentiated state [45–47], potentially by promoting symmetrical division and self-renewal, at the cost of differentiation resulting from asymmetrical division [48] (fig. 2B). In support of this, neural stem cells are depleted in Notch1–/– mice and in mice lacking key regulators of Notch signalling activity, such as presenilin 1 (PS1–/–), which cleaves Notch following ligand interaction, and RBP-Jκ (RBP-Jκ–/–), which helps mediate the signalling of the cleaved intracellular domain of Notch in the nucleus [48]. Alternatively, rather than maintaining an undifferentiated phenotype, Notch signalling has also been suggested to actively instruct glial cell fate decisions [49–51] (fig. 2B). Even transient Notch activation induced by exogenous Notch ligand was found to cause a rapid and irreversible loss of neurogenic capacity accompanied by accelerated glial differentiation [51] (fig. 2B). Similarly, analysis of activated Notch1 introduced into mouse embryonic forebrain by retroviral vector and tracked by ultrasound imaging revealed that Notch1-infected cells became radial glia in the developing

embryo [49]. Recent findings indicate that proliferative radial glia, while thought to be part of the glial lineage, can also function as neuronal precursors [52–54]. Postnatally, many of the Notch1-infected cells became periventricular astrocytes [49], the same cells shown to be the neural stem cells [23]. This evokes the interesting possibility that radial glia and SVZ astrocytes, the putative adult neural stem cells, are lineally related [49]. The seemingly contradictory findings that Notch1 signalling is instructive for gliogenesis and that Notch1 activation maintains neural stem cells as undifferentiated populations appear to be coming closer to resolution as the evidence accumulates supporting the hypothesis that astrocytes are the neural stem cell. Again, more work is necessary to resolve the temporal/spatial cues within the SVZ that control neural stem cell decisions.

Migration in the SVZ

The SVZ is one of the few sites in the adult brain where active migration of neuroblasts occurs. This is particularly evident when wholemounts of the lateral wall of the lateral ventricle are stained for the neuroblast-specific marker polysialylated neural cell adhesion molecule (PSA-NCAM), revealing an extensive network of highly motile neuroblasts arranged into chains (fig. 3D). The majority of these chains are oriented along the rostrocaudal axis, ultimately converging at the dorsal, rostral tip of the SVZ to form the RMS, which transports neuroblasts into the olfactory bulb (fig. 3A).

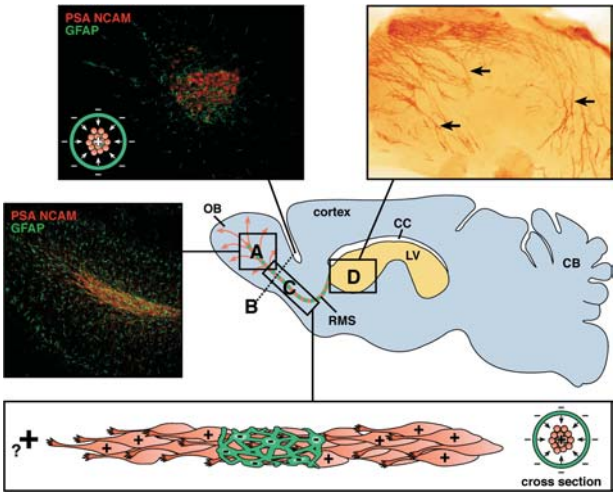

Figure 3. Neuroblast migration within the adult forebrain. (*A*) Chains of SVZ neuroblasts entering the olfactory bulb. Astrocytes (GFAP positive) encircle chains of migrating neuroblasts (PSA-NCAM positive). (*B*) Cross-section of the rostral migratory stream (RMS) as it enters the olfactory bulb. Astrocytes can be seen around clusters of migrating neuroblasts. (*C*) Shown here are the repellant forces (minus signs) from the astrocytes that are thought to contain the migrating neuroblasts in tight chains. Attractant cues (plus signs) between neuroblasts are also thought to maintain the neuroblasts as chains. Whether a chemoattraction molecule functions to direct neuroblast migration toward the olfactory bulb is not known [schematic adapted from ref. 57]. (*D*) Wholemount of the wall of the lateral ventricle (LV) stained for PSA-NCAM reveals chains of migrating neuroblasts (arrows). CB, cerebellum; CC, corpus callosum.

The mechanisms controlling this translocation of large numbers of cells over a considerable distance in the adult mouse brain are of particular interest. Understanding the molecular cues enabling neuroblast migration will influence how we approach cell transplantation in the adult brain, and the migration of neuroblasts from the SVZ to the olfactory bulb presents an excellent example of how cohorts of cells can be transported through the milieu of the adult brain. SVZ neuroblasts, unlike most other neurons, do not migrate via radial glia or other projection-guided mechanisms [55]. Rather, neuroblasts in the SVZ use a unique form of migration termed ‘chain migration’, or neurophilic migration (fig. 3B, C), to travel through the anterior forebrain and eventually enter the olfactory bulb. The term chain migration was first coined by Alvarez-Buylla and colleagues to describe the movement of tightly apposed chains of neuroblasts as they course into the olfactory bulb (fig. 3A), covering a distance of 3–8 mm [55–57]. These neuroblasts are surrounded by astrocytes, which most likely function in restraining the neuroblasts in their specific pathway (fig. 3B and C). The interaction between migrating neuroblasts and encircling astrocytes gives the appearance of neuroblast chains travelling through tunnels of astrocytes [57] (fig. 3B, C).

What are the molecular cues directing SVZ neuroblast migration? The secretion of a chemoattractant factor by the olfactory bulb would be a logical possibility. However, 3 weeks following removal of the olfactory bulb, by bulbectomy, SVZ neuroblasts continue to migrate toward the removed olfactory bulb, and experiments using culture assays showed that olfactory bulb tissue had no directive influence on the migration of SVZ neuroblasts to the olfactory bulb [58]. The presence of repulsive molecules in neighboring regions of the brain is another possible mechanism restricting SVZ neuroblast migration to a very discrete pathway, thereby avoiding neuroblast entry into adjacent tissues. For example, the caudal septum was shown to affect SVZ neuroblast migration [59], and a septum-derived factor, later identified as Slit1 and 2 [60, 61], showed a repellent effect on SVZ neuroblast migration in vitro [60, 61]. However, chain migration occurs only along the lateral wall of the lateral ventricles, and the septum, although in contact with the medial wall of the lateral ventricle, is separated from the lateral wall by the ventricle [62]. While neighboring tissues such as the striatum may benefit from using repulsive molecules to prevent SVZ neuroblasts from penetrating its boundary, this should not be a requirement of the septum.

PSA-NCAM is another candidate molecule for a role in SVZ neuroblast migration. Migrating SVZ neuroblasts express high levels of PSA-NCAM, and several studies have implicated PSA-NCAM in neuroblast migration. Genetic deletion of PSA-NCAM [63, 64] or enzymatic removal of the PSA moiety from NCAM [65] disrupt SVZ neuroblast migration to the olfactory bulb, and NCAM–/– mice show a severely reduced olfactory bulb. However, although PSA-NCAM is required to maintain the migration-permissive environment of the RMS, it is not thought to actively guide migration [59, 66]. Interestingly, the function of PSA-NCAM in chain migration is reminiscent of its function in axon fasciculation [59, 67]. This use of similar mechanisms for chain migration and axon fasciculation/guidance may also extend to the receptor tyrosine kinase family of Eph receptors and their ligands, the ephrins [30]. Eph receptors and ephrins promote axon fasciculation and direct axons by contact-mediated repulsion [for reviews see refs 68–71]. In addition, Eph/ephrin interactions direct a highly migratory cell population, the neural crest cells [72–74]. Eph/ephrin interactions seem to be unified by the principle of contact-mediated repulsion. Through the complementary expression of Eph receptors and ephrins by neighboring cells, these receptors and ligands act to guide cell or axon migration, bundle axons, or establish or maintain neuromeric boundaries. We have shown that Eph/ephrin interactions in the SVZ may also regulate neuroblast migration or their organization into chains [30]. By infusing truncated EphB2 or ephrin-B2 (lacking their cytoplasmic domains) into the lateral ventricle, we noted a dramatic disruption of migrating neuroblast chains. However, cell proliferation was also increased in the SVZ, so determining if these were two independent consequences of the infusion of truncated Eph/ephrin or if one resulted from the other was difficult.

Future research directions

The SVZ offers an excellent system with which to analyze how stem cell populations are maintained in the adult brain, the molecular cues that promote adult neurogenesis, and the organization and directional cues that guide migration of neurons in the adult brain. Research efforts will undoubtedly continue to focus on the identity of the neural stem cell with an emphasis on the need for unique markers that will discriminate neural stem cells from terminally differentiated glial populations within the SVZ. Once neural stem cells have been uniquely identified, key questions can be addressed, such as: How do neural stem cells fit into the cytoarchitecture of the SVZ? What is unique about the SVZ that allows it to persist as a germinal zone? What triggers asymmetric differentiation of neural stem cells to produce neurons? Once neurons are generated, the SVZ provides a milieu that permits neuroblast chain migration. Much remains to be learned about neuronal migration in the SVZ and the cues that direct the migration of large numbers of neurons from the SVZ through the adult forebrain. The occurrence of both neurogenesis and neuronal migration in this specialized region of the adult brain provides us with a powerful research platform from which we can increase our understanding of brain repair and more fully realize the potential of stem cell biology in replacement therapies.

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