

Cellular and Molecular Determinants of Stroke-Induced Changes in Subventricular Zone Cell Migration

Christopher C. Young,¹ Keith J. Brooks,² Alastair M. Buchan,² and Francis G. Szele¹

Abstract

A remarkable aspect of adult neurogenesis is that the tight regulation of subventricular zone (SVZ) neuroblast migration is altered after ischemic stroke and newborn neurons emigrate towards the injury. This phenomenon is an essential component of endogenous repair and also serves to illuminate normal mechanisms and rules that govern SVZ migration. Stroke causes inflammation that leads to cytokine and chemokine release, and SVZ neuroblasts that express their receptors are recruited. Metalloproteinases create pathways and new blood vessels provide a scaffold to facilitate neuroblast migration between the SVZ and the infarct. Most experiments have studied the peri-lesion parenchyma and relatively little is known about SVZ remodeling after stroke. Migration in the SVZ is tightly regulated by cellular interactions and molecular signaling; how are these altered after stroke to allow emigration? Do ependymal cells contribute to this process, given their reported neurogenic potential? How does stroke affect ependymal cell regulation of cerebrospinal fluid flow? Given the heterogeneity of SVZ progenitors, do all types of neuroblasts migrate out, or is this confined to specific subtypes of cells? We discuss these and other questions in our review and propose experiments to address them. *Antioxid. Redox Signal.* 14, 1877–1888.

Introduction

ADULT NEUROGENESIS is the generation of new neurons from resident neural stem cell (NSC) populations in the adult brain (65). In many mammalian species, including rodents, higher primates, and humans, heterogeneous neural stem cell populations reside in two distinct neurogenic niches in the adult brain, the subventricular zone (SVZ) surrounding the lateral ventricles (Fig. 1), and the subgranular zone (SGZ) of the hippocampal dentate gyrus (22, 24, 27, 98). In the SVZ, proliferating neural stem cells and progenitor cells reside in a specialized cellular and extracellular matrix niche (79), and give rise to neuroblasts that migrate long distances through the rostral migratory stream (RMS) to the olfactory bulb (OB), where they differentiate into periglomerular and granule GABAergic interneurons (68). In the SGZ, neurogenesis gives rise to granule interneurons and provides excitatory inputs to area CA3 (47). Although their functions are incompletely understood, evidence suggests SVZ neurogenesis is involved in olfactory discrimination, while SGZ neurogenesis may play a role in memory formation (138). Defective or insufficient adult neurogenesis has been associated with a wide spectrum of neurodevelopmental and neurodegenerative diseases ranging from schizophrenia to Alzheimer's disease (106).

Remarkably, adult neurogenesis contributes to endogenous repair after different types of brain damage such as traumatic brain injury, multiple sclerosis, intracranial hemorrhage, and stroke (14, 43, 77, 110). After focal ischemic stroke, in addition to increased cell proliferation in the SVZ, newly born neural precursors are able to migrate long distances and localize near injured brain regions. At the site of injury, these neural precursors may mediate neuroprotection and immune modulation (123). Furthermore, a small number of these cells will survive, differentiate and display evidence of synaptic integration (5, 36, 91, 126). Importantly, strategies that increase SVZ neurogenesis and migration towards the ischemic brain regions improve functional and histological outcomes after stroke (107, 108, 111, 112), while elimination of SVZ neurogenesis worsens them (45). There is also evidence that the human SVZ responds to ischemic injury (46, 71, 75). There is thus great impetus to understand the extent of the attempted repair process and the mechanisms which regulate each aspect of this phenomenon. The ultimate goal is to understand why endogenous brain repair is insufficient and to ask whether we will be able to manipulate the system for therapeutic brain repair. Intense research over the last decade has focused on molecular and cellular signals from the ischemic brain regions that induce SVZ proliferation, and

¹Department of Physiology, Anatomy and Genetics, and ²Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom.

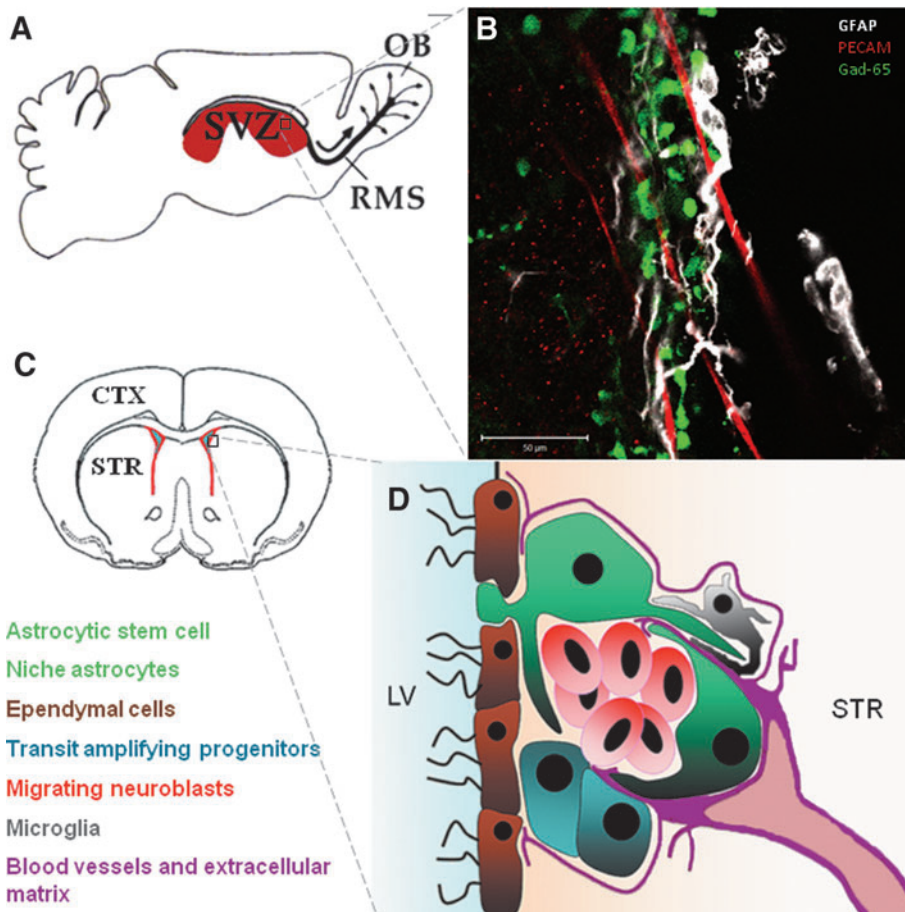


FIG. 1. Anatomical location and cell composition of the SVZ. (A) Schematic showing location of SVZ (red) in the sagittal plane. Neural stem cells and transit amplifying progenitors give rise to neuroblasts which migrate long distance in the rostral migratory stream (RMS) to the olfactory bulb. The RMS route is shown with a *thick black line* and the normal direction with a *thick arrow*. Neuroblasts migrate out of the RMS into the olfactory bulb (OB) in random fashion (*thin arrows*). (B) Whole-mount immunohistochemistry showing SVZ astrocytes (glial fibrillary acidic protein, GFAP - white), neuroblasts (Gad-65-GFP, green) and blood vessels (platelet endothelial cell adhesion molecule PECAM, red). Note that neuroblasts are frequently associated with astrocytes and blood vessels. (C) Coronal cross section showing location of SVZ (red). (D) Cell composition of SVZ with cells color coded. Note that SVZ astrocytic stem cells have a basal process protruding amongst the ependymal cells and make ventricular contact. Niche astrocytes are generally located on the striatal (STR) side of the SVZ. Small microglial cells have processes that interdigitate other cells. Mercier

has described a complex network (fractones) of specialized extracellular matrix around SVZ cells emanating from blood vessels. LV lateral ventricle. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

recruit newborn neural precursors (reviewed in Refs. 48, 59, 76, 88, 123). In the current review, we will present a novel perspective on the cellular and molecular mechanisms that facilitate SVZ neuroblast migration into the ischemic striatum. We will focus on how dynamic changes within the SVZ neurogenic niche after ischemic stroke permit neuroblasts to exit their tightly regulated migratory pathway.

Tangential Migration During SVZ Adult Neurogenesis

In order to understand the mechanisms that govern the migration of SVZ neuroblasts into the striatum after ischemic stroke, it is important to appreciate constitutive tangential neuroblast migration, from the SVZ, through the RMS to the olfactory bulb (SVZ-RMS-OB). Niche mechanisms operating at cellular and molecular levels tightly regulate this long-distance migration (Fig. 2). For a comprehensive review, see Ref. 16. Neuroblasts form chains and migrate along one another, under the influence of cell-surface molecules, such as polysialylated NCAM and $\alpha 6 \beta 1$ integrin, and extracellular matrix proteins (18, 21, 26, 37, 40, 120). In addition to homotypic migration, neuroblast chains are closely associated with blood vessels that form a migratory scaffold and mediate neuroblast migration through BDNF signaling (12, 104, 119). Glial processes ensheath neuroblast chains to form “glial

tubes” and regulate cell movements via GABA signaling (11). Niche astrocytes also mediate neuregulin/ErbB4 interactions that maintain astrocytic cytoarchitecture and normal neuroblast migration (29). SVZ microglia are constitutively semi-activated and neuroblasts express several chemokine receptors, including CXCR4 and CCR2, the receptors for SDF-1 α and monocyte chemoattractant protein 1 (MCP-1), respectively (31, 116). Although the role of chemokines in normal SVZ neuroblast migration is yet to be determined, chemokines are known to affect normal migration in other contexts, for example, SDF-1 α plays important roles in granule neuron migration in cerebellar development (70). The chemorepulsive Slit-Robo signaling pathway appears to play an important role in directing neuroblasts away from the SVZ. Slit is expressed in the SVZ, septum and choroid plexus, and its receptors, Robo-2 and Robo-3, are expressed by neuroblasts (86, 125). CSF flow, which is propelled by the beating cilia of ependymal cells, establishes a chemo-repulsive Slit gradient to direct neuroblast migration rostrally towards the olfactory bulb (99, 125). In addition, there is evidence that the olfactory bulb may be the source of chemoattractants that direct neuroblasts. Prokineticin-2, Netrin-1, GDNF, and BDNF have been suggested to orient neuroblast migration towards the olfactory bulb (17, 83, 85). Furthermore, while removal of the olfactory bulb does not completely stop migration of neuroblasts, nor

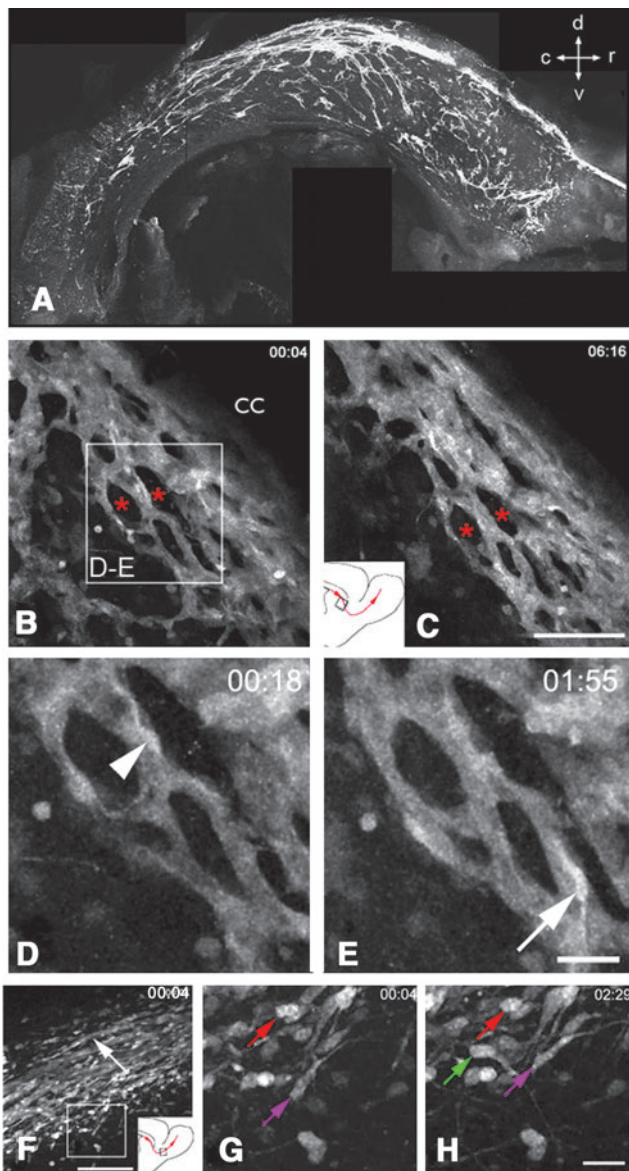


FIG. 2. SVZ neuroblasts migrate in chains. (A) Whole-mount immunohistochemistry of doublecortin showing low magnification view of neuroblast chain orientation in the SVZ viewed in a sagittal plane. Note that in the dorsal SVZ, most chains are oriented rostral-caudally, but that in ventral locations, they have a variety of orientations. c, caudal; d, dorsal; r, rostral; v, ventral. (B, C) Neuroblast chains visualized in Dex-GFP mice under the corpus callosum (cc) were remarkably stable for over 6 hours (time stamps in hours and minutes in upper right corner). Asterisks show examples of areas avoided by these chains and are likely populated by SVZ astrocytes, transit amplifying progenitors, and microglia. Inset in B shows location of D, E. Inset in C shows location of movie. (D, E) shows neuroblasts migrating along chains. (F) low magnification of Dcx-GFP neuroblast chains migrating in RMS into the OB. White box shows location of G, H, and schematic shows location of movie. (G, H) show that cells at the edge of the RMS that are largely stationary (red and purple arrows) and one motile neuroblast (green arrow). Most cells that emigrate from the SVZ and RMS slow down precipitously. [B–H adapted from (84).] (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

disturb the directionality of migration, there is evidence that loss of the olfactory bulb results in decreased numbers of SVZ neuroblasts which migrate into the RMS (41, 51, 62).

Post-Stroke SVZ Neuroblast Migration

Following animal models of stroke, large numbers of SVZ neuroblasts are able to overcome the tight regulation described above to exit their normal pathway and migrate towards the injured brain regions (5, 44, 91, 133). Neuroblast emigration commences 3–4 days after stroke, remains robust for several weeks, and has been observed to continue for as long as 4 months (113). Several molecular signals and cellular interactions that direct neuroblasts towards the ischemic brain regions have been described. The role of reactive astrocytes and activated microglia/macrophages at the site of injury is important, as are blood vessels and astrocytic processes that form migratory scaffolds, recapitulating the cellular interactions of constitutive SVZ neuroblast migration (Fig. 3).

Role of reactive astrocytes and activated microglia/macrophages

With the onset of ischemic stroke, delivery of oxygenated blood to the brain is drastically decreased. Neurons have high metabolic demands and come under increasing oxidative stress (55). This results in the accumulation of reactive oxygen

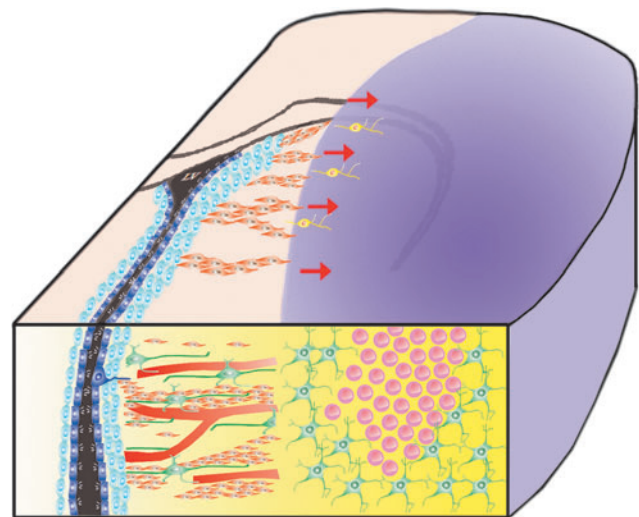


FIG. 3. Neuroblast emigration towards the ischemic striatum after MCAO stroke. The location of the middle cerebral artery occlusion lesion is shown in purple. Red arrows show direction of neuroblast emigration. Ischemic stroke lead to a robust inflammatory response in the infarct area, with accumulation of large numbers of reactive astrocytes (green cells) and activated microglia/macrophages (pink cells). Inflammatory cells release various chemokines and chemoattractants such as stromal-derived factor 1 alpha (SDF-1 α) and monocyte chemoattractant factor 1 (MCP-1). Neuroblasts from the SVZ migrate up chemotactic gradients along blood vessels and astrocytic processes towards the injury. Relatively little is known about the changes in the SVZ neurogenic niche which may facilitate the exit of neuroblasts out of their normal migratory pathway into the striatum. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

species and ischemic cell death. Neuronal cell death leads to activation of the complement cascade and the initiation of the inflammatory response (49). In ischemic brain regions, reactive astrocytes and activated microglia/macrophages secrete a variety of substances, including a number of chemokines and chemoattractants that recruit SVZ neuroblasts towards the ischemic striatum. Reactive astrocytes secrete SDF-1 α , and neuroblasts express the corresponding CXCR4 receptor (38, 42, 116). Overexpression of SDF-1 α results in increased neuroblast recruitment, while functional blocking antibodies or siRNA to the CXCR4 receptor had the opposite effect (65, 95, 112). ERK signaling may mediate the effect of SDF-1 α on neuroblast migration (69). Interestingly, a recent report suggests that complement-derived anaphylatoxin C3a potentiates neuroblast migration at low SDF-1 α concentration, while inhibiting neuroblast migration at high SDF-1 α concentration in an ERK1/2 phosphorylation-dependent process (103). This would imply that neuroblasts can respond dynamically to the concentration of this chemokine. Monocyte chemoattractant protein-1 (MCP-1) also induces post-stroke neuroblast emigration into the striatum. MCP-1 is highly upregulated by reactive astrocytes and activated microglia/macrophages in the ischemic striatum and cortex, while emigrating neuroblasts express its cognate receptor CCR2 (66, 116, 128). Accordingly, MCP-1(-/-) and CCR2(-/-) mice had significantly decreased post-stroke neuroblast emigration (128). However, it is worthwhile to note that in a separate study, CCR2(-/-) mice exhibited decreased post-stroke neutrophil recruitment and reduced expression of pro-inflammatory cytokines such as TNF α , resulting in reduced infarct size after middle cerebral artery occlusion (MCAO) compared to wild-type mice (20).

In addition to classic chemokines, activated microglia/macrophages secrete vascular endothelial growth factor (VEGF) which has chemoattractant, angiogenic, and neurogenic properties (93). *In vitro*, VEGF is a chemoattractant and promotes neuroblast migration through VEGFR-2 (6, 132). Transgenic overexpression of VEGF increased SVZ cell proliferation and the number of neuroblasts in the ischemic brain regions after ischemic stroke (118). However, the authors of the study point out that *in vivo* it is difficult to distinguish whether the increased number of neuroblasts observed is due to a direct effect on migration, or merely increased proliferation. Activated microglia/macrophages in the ischemic brain also express high levels of osteopontin, an acidic glycoprotein, which has chemoattractive properties, as well as cell adhesion and extracellular matrix signaling functions via activation of integrin receptors (23, 78). After ischemic stroke, osteopontin mediates neuroblast emigration in a β 1-integrin-dependent manner (127). Osmotic pump infusion of a functional blocking antibody to osteopontin decreased neuroblast emigration into the striatum without affecting SVZ proliferation, compared to infusion of IgG controls. *In vitro*, blockade of β 1-integrin which is expressed by neurosphere-derived migrating neural precursor cells, decreased cell migration on a laminin substrate (40), further supporting the notion that integrins are integral to neuroblast migration. Reactive astrocytes and activated microglia/macrophages are also involved in tissue remodelling of the ischemic striatum, and express matrix metalloproteinases (MMPs) which cleave and degrade extracellular-matrix components to facilitate neuroblast migration through the

striatum (56, 97). Thus, a variety of different molecules are secreted by glial cells in response to stroke. These molecules diffuse from the injury to the SVZ and recruit migratory neuroblasts (Table 1).

Role of angiogenic vasculature as substrate for migration

Following ischemic stroke, there is increased endothelial proliferation and formation of new blood vessels (angiogenesis) in the peri-infarct region (7, 54, 63, 74, 137). Endothelial proliferation in the peri-infarct region is seen as early as 12–24 hours post-stroke, resulting in significantly increased blood vessel density by 3 days (8). Peri-infarct angiogenesis is increased for more than 3 weeks following cerebral ischemia (35). Angiogenesis functions to increase blood supply to vulnerable brain regions, and to provide trophic support that plays an important role to reduce further neuronal death in the days and weeks following stroke (57, 92, 101). Endothelial cells secrete growth factors such as BDNF and angiopoietin (Ang-1) to promote neuroblast recruitment towards the ischemic brain tissue. BDNF is known to promote proliferation, migration, survival, and differentiation of SVZ neural precursor cells (9, 57). After focal stroke, endothelial cells express Ang-1, which acts on Tie-2 receptors on neuroblasts to promote emigration (89). A recent study found that Ang-1 also promotes SVZ proliferation constitutively (96). In addition, extracellular matrix proteins associated with blood vessels such as laminin are important for the maintenance of neural precursor cells (79, 102). Thus, the vasculature changes after stroke and makes important contributions to the molecular milieu into which SVZ neuroblasts are enticed to migrate.

Migrating cells frequently exhibit haptotaxis and durotaxis, migration up adhesion or mechanical stiffness gradients, respectively. Thus the question arises; do emigrating SVZ neuroblasts have preferred physical substrates for emigration? As discussed above, SVZ neuroblast migration to the olfactory bulb is partly mediated by the vascular scaffold that is present in the SVZ–RMS–OB migratory pathway. Several studies using different models of cerebral ischemia have shown histologically that neuroblasts migrating into the striatum after stroke are frequently in close proximity to blood vessels (89, 113, 126). Time-lapse microscopy of acute slices after focal ischemia suggests that some of the Dcx+ neuroblasts made contacts with blood vessels during active migration, both in the early phase as the neuroblasts exit the SVZ, as well as in the striatum (53, 134). These experiments suggest that blood vessels not only form dynamic molecular interactions with neuroblasts to provide directionality and trophic support in a hostile environment, but in a recapitulation of the normal migratory pathway also provide a physical substrate for migration.

Role of SVZ Remodelling in Neuroblast Emigration to Stroke

The experiments described above point to a model whereby release of soluble factors recruit neuroblasts towards ischemic brain regions with guidance from astrocytic processes and blood vessels. Overwhelmingly, the emphasis has focused on factors outside the SVZ that act to divert neuroblasts. We propose that *de novo* cellular or molecular processes localized in the SVZ facilitate early events in post-stroke neu-

TABLE 1. MOLECULES REGULATING SVZ NEUROBLAST MIGRATION

Families of molecules	Constitutive SVZ-RMS-OB migration	Emigration to Model of Stroke
Chemoattractant (ligand/receptor)	BDNF/TrkB	?
	GDNF/GFR α 1	?
	VEGF/VEGFR-1,2	VEGF/VEGFR-2
	ProK2/ProKR2	?
	Netrin-1	?
	Anosmin-1	?
	HGF/Met	?
	SHH/Patched	?
	?	SDF-1 α /CXCR4
	?	MCP-1/CCR2
Chemorepellant(ligand/receptor) Signaling (ligand/receptor)	?	Osteopontin
	?	Ang-1/Tie-2
	Slit1,2/Robo2,3	?
	Ephrin-B2/EphB2	?
	Reelin/disabled	?
	Neuregulin/ErbB4	?
	EGF/ErbB1	?
	FGF2/FGFR1	?
	NPY/Y1	?
	NCAM/NCAM	?
Adhesion (ECM or homotypic)	PSA-NCAM	?
	α 6 β 1 Integrin/Laminin	?
	Tenascin	?
	Connexins 43 & 45	?
Matrix metalloproteinases	?	MMP(s)
	GABA	?
Neurotransmitters	Glutamate	?
	Dcx	?

?, unknown.

roblast emigration (*i.e.*, exit from the SVZ-RMS-OB migratory pathway). What are the changes within the SVZ which facilitate neuroblast emigration? Are SVZ components such as scaffolds neuroblast chains, astrocytic “glial tubes”, vascular scaffolds, and extracellular matrix proteins, which regulate normal SVZ migration, altered after ischemic stroke?

Molecular and migratory properties of SVZ neuroblasts are altered after stroke

Indeed, SVZ neuroblasts undergo intrinsic changes after focal stroke. Neuroblasts express matrix metalloproteinases (MMPs) which can cleave and degrade extracellular matrix components. MMP-3 and MMP-9 are upregulated by SVZ neuroblasts in response to chemokine stimulation and focal ischemia (6, 56). Neuroblast emigration into the ischemic striatum is significantly reduced by administration of the broad spectrum MMP inhibitor, GM6001, while MMP-3 and MMP-9 blockade with specific siRNAs decreased neuroblast migration *in vitro* (6, 56). However, it is unclear whether MMPs are required to merely “digest” a pathway through the extracellular matrix to facilitate neuroblast emigration, or whether MMPs directly influence extracellular matrix protein interactions such as integrin and laminin, and thus affect intracellular signaling. Nevertheless, these studies suggest a model wherein the striatum presents a molecular/mechanical barrier through which neuroblasts have to bore to reach the lesion. It may be that this feature is what restricts neuroblasts from migrating errantly into the striatum under normal con-

ditions. It would be interesting to test this hypothesis by decreasing extracellular matrix stiffness with chondroitinase, as has recently been carried out to augment spinal cord axon outgrowth (28).

Attempts have been made to characterize changes in gene expression in the SVZ following ischemic stroke. Using combination of gene microarray and real time RT-PCR, Liu and colleagues showed the upregulation of several genes, including Hif-1 α , Notch4, and Ephrin B2, in both dissected SVZ tissue and cultured SVZ neurospheres after MCAO (64). Their functional implication in the post-stroke SVZ niche and their effects on neuroblast emigration remains to be elucidated. Another important approach will be to isolate neuroblasts which are migrating through the ischemic striatum and compare their gene/protein expression at a single cell level in comparison to non-emigrating neuroblasts.

Time-lapse microscopy demonstrated that neuroblasts actively exiting the SVZ migrate significantly faster than neuroblasts inside the SVZ (134). This was surprising since 2-photon time-lapse data from our lab show that SVZ neuroblasts significantly slow down when emigrating from the (84) (Fig. 2) and it suggests that mechanisms such as GABAergic signaling that regulate speed, as mentioned above, may be significantly altered after stroke. *In vitro*, SVZ cells derived from post-stroke animals spent less time in cytokinesis, and migrated further when plated on Matrigel substrate (135). Using 2-photon time-lapse imaging, we have shown that neuroblast chains remain very stable during normal migration (84) (Fig. 2). After ischemic stroke, there is evidence in

static sections that neuroblast chains may be dispersed as neuroblasts exit their normal migratory pathway (44). It will be important to detail the extent to which neuroblast chains are disturbed and the molecular signals within the SVZ which facilitate neuroblast emigration. For example, reelin has been shown to be a chain detachment signal for migrating neuroblasts as they commence radial migration in the olfactory bulb (33). Does stroke alter reelin signaling to facilitate neuroblast exit from the SVZ? Interestingly, after stroke, reelin deficient mice have larger stroke volume, and showed decreased number of neuroblasts in the ischemic border, despite preserved SVZ cell proliferation (124). This suggests that reduced neuroblast emigration may exacerbate stroke injury.

Stroke may induce migration in SVZ cells that are normally stationary

The first thorough, and classic, descriptions of the SVZ and RMS were by Altman in the 1960s. They clearly delineated a proliferative population of cells that were concentrated in the SVZ and a migratory population of cells that predominated in the RMS (2, 3). This general notion has been challenged to a certain extent by the finding that migratory neuroblasts occasionally divide in the SVZ and RMS. In addition, transit amplifying progenitor cells have been proposed to be constitutively migratory (1). *Dcx* labels the entire neuroblast population, yet we found *Dcx*-negative cells that were motile, suggesting that we were observing migratory stem or progenitor cells (84). We therefore directly examined the hypothesis that SVZ astrocytes or transit amplifying progenitor cells may be motile. Despite analyzing close to 900 cells in multiple transgenic lines with 2-photon time-lapse microscopy, we did not find any evidence of astrocyte (stem cells and niche astrocytes) or transit amplifying progenitor cells that were motile (50). The question then arises whether the SVZ stem or progenitor cells can become motile after stroke? This would be extremely interesting since these precursor cells are less committed and may better effectuate repair than neuroblasts. Indeed there is evidence that multiple types of SVZ cells migrate into the striatum after injury. SVZ cells with all the characteristics of transit amplifying progenitor cells emigrate towards the striatum following the 6-hydroxydopamine model of Parkinson's disease (19). Furthermore, using tamoxifen-inducible Cre-recombinase reporter mice driven by the nestin promoter (nestin-CreER^{T2}:R26R-YFP), which permit labeling and fate-mapping of nestin+ SVZ cells, Cunningham and colleagues report significant waves of astrocyte and oligodendrocyte-precursor cell emigration after ischemic stroke (58). In their studies, astrocyte emigration appears to precede neuroblast emigration. It remains to be determined whether the same mechanisms facilitate emigration of other SVZ cell types and to what extent they interact with emigrating neuroblasts.

Several sublineages of SVZ neuroblasts have recently been discovered (53, 80, 117, 121, 123, 131). The lineages arise from distinct dorsoventral embryonic regions, their stem cells reside in spatially nested domains of the adult SVZ, and they give rise to different interneurons in the olfactory bulbs. These comprise periglomerular calretinin-, calbindin-, and tyrosine hydroxylase-positive neurons, as well as GABA-ergic granule neurons. These new findings have given rise to myriad questions including whether the migratory properties of the

lineages are equivalent. SVZ-derived interneuron migration ends either in the periglomerular or granule cell layers during the last stage of migration in the olfactory bulb, suggesting the lineages differ in their response to stop signals in the OB. Thus far, the greatest migratory difference seems to be between periglomerular neurons and granule neurons, simply because the two groups arrest migration in distinct layers of the olfactory bulb. Do certain lineage(s) of neuroblasts emigrate preferentially after stroke? Interestingly, a couple of studies suggest that calretinin+ neurons preferentially emigrate; they were frequently found in neonatal hypoxia/ischaemia injuries (130) and stroke (61). To directly answer the question of differences in SVZ lineage emigration, radial glia viral infection at P0 or transgenic reporter lines could be used to label specific SVZ subpopulations.

Stroke may induce fate switches in SVZ cells

There has been much controversy and inconsistency as to whether emigrating neuroblasts are able to generate projection neurons, the cells mostly responsible for functional loss after stroke. Early studies in rats (5, 91) reported the generation of striatal medium spiny neurons, while work in mice suggested that only parvalbumin+ striatal interneurons (111), or calretinin+ interneurons were generated (61). The conflicting results could be explained by inter-species differences, or the heterogeneity of SVZ cell types described above. However, it is important to point out that normally the SVZ makes small interneurons with short or no axons. Nevertheless, SVZ cells have been shown to emigrate into the striatum, survive, and differentiate into neurons with evidence of synaptic formation and electrophysiological activity (36). It is not known whether these neurons form long projections to target structures such as the globus pallidus after stroke. Focal apoptosis-induced neurogenesis in periventricular regions gave rise to a few projection neurons which were retrograde labeled from their projection targets (72). Also, SVZ progenitors can be re-specified into a glutamatergic phenotype and exhibit cortical recruitment after injury (10, 13). Thus, a key goal is to coax SVZ neuroblasts to differentiate into projection neurons. Partial reprogramming with induced pluripotent stem cell approaches may revert SVZ progenitors to the fate competence their forebears exhibited in the embryonic lateral ganglionic eminence, thus allowing them to generate striatal projection neurons.

Stroke may also re-specify the fate of SVZ neuroblasts and induce glial phenotypes. SVZ neuroblast plasticity was demonstrated when they were isolated via PSA-NCAM expression based magnetic cell sorting, transplanted into the striatum, and differentiated into astrocytic and oligodendrocytic cells (100). In a dramatic recent example, SVZ neuroblasts could express glial proteins, mediated by the BMP antagonist chordin after a demyelinating lesion (39). Thus, the SVZ may also contribute glial precursors to restore or replace oligodendrocytes or astrocytes lost to the injury.

SVZ astrocyte and ependymal cell alterations after stroke

Adult SVZ astrocytes envelop migrating neuroblasts in a glial tube-like configuration (21, 22). Although SVZ neuroblasts are capable of migrating in chains in the absence of SVZ

astrocyte tubes (120), it is clear that astrocytes contribute to neuroblast migration *in vivo*. SVZ astrocytes regulate GABA that decreases neuroblast speed (11), and they also dampen BDNF's effect on migration by reducing its bioavailability via TrkB receptors (104). It may also simply be that the morphology of SVZ astrocytes helps guide them to the RMS and OB; they bear long processes that elongate in the anterior/posterior direction (81). Mice deficient in ErbB4 signaling exhibit disruption of SVZ astrocyte cytoarchitecture and concurrent alterations in SVZ migration (4). The extent to which SVZ astrocyte cytoarchitecture changes after stroke and whether such morphological changes contribute to emigration is unclear but deserves to be examined.

Both SVZ astrocytes and ependymal cells are derived from radial glia, the stem cells of embryonic neural development (105, 115). The role played by GFAP+ SVZ astrocytes in neuroblast emigration is not thoroughly understood. Early reports suggested that new astrocytic processes emanate from the SVZ into the striatum after injury (110) and that neuroblast emigration into the striatum occurs along vimentin+ astrocytic processes in a similar manner to the SVZ-RMS-OB pathway (91, 111). Radial glia-like cells have been found in the uninjured murine brain, emanating from the ventral SVZ into the nucleus accumbens (109). These specialized astrocyte-like cells express BLBP and GLAST, markers of radial glia and are juxtaposed to Dcx+ neuroblasts that appear to migrate along them (109, 129). Although a cerebral cortex model of TBI does not seem to alter rates of ventral emigration along these fibers, it would be interesting to test if ischemic injuries of the ventral forebrain do so. Until now, it has been difficult to ascertain the exact role of normal and post-injury adult radial glia-like cells, but it is intriguing to speculate that injuries may partially reprogram SVZ astrocytes or ependymal cells to express a radial glial phenotype. Were this true, they could not only provide a convenient substrate for emigration but in theory could increase the fate potential of their progeny.

The role of ependymal cells after stroke remains poorly understood, although clues are emerging suggesting that they may contribute to the neurogenic response. Although ependymal cells are largely post-mitotic in the normal brain (105), they can proliferate and give rise to neuroblasts and astrocytes after cerebral ischemia (15). In another study, S100 β ⁺ ependymal cells incorporated BrdU and took on a radial glia-like morphology, extending processes into the SVZ (136). Interestingly, some neuroblasts are closely associated with these radial glial-like processes, reminiscent of migration during cortical development (87) and the radial glia transformation of SVZ astrocytes described above. An obvious and unanswered question from this observation is whether ependymal cells have a role in facilitating neuroblast emigration out of the SVZ. Ependymal cells regulate the SVZ niche through expression of Noggin, which is a BMP antagonist and promotes neurogenesis (60). As discussed earlier, the beating cilia of ependymal cells generates CSF flow and creates the Slit gradient shown to direct neuroblasts towards the OB. Stroke is one of the most common causes of non-communicating hydrocephalus in humans and it will be interesting to examine if loss of ependymal cells after stroke lead to disruption of normal CSF flow. Thus, it is likely that ependymal cells contribute to the post-stroke SVZ response, by regulating the niche and even becoming neurogenic themselves.

A role for SVZ microglia in post-stroke SVZ response?

Several data suggest that SVZ microglia are specialized and could contribute to SVZ neuroblast emigration. As noted above, SVZ microglia in the SVZ are normally semi-activated (31). Interestingly, the same study showed that compared to adjacent striatal and cortical microglia, they have a dampened activation response to cerebral cortex lesions. Another set of data suggesting SVZ microglia are a breed apart showed their rates of proliferation *in vitro* is far greater than non-neurogenic niche microglial (73). We found that after cortical lesions, fluorescent bead-labeled SVZ microglia emigrated rapidly toward the lesion, along paths very similar to those subsequently taken by neuroblasts (31). In other studies, a viral model of MS in which SVZ neuroblasts emigrate to periventricular regions was characterized by very early infiltration into these regions of hematopoietic cells (30). We hypothesize that SVZ microglia could influence SVZ neuroblast emigration by clearing paths or creating molecular gradients for neuroblast emigration.

The most commonly used MCAO models do not result in lesions which encompass the SVZ. Thus, it is unlikely that significant SVZ cell death occurs after stroke, predicting that SVZ microglial function should not be significantly altered. Thored and colleagues have shown that similar to cortical lesions, after stroke, SVZ microglia activation is not as pronounced as in the adjacent ischemic striatum (114). However, they also showed that SVZ microglia upregulated insulin-like growth factor-1 (IGF-1) after stroke which boosted proliferation and neurogenesis. This is interesting since activated microglia dampen hippocampal neurogenesis (25, 82). It is clear that the role of microglia in the post-stroke SVZ deserves further investigation since they may significantly contribute to the regulation of neurogenesis.

The SVZ vasculature is altered after ischemic stroke

Seven days after MCAO, endothelial proliferation in the SVZ is increased (113). Similarly, 7 days following thermo-coagulatory cortical lesions, SVZ blood vessels increase vascular permeability, with concomitant increases in endothelial cell proliferation and VEGF expression (32). VEGF and MMPs which are upregulated in the SVZ after focal ischemia are known to increase blood vessel permeability (32). Furthermore, given the presence of the vascular scaffold and the molecular regulation of neuroblast migration via BDNF signaling (104), it will be interesting to see how these are altered to facilitate neuroblast emigration after focal ischaemia. The orientation of blood vessels in the SVZ may be diverted after stroke to orient cell migration from rostral to lateral.

The role of hypoxia in the SVZ after ischemic stroke

The triggers for the changes in the SVZ niche described above are not clear. Cellular and molecular signals from the inflammatory response in the ischemic tissue clearly play important roles. However, after the MCAO model of ischemic stroke, the SVZ is transiently rendered hypoxic to <10 mm Hg (113). Hypoxia induces upregulation of hypoxia-inducible factor 1 alpha (Hif-1 α) in neural precursor cells (34). Hif-1 α , a transcription factor with downstream targets such as VEGF and erythropoietin, is involved in many critical functions, including angiogenesis, cell proliferation, and glucose

metabolism (94). Therefore, even transient hypoxia, which does not lead to profound cell death, can have considerable effects on the neurogenic niche.

Conclusion and Future Directions

The migration of SVZ neuroblasts towards areas of ischemic injury remains one of the most remarkable aspects of adult neurogenesis. A key question of various forms of cellular replacement therapy for neurological diseases is one of delivery to the site of injury. Therefore, in addition to exploring their therapeutic potential, a better understanding of mechanisms which regulate neuroblast emigration after stroke will help address this question. Much progress has been made to understand the cellular and molecular interactions which facilitate neuroblast emigration, and we are beginning to grasp that significant and complex changes occur at a system/niche level, both in the ischemic/peri-ischemic tissue, and in the SVZ neurogenic niche.

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Address correspondence to:

Francis G. Szele
Department of Physiology, Anatomy and Genetics
University of Oxford
Oxford
United Kingdom

E-mail: francis.szele@dpag.ox.ac.uk

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Abbreviations Used

Ang-1 = angiopoietin
BDNF = brain-derived neurotrophic factor
BMP = bone morphogenic protein
BrdU = 5-bromo-2-deoxyuridine
CCR2 = chemokine (C-C motif) receptor
CSF = cerebral spinal fluid
CXCR4 = C-X-C chemokine receptor type 4
Dcx = doublecortin
GDNF = glial cell-derived neurotrophic factor
GFAP = glial fibrillary acidic protein
Hif-1 α = hypoxia-inducible factor 1 alpha
IGF-1 = insulin growth factor-1
MCAO = middle cerebral artery occlusion
MCP-1 = monocyte chemoattractant protein-1
MMP = matrix metalloproteinase
OB = olfactory bulb
PSA-NCAM = polysialylated neuronal cell adhesion molecule
RMS = rostral migratory stream
RT-PCR = reverse transcription polymerase chain reaction
SDF-1 α = stromal derived factor 1 alpha
SGZ = subgranular zone
SVZ = subventricular zone
TBI = traumatic brain injury
VEGF = vascular endothelial growth factor
VEGFR2 = vascular endothelial growth factor receptor 2