Chapter 8

A Vascular Perspective on Neurogenesis

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Additional information is available at the end of the chapter

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1. Introduction

The vasculature has been identified as a prominent feature across several stem cell niches, suggesting a crucial role in their regulation and maintenance. While a critical component of every organ and tissue, it has adopted specific features for specialized microenvironments. Most notably, the subventricular (SVZ) and subgranular (SGZ) zones of the adult brain harbor unique vascular plexi that are finely tuned to support neural stem cell (NSC) function and behavior. Whether it is through direct contact with, and paracrine signaling from, endothelial and mural cells that comprise blood vessels, or systemically via distribution of soluble factors from the circulation, the vasculature serves as a multifaceted stem cell niche regulator. As emerging evidence continues to emphasize the importance of vascular and nervous system interdependency, it is clear that the vascular compartment in the neural stem cell niche is uniquely poised to coordinate responses of both systems to ensure proper maintenance and regeneration, as needed.

2. Vascular composition and function in the brain

2.1. Brain vascular endothelium

The vasculature is a critical component of every organ and tissue, and has the remarkable ability to integrate systemic signals and directly regulate the local microenvironment. In general, the vasculature provides nutrients and protection; however, it has adopted specialized features for specialized microenvironments. Accordingly, not only does the composition of blood vessels vary (e.g. smooth muscle cell and pericyte coverage, perivascular cell recruitment, extracellular matrix (ECM) deposition), but heterogeneity among the endothelium itself is recognized. Indeed, this endothelial cell (EC) heterogene-

ity may be at the heart of their vast regulatory potential, allowing control of multiple processes. These include, but are not limited to, angiogenesis, microvascular permeability, vessel wall tone, coagulation and anticoagulation, blood cell generation and trafficking, inflammation, and microenvironment regulation [1-3]. From a functional standpoint, the endothelium displays an incredible division of labor, where a spectrum of responses, both to internal and external stimuli, is carried out. Thus, heterogeneity among the vascular endothelium is a core property bestowing vast regulatory potential [4].

Within the brain, capillaries are tightly integrated within the neural parenchyma. As arterioles traverse deeper into the brain, they become progressively smaller and lose portions of their smooth muscle layer, and are thus termed cerebral capillaries [5]. These capillaries are tubes of EC that are variably surrounded by pericytes or pericyte processes, astrocytes, neurons, and ECM. This minimal composition of capillaries allows for a unique interface that facilitates communication with the underlying tissue environment. Distribution of cerebral capillaries within the brain is relatively heterogeneous, due to regional differences in blood flow and metabolic demand. Owing to their thin walls and slow rate of blood flow, capillaries are engineered to minimize diffusion path length and optimize diffusion time [2]. Surprisingly, the average luminal diameter is ~4.8 μm [6], a length that is somewhat smaller than the diameter of an erythrocyte, requiring red blood cells to deform slightly as they progress through these vessels.

The brain endothelium is characterized by unique features that allow it to selectively control permeability between blood and the central nervous system, which manifests as the blood-brain-barrier (BBB). Specifically, this endothelium is discontinuous and nonfenestrated, with few caveolae at the luminal surface and large numbers of mitochondria [7]. The barrier function is mediated by both a physical barrier, owing to high expression of tight interendothelial junctions, and a highly selective transport system. Interestingly, the basal lamina in capillary beds is common with that of perivascular astrocytic endfeet and pericytes, allowing direct contact of neural cells with the underlying endothelium [8]. These capillary EC are ~0.1 μm thick, giving them a cell volume of only ~20μL/cm^3, cumulatively amounting to just 0.2% of the volume of the entire brain [9]. As the demand for energy must be matched by nutrient supply, the remarkable thinness and surface area of these EC allows for quick, selective, and efficient transport across endothelial membranes.

3. Development and vascularization of the brain

3.1. Embryonic brain development

The initial steps of central nervous system (CNS) development occur prior to gastrulation, beginning with neural plate induction from ectoderm [10]. The neural plate is then patterned along its anterioposterior (AP) and dorsoventral (DV) axes in a dose-dependent fashion, where gradients of secreted morphogens specify distinct neural fates by inducing expression of region-specific transcription factors. It has been reported that fibroblast growth factor (FGF), retinioic acid, and secreted Wnt family members determine AP polarity, while bone morpho-

genetic proteins (BMPs) and members of the Hedgehog family control mediolateral polarity [11-18]. As the neural tube fuses from the neural plate, the neuroepithelium begins to undergo a complex series of morphological transformations, and begins expressing proteins such as vimentin and nestin, thus marking the first appearance of radial glia in the cerebral cortex [19]. The appearance of projection neurons, originating from the neuroepithelium between E8.5 and E10, is followed closely by the onset of neurogenesis at E11 [20].

In the early stages of embryonic neurogenesis (E11-E13), the first mitotic cortical neurons leave the VZ to form the preplate via interkinetic nuclear migration, independent of radial fibers, creating an intermediate zone (IZ) where postmitotic neurons accumulate to commence differentiation [21]. Subsequently generated neurons continue to leave the VZ and enter the preplate to form the CP (E13-18), further subdividing this region into the subplate and marginal zone (MZ), where the latter becomes lamina I, the most superficial layer of the brain [22]. At this same time, SVZ progenitors generated in the VZ divide and expand the progenitor pool. Excluding layer I, subsequent development is said to occur in an "inside-out" manner, where earlier-born neurons reside in the deeper layers (V, VI), and later-born neurons occupy the more superficial layers (II,III) [23].

Between E11 and E18, neurons proceed radially from the ventricular zone (VZ) to the CP, while interneurons originating from the ganglionic eminence migrate tangentially, traveling perpendicular to radial fibers and parallel to the pial surface [24]. As these neurons reach their final destination, migration ceases, detachment from radial glia occurs, and differentiation begins. Cell lineage studies have revealed that proliferative progenitors of the neural epithelium are for the most part multipotent up until their final mitosis [25-30]. However, committed progenitors appear to be an exception, as their existence in secondary proliferative zones, such as the SVZ and other regions in the adult, have been documented to give rise to various neuronal subtypes, astrocytes, and glia [31, 32].

3.2. Vascularization of the brain

The brain, in general, has a specialized vasculature relative to other organs, and there are specialized microenvironments within the brain that exhibit distinct characteristics and functions. For example, it has been proposed that a unique vascular plexus exists in neurogenic regions of the brain, both during embryonic and adult neurogenesis [33-35], where EC-NSC interactions aid in stem cell maintenance while promoting cell division and NSC expansion [36, 37]. How then, does the vasculature become specialized to fulfill such distinct roles, even within the same tissue?

During early stages of embryonic brain development, the perivascular neural plexus (PVNP) forms around the neural tube at E8.5-E10, from anterior to posterior, yet does not invade the neural tissue until later in development [38]. During E10-E11, the periventricular vascular network advances into the dorsal telencephalon, and by E11 forms a lattice shaped plexus. However, a distinct vascular plexus of periventricular vessels appears in the ventral telencephalon at E9, and by E13 EC invasion into the ventricular zone (VZ) and subventricular zone (SVZ) has generated radially oriented capillaries that extend towards the cortical plate (CP), eventually joining the pial vasculature [39, 40].

Recently, the identification of distinct vascular origins within the developing brain [41] suggests that specialized features of vascular beds of adult germinal regions may begin during embryonic development and persist into adolescence. Previously, the long-standing model of CNS angiogenesis suggested that pial vessels, originating from the perineural plexus surrounding the neural tube, passively sprout into the brain parenchyma and extend radial branches toward the ventricles, where the neurogenic VZ and SVZ are established. Upon arrival to the periventricular area, these pial vessels were thought to form new branches, reverse direction to grow towards the pial surface, and ultimately branch into plexuses [42-44]. However, recent studies suggest that pial and periventricular vessels not only have distinct origins, but develop along independent schedules. In fact, periventricular vessels in the ventral telencephalon are thought to originate from a basal vessel, most likely arising from pharangeal arch arteries [42, 45], situated on the floor of the telencephalic vesicle within the basal ganglia primoridum. As early as E9, pial vessels are observed to encircle the telencephalon, while a spatially distinct population of periventricular vessels is restricted to the ventral telencephalon. From E9-E10, the basal vessel matures to produce periventricular branches in a ventral-to-dorsal and lateral-medial direction, eventually giving rise to a vascular lattice in the dorsal telencephalon. As narrow branches from the periventricular and pial networks fuse, the first arterial-venous communication is thought to occur, as early reports suggest venous sinuses and arterial networks develop from pial and periventricular vessels, respectively [41, 45]. At E15, the first tangential vessels to the pial surface emerge in the intermediate zone, and by E16, these vessels appear in the presumptive rostral migratory stream (RMS). By E18, extensive vascular remodeling has taken place, and the ventricular plexus loses much of its definition. However, upon reaching postnatal ages and adulthood, blood vessels begin to align themselves longitudinally and parallel to each other in the direction of the RMS, presenting a more homogeneous structure [35, 40].

Interestingly, the periventricular vascular network is present in the telencephalon prior to the formation of neuronal networks and before the appearance of radial units and striosome-matrix compartments in the dorsal and ventral telencephalon, respectively. Thus, the periventricular network is temporally and spatially poised to influence neural maturation, as well as guide tangential migration in the developing brain [41]. A similar vascular niche for NSC has been reported to exist in the adult SVZ and SGZ, and may have been established early during embryonic brain development. This suggests that the vasculature may be critical in promoting and regulating neural development.

3.3. Establishment of neurogenic regions of the brain

During brain development, three different NSPC types make their appearance in a tightly coordinated spatiotemporal manner, seeding the brain with committed progenitors that differentiate into the various cell types of the mature brain. The first of these to appear are pseudostratified epithelial cells termed radial glia, regarded as the *bona fide* NSC in the embryonic VZ [46, 47]. Morphological studies have identified two processes emanating from their cell bodies, suggesting an inherent bipolar nature. A short and thick apical process directed towards the ventricle is thought to anchor radial glia, while a longer basal radial fiber

projects towards the basement membrane of the pia mater, acting as a scaffold for prospective neuronal migration [21, 48]. These radial fibers are often observed to contact blood vessels and exhibit multiple branched endfeet at the pial surface [49]. Interestingly, their apical regions are typically folded and contain a single cilium [50, 51], reminiscent of the proposed location, structural morphology, and vascular contacts of adult NSC in the SVZ.

During the early stages of cortical development, the cerebral cortex is composed almost exclusively of proliferative radial glia dividing at the ventricular surface in the VZ [52]. As proliferating radial glia progress through the cell cycle, they undergo interkinetic nuclear migration, where the nucleus migrates away from the ventricle during G1 phase, and enters S phase at the top of the VZ. Upon return through the VZ to the ventricular surface, they proceed through G2 phase and M-phase, respectively [19, 52-54]. A switch from symmetric self-renewing to asymmetric neurogenic divisions occurs as development proceeds, leading to pairs of daughter cells with distinct progenitor or early neuronal fates; symmetric divisions have also occasionally been observed to produce early neurons or intermediate progenitor cells (IPC) [19, 23, 49]. However, during peak neurogenesis, radial glia give rise to one radial glial cell, and either one post-mitotic neuron or a neuronally committed IPC [49, 55]. Similarly in adult neurogenesis, adult NSC asymmetrically divide to generate transit-amplifying cells that produce committed progenitors. In both cases, regulation of the symmetry of cell division is critical, and ultimately controls cerebral cortical size during brain development [52].

At the onset of neurogenesis, radial glia progeny migrate away from the ventricle and begin to establish the first layers of the developing brain, separate from the VZ. IPC establish the SVZ as a distinct proliferative region, while young cortical neurons migrate to a superficial position to establish the cortical plate [48]. These migrating cortical neurons are intimately associated with the long pial fiber of radial glia, utilizing it to traverse relatively long distances to the overlying cortex in a process termed radial migration. Once telophase is complete and radial glia have entered M-phase, the apical plasma membrane becomes unequally segregated into the two daughter cells. Interestingly, the apical daughter inherits a larger portion of the membrane while the basal daughter receives a smaller proportion in addition to the radial fiber, indicating the latter assumes the stem cell radial glia fate [46, 47, 49, 56]. However, this is not absolute, as instances of basal daughters becoming post-mitotic and apical daughters remaining proliferative have been reported. Instead, it has been suggested that fate decisions involving asymmetric division may also depend on developmental stage [47, 48]. Thus, the function of radial glia is two-fold, wherein they generate and guide migration of their own daughter cells [52, 57].

After the VZ reaches its maximal size during midstage cortical neurogenesis, the VZ begins to shrink while the SVZ begins to expand [57]. Derived from radial glia, IPC are the first cell types to initially seed the SVZ [48]. While some observations describe the distribution of IPC throughout the upper VZ and lower intermediate zones [49, 58], they are predominantly concentrated in the SVZ, where they almost exclusively divide symmetrically to generate postmitotic daughter neurons [59-62]. In contrast to radial glia, IPC are multipolar, extending and retracting multiple processes [19, 49]. Additionally, they do not appear to sustain contact with either the ventricular or pial surfaces, and are in fact defined by their lack of prominent

apical or basal processes and a basal location relative to the apical surface [52]. While their contact with neighboring blood vessels has not been confirmed, their appearance in the cortex seems to follow that of blood vessel invasion in the cortical wall [19]. Furthermore, behavioral differences between radial glia and IPC have been noted. IP cells progress through the cell cycle away from the ventricle, and do not undergo interkinetic nuclear migration, thus, allowing differentiation from radial glia based on spatial location during mitosis [19, 63].

At later stages of cortical development, the SVZ progenitor pool continues to expand via IPC symmetric divisions. Further aiding in expansion, progenitors from the ventral telencephalon may even migrate dorsally to contribute to the SVZ progenitor pool [19]. Upon completion of cortical neurogenesis, radial glia transition into astrocytes and exit the VZ, leaving a single layer of ependymal cells lining the ventricle [57]. Consequently, proliferative IPC become the predominant component of the cortical progenitor pool, and eventually comprise the majority of mitotic progenitors as embryonic neurogenesis nears completion. Interestingly, while only a single layer of VZ-derived ependymal cells remains postnatally, IPC are present in large numbers in the postnatal SVZ, and persist into adulthood [19]. Aside from generating cortical neurons, postnatal and adult progenitors have been demonstrated to generate neurons destined for the olfactory bulb [49, 58, 64], and possibly all excitatory neurons of the upper cortical layers [58]. Thus, IPC in the SVZ play a vital role in cortical neurogenesis during embryonic development as well as in the adult.

Interestingly, a novel progenitor type termed the outer SVZ (OSVZ) progenitor has recently been identified and appears to exist in all mammals, albeit to varying extents [52]. These progenitors have a modified radial morphology, but are exclusively localized to the SVZ. OSVZ cells are enriched in mammals with larger cerebral cortices, and their appearance during mid-gestation seems to coincide with the onset of neurogenesis [52, 65-69]. OSVZ progenitors are peculiar in that they possess characteristics reminiscent of both radial glia and IPC. They display radial morphology and express radial glial markers paired box protein-6 (Pax6), phospho-vimentin, glial fibrillary acidic protein (GFAP), and brain lipid-binding protein (BLBP), and also display random cleavage planes, where both proliferative self-renewing symmetrical divisions and asymmetric divisions producing OSVZ daughter and progenitor have been reported. However, an apical process is absent in these cells while their basal process is retained throughout mitosis [65-67].

3.4. Vascular cues during embryonic neurogenesis

It has been suggested that the developing cortical vasculature within the SVZ promotes IPC expansion during neurogenesis by providing a suitable microenvironment for IPC accumulation and division [39]. It is noteworthy that brain EC share similar molecular profiles with their neighboring NSC. For example, ventral and dorsal EC, as well as NSC, express Dlx1/5 and Nkx2.1, and Pax6, respectively, while pial EC are negative for all three [41]. This strongly suggests that mechanisms of patterning during early angiogenesis and neurogenesis in the brain are shared.

A strong association between NSC and blood vessels exists during embryonic and adult neurogenesis, especially in regard to cell cycle regulation [33-35]. The filopodia of endothelial tip cells

extend towards the ventricular surface where radial glia divide, and even interact with pial fibers of radial glia in the hindbrain [39]. Additionally, dividing cells in the embryonic SVZ reside statistically closer to blood vessels than predicted by chance, and recent studies report a synchronization of SVZ cell division with the formation of ventricular vascular plexuses [40]. This vascular relationship is apparent in the emerging RMS as well, where dividing cells have been reported to associate with blood vessels at E16, E18, and P4 [35]. On the other hand, progenitor migration in the RMS does not seem to rely on the vasculature, as the vast majority of neuroblast neurites in P4 RMS have little or no association with blood vessels [35]. This is in contrast to radial migration outside the RMS, where postmitotic doublecortin (DCX) and glial fibrillary acidic protein (GFAP)-positive cells associate with blood vessels during migration into superficial cortical layers [40]. Interestingly, IPC have been suggested to maintain a stronger interaction with blood vessels, as T-brain gene-2 (Tbr2)-eGFP progenitors in M-phase reside closer to blood vessels when compared to total phosphohistone H3-positive progenitors [40]. Furthermore, these dividing IPC are often found at vessel branch points, which have previously been observed to be sites of glial tumor mitosis and subsequent migration [70].

Mounting evidence suggests that Tbr2 progenitors are temporally and spatially correlated with the appearance of cortical vasculature, and even follow and mimic the pattern of nascent blood vessels. Similarly, the positions of IPC during mitosis, migration and differentiation are all correlated with EC development in the SVZ. Even detection of Tbr2-positive cells correlates with the appearance of vascularization, as Tbr2 cell density is highest in the vascularized lateral regions as compared to the nearly avascular medial regions in the dorsal cortex of E12 embryos [39]. Moreover, ectopic overexpression of vascular endothelial growth factor (VEGF)-A causes IPC to follow a pattern of aberrant vascular growth. Interestingly, leading EC tip cells have been observed to associate with some Tbr2-positive IPC in M-phase, suggesting a functional interaction during division. These data collectively suggest the SVZ vasculature serves as a niche for mitotic IPC [39], and provides instructive and permissive cues for stem and progenitor cell expansion and tissue invasion [71].

3.5. Parallels between embryonic neurogenesis and adult neurogenesis

Similarities between embryonic and adult NSC at the cellular level and across their extracellular microenvironments have been reported, and selective labeling of radial glia has demonstrated a direct link between these cells, indicating that NSC are most likely contained within the neuroepithelial-radial glia-astrocyte lineage [72, 73]. Furthermore, reports indicate adult SVZ NSC retain specialized characteristics of radial glia. However, the molecular characteristics that confer progenitor potential onto astroglial cells and distinguish them from those with normal support function remain largely unknown [53].

From adult NSC, also referred to as Type B cells in the SVZ, an apical process at times intercalates between ependymal cells lining the lateral ventricular surface, potentially serving to both anchor and present NSC to circulating factors in the cerebrospinal fluid (CSF). Embryonic radial glia also share this apical process, and most likely contain a similar profile of specialized apical junctions at the site of this primary cilium [53]. Similarly, the longer basal process that radial glia extend towards the surface of the brain during embryonic development

is also shared by adult NSC of the SVZ. In the adult SVZ, this basal process projects radially or tangentially, depending on location, eventually terminating in specialized endfeet on the surface of blood vessels [33, 74, 75]. These vascular contacts may be analogous to those of radial glia during development, as branch contacts with the overlying vasculature also occur [53]. This suggests that adult SVZ NSC share core properties with the embryonic radial glia from which they are derived from, allowing them to retain progenitor function throughout life.

These similarities are also observed in adult NSC of the SGZ in the hippocampal dentate gyrus. Early anatomical studies suggest that radial glia in the dentate neurepithelium transition to the different astrocyte populations of the dentate gyrus, including radial astrocytes [76, 77]. While experimental evidence linking radial glia to adult SGZ radial astrocytes is lacking [53], it is possible that this derivation occurs, and further studies will be needed to clarify this lineage relationship. However, the primary cilium of radial glia is present on SGZ progenitors and adult radial astrocytes, and is essential for progenitor proliferation and generation of postnatal radial astrocytes, thus establishing its requirement for neurogenesis. From a signaling standpoint, the primary cilium serves as an integration site for signaling via pathways such as Shh. Interestingly, this cilium seems to be specific to the radial astrocytic NSC pool in the hippocampus. Non-stem cell astrocytes are not affected by lack of primary cilium or Shh signaling, suggesting a unique requirement among these NSC [78, 79].

As in the adult SVZ [80], location seems to dictate specificity, where radial glia in the dorsal telencephalon generate only pyramidal excitatory neurons, while those located in the ventral telencephalon give rise to nonpyramidal inhibitory interneurons [81]. Studies from several mouse models demonstrate that neurons can migrate into the cortical plate (CP) radially or tangentially [82-84]. This type of migration is mirrored in the adult SVZ, where neuroblast progenitors migrate tangentially through the rostral migratory stream towards the olfactory bulb, destined to become inhibitory interneurons. Features of interkinetic nuclear migration are also shared by radial glia and adult NSC. While mitotic cells are found only adjacent to the lumen of the neural tube, nuclei of cells in S-phase are found in the outer half of neural epithelium [19, 54]. This correlation of cell cycle with spatial location occurs in the adult SVZ as well, where basally located blood vessels are proposed to exert growth control over proximal NSC by providing a proliferation-inducing microenvironment. This is in contrast to NSC located apically, either adjacent to or within the ependymal layer, which are immunoreactive for mitotic markers [33, 34, 75, 85].

These findings highlight basic properties that are common to embryonic radial glia and adult SVZ and SGZ NSC. Given the evidence, it is highly likely that a microenvironment similar to the one which supports embryonic neurogenesis persists throughout development and is maintained in the adult neural stem cell niche.

4. The adult NSC niche

4.1. Cellular architecture of the adult SGZ and SVZ

As previously mentioned, two prominent germinal regions of the adult brain have been identified to function as stem cell or neurogenic niches, allowing for continuous generation of

new neurons. The SVZ represents the largest neurogenic stem cell region within the adult brain. It resides within a narrow region of the lateral ventricular wall, roughly four to five cells in diameter [86]. Progenitors generated from this region migrate through the RMS towards the olfactory bulb, where differentiation into at least five interneuron subtypes has been reported. In fact, it is estimated that 30,000–60,000 new neurons are generated in the rodent olfactory bulb per day [87, 88]. Differentiation into oligodendrocytes of the corpus callosal white matter also occurs, albeit to a lesser extent [89, 90]. A second neurogenic region, the SGZ, is located between the hilus and the granule cell layer of the dentate gyrus within the hippocampal formation. In contrast to SVZ progenitors, granule neurons born from this region migrate short distances to the granule cell layer, where differentiation commences [91]. Whether *bona fide* NSC exist in the adult mammalian hippocampus is currently under investigation, as *in vivo* lineage tracing assays suggest that separate progenitors responsible for neurogenesis and gliogenesis exist in the SGZ [92-94].

A group of distinct cell types in the adult SVZ help maintain this specialized niche microenvironment: putative NSC (type B cells), transit-amplifying cells (type C cells), neuroblasts (type A cells), ependymal cells, and specialized vascular endothelium [34, 95]. There is no definitive marker of NSC, and researchers rely on combinations of overlapping markers, as well as spatial location within the niche to identify NSC. Accordingly, NSC are usually identified by their apical location, superficial to the ependymal layer, and slow cell cycle time of ~ 28 days [96]; however, their expression of Sox 2 and 9, GFAP, and CD133/prominin-1 are not exclusive [33, 34, 74]. The presumptive lineage progression from stem cell to more differentiated progenitor is as follows: NSC generate transit amplifying cells that differentiate into migrating neuroblast progenitors.

Non-dividing ependymal cells are multiciliated, and form a single layer lining the ventricle surface, acting as a physical barrier separating the brain parenchyma from the cerebrospinal fluid (CSF) [97]. While ependymal cell cilia contribute to CSF flow, they have also been reported to affect the migration of young neurons by creating gradients of Slit chemorepellents that guide anterior neuroblast migration [98]. An *en face* view of the lateral ventricle wall reveals a planar organization, commonly referred to as "pinwheel organization", where the apical process of NSC is surrounded by a mosaic of ependymal cells [33, 74, 99]. Through studies mapping numbers of ventricle-contacting NSC along the ventricular surface, "hot spots," or areas of stem cell activation, have been revealed [100-102]. Currently a topic of debate is whether ependymal cells can function as multipotent NSC. Previous studies have demonstrated that CD133/prominin-1 positive ependymal cells are in fact multipotent, and during ischemia become active to generate neuroblasts and astrocytes [103, 104]. However, a more recent study using split-Cre technology demonstrated a subset of CD133/prominin-1 positive cells within the ependymal layer are immunoreactive for GFAP, suggesting that these double positive radial-like cells are NSC, not ependymal cells [98, 105].

Two astrocytic populations have been proposed to reside in the SVZ [100]. Type B NSC astrocytes reside underneath the ependymal layer, while non-stem cell astrocytes are more superficial and differ in morphology [33, 34, 74, 99]. NSC are closely associated with ependymal cells, and at times extend a short, apical, non-motile primary cilium that innervates

between the ependyma to directly contact the CSF within the ventricle [33, 74, 99]. While NSC are relatively quiescent, transit-amplifying cells are highly proliferative, and remain localized to the SVZ [95, 100]. Neuroblasts, on the other hand, migrate through astrocytic tubes in the RMS to the olfactory bulb, where interneuron differentiation occurs [106, 107]. Interestingly, experiments using viral targeting and genetic lineage tracing in neonatal and adult mice have revealed that specific subtypes of interneurons in the olfactory bulb are derived from specific locations within dorsal, medial, and ventral portions of the adult SVZ [108-112]. Interestingly, while the vascular beds of the SVZ and SGZ both support adult neurogenesis, the SVZ vasculature is somewhat unique. Differences in permeability, stability, and perivascular cell coverage are thought to account for these differences. NSC and transit-amplifying cells both display an intimate relationship with SVZ blood vessels, as 3-dimensional niche modeling indicates closer proximity and increased vascular contact relative to other SVZ cells. Interestingly, these vascular associations are further exaggerated in niche regeneration models [33, 34]. Additionally, NSC extend a long basal process that terminates on blood vessels in the form of specialized endfeet, potentially serving to integrate vascular cues [33, 74, 99].

4.2. NSC-Vascular EC associations within the SVZ and SGZ

NSC are not randomly distributed throughout the brain; rather, they are concentrated around blood vessels, allowing constant access to circulating signaling molecules and nutrient metabolites [113, 114]. The SVZ and SGZ both present functional neurogenic environments, maintaining neural stem and progenitor cells (NSPC) in poised and undifferentiated states. Regulatory processes within the SVZ niche can be controlled via secreted neurotrophic and angiogenic factors, such as Wnt, Shh, and TGF-β [115]. For example, circulating complement factors have been shown to promote basal and ischemia-induced neurogenesis, and components of complement signaling are present on transit-amplifying cells and neural progenitors *in vivo* [116]. The vascular-derived factors, stromal cell derived factor (SDF)-1 and angiopoietin (Ang)-1, promote neuroblast proliferation and survival [117], and when expressed on EC, serve as "molecular migratory scaffolds" [118, 119] to damaged areas post stroke [120]. EC themselves have even been shown to regulate NSC self-renewal [37, 86, 101, 121]. Interaction with the vascular endothelium may in fact be a vital component of the niche, as radiation-induced disruption of endothelial cell–SGZ precursor cell interaction results in a loss of neurogenic potential, as is the case after NSC transplantation into an irradiated host. [122].

Within the SGZ, nestin-expressing radial astrocytes are localized to areas near blood vessels [91], and there exists an anatomical relationship between proliferating neural progenitors and EC in the hippocampus [101, 123, 124]. In contrast to the SVZ, where angiogenic sprouting and division of EC are absent [34], surges of EC division are said to be spatially and temporally related to clusters of neurogenesis in the SGZ [101]. In the hippocampus, angiogenesis and neurogenesis are coupled, as suggested by high levels of VEGF and VEGFR2 [101], and the shared responsiveness to similar growth factors, e.g., neurotrophins, neuropilins, semaphorins and ephrins [125-127]. In fact, similar bidirectional communication occurs within the higher vocal center (HVC) of the songbird brain, where increases in angiogenesis are said to be coupled to testosterone-induced upregulation of VEGF and VEGFR2 in neurons and astro-

cytes, respectively. The newly generated capillaries produce BDNF (brain-derived neurotrophic factor) that subsequently promotes the recruitment and migration of newly born neurons [121]. Similarly, exercise-induced angiogenesis in the hippocampus is met with increased expression of NGF (nerve growth factor) and BDNF [126], leading to robust increases in neurogenesis [128-130].

In contrast to other areas of the brain, where the BBB is strictly maintained by EC tight junctions, pericyte coverage, and astrocyte endfeet, a modified BBB has been proposed to exist in the SVZ. The lack of astrocyte endfeet and endothelial cell tight junctions, as revealed by aquaporin-4 and zonula occludens-1 immunostaining, respectively, demonstrate major structural differences in the SVZ vascular endothelium. Under homeostatic conditions, the majority of $BrdU^+$ label-retaining NSC and transit amplifying cells reside significantly closer, and frequently make direct contact, to the vasculature; furthermore, after antimitotic cytosine-β-D-arabinofuranoside (Ara-C) treatment to ablate rapidly proliferating cells and induce NSC-mediated repopulation, these vascular associations are increased [33, 34]. At times, transit-amplifying cells can be seen contacting the vasculature at sites lacking astrocyte endfeet and pericyte coverage, suggesting that sites along the vessel are primed for intercellular communication. In fact, fluorescent tracer experiments have proposed that differences in the ultrastructural composition of SVZ blood vessels may be responsible for the detection of sodium fluorescein in the SVZ after perfusion into the blood; however, access to the SVZ from the cerebral spinal fluid cannot be dismissed as an entry point. Integrin-$\alpha 6\beta 1$ partially mediates the adhesion between NSPC and blood vessels through the binding of laminins that are highly concentrated around SVZ blood vessels. *In vitro* and *in vivo* blocking experiments using an integrin-blocking antibody (GoH3) have demonstrated a crucial role for this interaction in the attachment, spreading, and proliferation of NSPC [33].

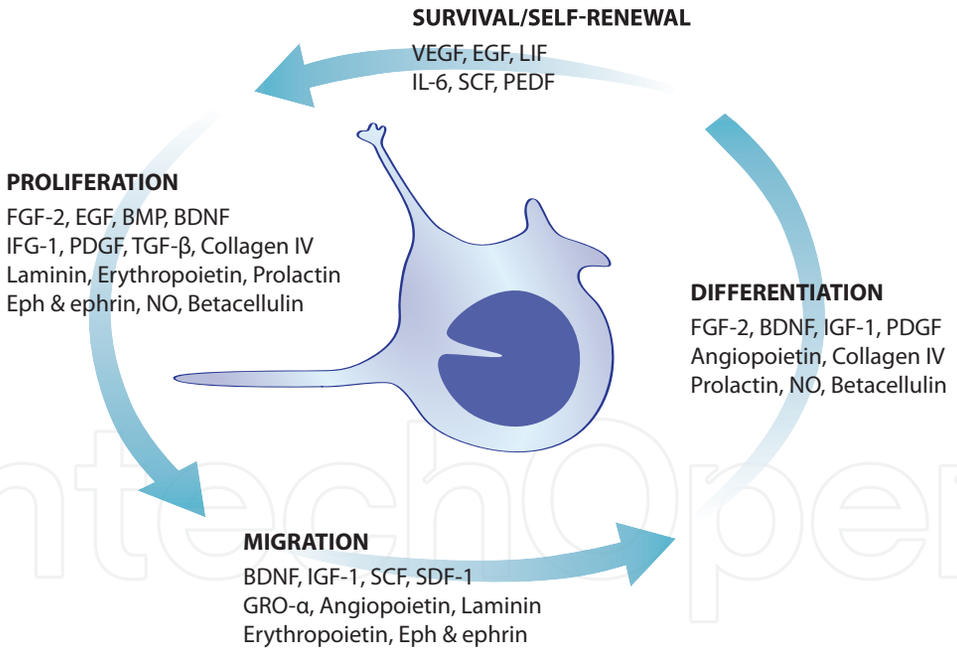
The vascular environment in the RMS has also been suggested to be somewhat specialized, where migrating neuroblasts en route to the olfactory bulb are found closely apposed to blood vessels. Interestingly, blood vessels in this region are parallel and aligned with the direction of the RMS, and the density of vessels is significantly higher when compared to equally cell-dense areas of the brain [131]. It has been reported that over 80% of RMS vessels are lined with migrating neuroblasts [132], and degradation of ECM through vascular EC secretion of matrix metalloproteinases (MMPs) opens a path for their migration [133]. This observation has prompted some to suggest that increased vessel density is a consequence of greater metabolic demand by migrating progenitors.

5. Vascular regulation of adult neurogenesis

5.1. EC regulation of NSPC

Through cytokines and secreted factors, direct contact *in vivo*, or within the confines of the coculture system, EC exert their influence over NSC to regulate fate specification, differentiation, quiescence and proliferation (Figure 1). Early experiments established a crude role for EC regulation of NSC, where increases in neurite outgrowth and maturation, and enhanced

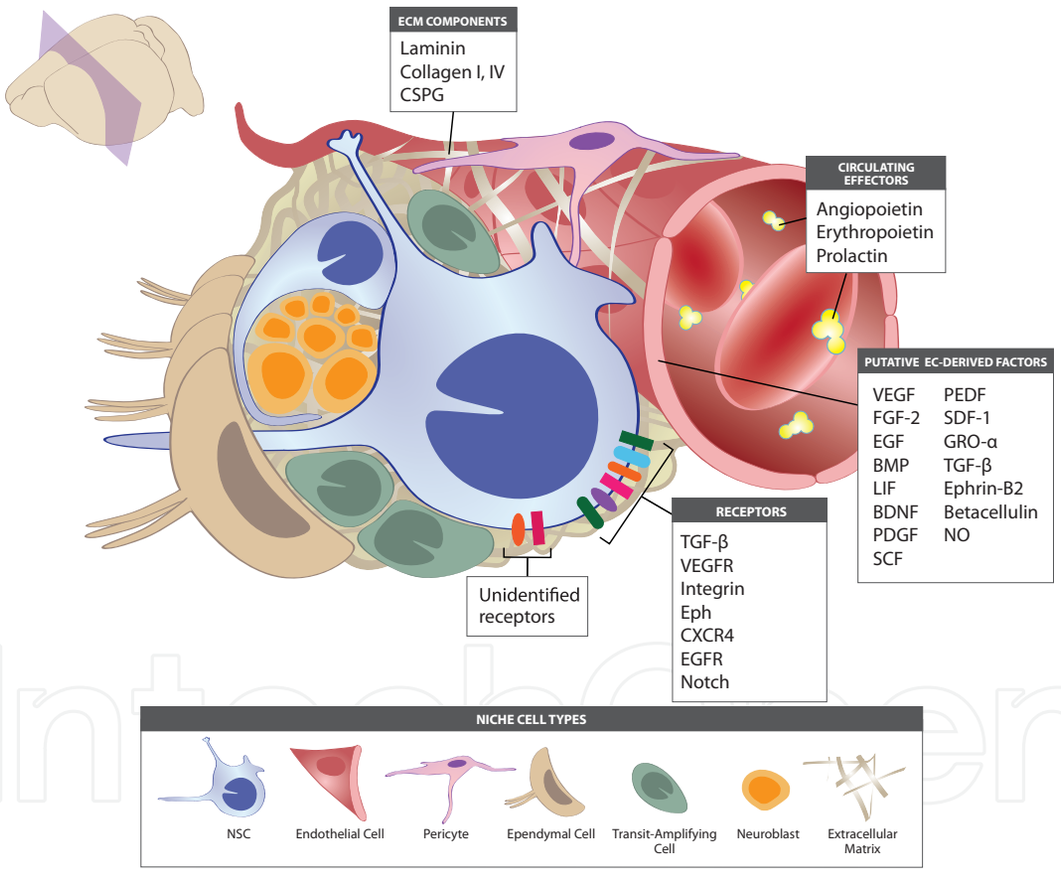
migration were observed in cocultures of SVZ explants with EC [134]. NSC are reported to respond to pro-angiogenic factors [135-137] that promote NSPC proliferation, neurogenesis, synaptogenesis, axonal growth, and neuroprotection [138]. Studies in tumor and stroke models have also uncovered neural regulatory roles of EC. EC can protect stem cells and tumor cells from radiation damage [139, 140], and in preclinical models where NSPC isolated from stroke boundary are cocultured with cerebral EC, significant increases in neural progenitor cell proliferation, neuronal differentiation, and capillary tube formation are observed [141]. Even cotransplantation of EC with NSPC increases survival and proliferation as compared to transplantation of neural precursors alone [142]. Similarly, coculture of adult NSC with EC results in self-renewal and symmetric neural cell division, leading to enhanced neurogenesis through an increase in nestin^{+} precursor number [37]. Interestingly, when stroke-activated rat brain EC are cocultured with SVZ cells, progenitor proliferation and neuron number are increased by 28% and 46%, respectively, when compared to coculture with normal EC. This suggests that activated EC are more potent in promoting neurogenesis, potentially through modulation of Sox2 and Hes6 levels in SVZ cells [143], although further investigation is required to identify the mechanisms involved.



Influence of niche effectors on adult neural stem cell behavior.*Referring to adult suvbentricular and subrangular-zones. BDNF: Brain-derived neurotrophicfactor;GRO-oz Growth-related oncogene alpha; LIF: Leukemiainhibitoryfactor;VEGF: Vascularendothelial growth factor; FGF-2: Fibroblastgrowthfactor-2; EGF: Epidermal growth factor; BMP: Bone morphogenetic protein; PDGF: Platelet-derived growth factor; SCF: Stem cell factor; PEDF: Pigmentepithelial-derived factor; SDF-l: Stromal cell-derived factor-l;TGF[3: Transforming growth factor beta; NO: Nitric oxide; CXCR4: Chemokine receptor type 4; EGFR: Epidermalgrowthfactorreceptor;CSPG: Chondroitin sulfate proteoglycan

Figure 1. Regulatory effects on adult neural stem and progenitors

Mock treatment with serum-rich endothelial growth media induces NSC differentiation into neurons and astrocytes [31], indicating that EC-mediated regulation of NSPC self-renewal and differentiation may be mediated through the release of certain growth factors, including PEDF or VEGF [144, 145]. Cytokine expression profiles of human umbilical vein and cerebral microvascular EC reveal that a large number of chemokines, growth factors, adhesion molecules and ECM proteins are expressed by these cells [146]. Levels of these signaling molecules varied under stimulating and nonstimulating conditions as well as by EC type, highlighting the diverse signaling potential that exists even among endothelial subtypes. Studies of adult neurogenic niche regulation have identified a number of growth factors and secreted molecules, although the origin of some remains unknown (Figure 2).



Sources of vascular – derived adult NSC niche effectors horiginate from the endothelium, circulation, ECM deposition, and perivascular cell types. *Referring to the adult suvbentricular zone BDNF: Brain-derived neurotrophic factor; GRO-a: Growth-related oncogene alpha; LIF: Leukemia inhibitory factor; VEGF: Vascular endothelial growth factor; FGF-2: Fibroblast growth factor-2; EGF: Epidermal growth factor; BMP: Bone morphogenetic protein; PDGF: Platelet-derived growth factor; SCF: Stem cell factor; PEDF: Pigment epithelial-derived factor ; SDF-1: Stromal cell-derived factor-1; TGF_: Transforming growth factor beta; NO: Nitric oxide; CXCR4: Chemokine receptor type 4; EGFR: Epidermal growth factor receptor; CSPG: Chondroitin sulfate proteoglycan

Figure 2. Putative vascular – derived regulators of the adult neural stem cell niche*

The vascular-derived molecules shown to locally regulate the adult NSC niche include leukemia inhibitory factor (LIF), brain-derived neurotrophic factor (BDNF), VEGF, platelet-derived growth factor (PDGF), pigment epithelial-derived factor (PEDF), betacellulin (BTC), and laminins and integrins [33, 121, 147]. However, there are additional factors reported to influence NSPC behavior which may be derived from the NSC niche vasculature, although this has not yet been demonstrated, including fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), interleukin-6 (IL-6), stem cell factor (SCF), insulin growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), bone morphogenic proteins (BMP), SDF-1/CXCR4, collagen IV, Eph/ephrins, angiopoietin, nitric oxide (NO), erythropoietin and prolactins. We review advances made toward understanding the cellular and molecular role of these factors since last reviewed [148].

5.2. Endothelium-derived niche effectors

5.2.1. VEGFs

VEGF signaling is a complex signaling hierarchy involving several isoforms (e.g., VEF-A, -B, -C, -D) that result from alternative splicing of the *VEGF* gene. VEGFs are highly implicated in NSPC survival, proliferation, and neuroblast migration and maturation [149-154]. Along with the recent identification of VEGFR3/Flt4 expression in the adult SVZ, all corresponding receptors, including VEGFR1/Flt1 and VEGFR2/Flk1, are expressed within the NSPC pool [149, 154, 155]. While VEGFR1 negatively regulates adult olfactory neurogenesis and RMS migration by altering VEGF-A bioavailability, VEGFR2 and VEGFR3 both appear to positively regulate neurogenesis [133, 155]; in addition, VEGFR2 has also been reported to affect vascular proliferation [154]. This ability of VEGF family members to regulate both neurogenesis and angiogenesis may be important in clinical settings of intracerebral hemorrhage, where transplantation of human NSPC overexpressing VEGF have been shown to increase microvessel density and promote NSPC engraftment in sites of tissue damage [156, 157].

In VEGFR1 signaling-deficient (Flt-1 $TK^{-/-}$) mice, the increased levels of VEGF-A and subsequent phospohorylation of VEGFR2 in NPSC are thought to account for the altered RMS migration, demonstrating a critical role for VEGF-A in this process [154]. Reported to be required for hippocampal neurogenesis in the adult rat [145], EC, ependymal cells and the choroid plexus secrete VEGF at neurogenic sites, which serves as a survival factor to stimulate NSPC self-renewal. Neurospheres, as well as reactive astrocytes, have been shown to express VEGF-A [158, 159], and infusion into the lateral ventricle after cerebral ischemia acts as a trophic survival factor for NSPC and increases neurogenesis, most likely through the VEGFR2/Flk-1 receptor [37, 150, 152]. Similarly, other studies suggest that *in vitro* VEGF stimulation increases the number of BrdU-labeled precursors, which is attenuated in the presence of SU1598, a Flk-1 receptor tyrosine kinase inhibitor, further supporting mediation through VEGFR2/Flk-1 [123]. Although VEGF-A is reported to have a direct role in signaling during development [101, 123, 150], evidence also supports an indirect role when it is secreted by ependymal cells, through the stimulated release of BDNF from EC [121, 152].

However, in experiments comparing the numbers of primary Ki67$^+$ adult neural precursors in Nestin^{cre}Flk1$^{+/-}$ and Nestin^{cre}Flk$^{-/-}$ short-term cultures, it was found that VEGF-A signaling does not appear to affect the proliferation of these cells, and individual neurospheres that proliferate clonally from Flk1$^{+/+}$ and Flk1$^{-/-}$ mice are of comparable size and cell number [160]. Similar studies demonstrate VEGF-A secreted from cerebral endothelial cells promotes migration of oligodendrocyte precursor cells (OPCs), but not proliferation, as treatment with a Flk-1 neutralizing antibody only affected OPC propagation [161]. Therefore, VEGF-A signaling may exert control over NSCs via the regulation of survival; this potential mechanism should be further explored, especially given that an internal autocrine role for VEGF-A in HSC survival has been demonstrated[162].

More recently, a direct requirement for VEGFR3 in neurogenesis has been established, and Vegfr3::YFP reporter mice demonstrate expression in NSC [155]. Interestingly, coexpression with VEGF-C along the walls of the lateral ventricle is also observed. Accordingly, an increase in neurogenesis is said to occur from VEGFR3$^+$ NSC after VEGF-C stimulation, deletion of VEGFR3 in neural cells and SVZ astrocytes, as well as VEGFR3 inhibition via blocking antibodies, all lead to a reduction in neurogenesis. *In vitro*, VEGF-C treatment also increases BrdU incorporation in YFP$^+$EGFR$^+$ NSC [155].

5.2.2. BDNF & IGF

BDNF is secreted by EC and induces the differentiation of astrocyte precursors [147, 163], and *in vivo* has been shown to influence proliferation and differentiation of NSPC in adult neurogenic regions [121, 134]. As mentioned previously, *in vivo* experiments suggest that VEGF-induced secretion of BDNF from higher vocal center (HVC) capillary vasculature in the songbird brain results in newly born neuron recruitment. Interestingly, BDNF secretion in this region is quite high, as canary brain EC secrete an average of 1 ng BDNF/10^6 cells/24 h [121, 164]; a study of adult-derived human brain EC revealed a comparable amount of BDNF secretion [147]. *In vitro*, BDNF release from EC supports SVZ-derived neuron outgrowth, survival, and migration [147]. Although subependymal astrocytes also secrete BDNF, it may be sequestered at the cell surface; this is partly mediated by the truncated gp95 extracellular domain of TrkB, a high affinity receptor for BDNF, which prevents its release into the surrounding space [147]. This has been proposed to be a mechanism whereby regions of NSC expansion exclude BDNF, limiting its availability only to those areas supporting differentiation and maturation. Interestingly, while NSC and transit-amplifying cells express the low-affinity neurotrophin receptor p75, expression of TrkB is only found on lineage-restricted neuroblasts. Additionally, it has been suggested that BDNF acts in a positive feedback loop to reduce proliferation and increase neuroblast differentiation through the release of NO by NSPC [165, 166]. Thus, endothelial-derived BDNF appears to serve chemoattraction and survival roles for neuronal progenitors [167].

Studies of exercise-induced neurogenic cognitive enhancement in the dentate gyrus have linked BDNF with IGF-1 [168]. Exercise stimulates uptake of IGF-1 from the bloodstream in the hippocampus, leading to an increase in the number of BrdU$^+$ hippocampal neurons as well as upregulation of BDNF mRNA and protein levels [169, 170]. The neurogenic effect of IGF-1

may be mediated in part through estrogen signaling, as estrogen antagonists reduce neurogenesis within the dentate gyrus [171]. From a clinical standpoint, IGF-1 may be involved in neurodegenerative disease progression, such as Alzheimer's and stroke, where levels of circulating IGF-1 are altered [170].

5.2.3. PDGF

PDGF signaling has been shown to affect stem cell properties and lineage bias [98, 172]. Vascular EC secrete PDGF-B as a disulfide-linked homodimer (PDGF-BB), and via a specific positively charged C-terminal retention motif, it interacts with heparin sulfate proteoglycans within the ECM to aid in localized retention [173-176]. Specifically within the CNS, it regulates oligodendrocyte precursor cell number. Interestingly, PDGF-B is implicated in brain tumor formation, where activation of its signaling pathway is present in more than 80% oligodendrogliomas and 50–100% of astrocytomas[177]. Thus, identifying which cells respond to PDGF is crucial to elucidate mechanisms involved in these brain cancers.

In the SVZ, putative NSC and most $GFAP^+$ cells have been shown to express PDGFRα, and become activated in the presence of PDGF-AA [178]. Accordingly, PDGF is reported to have mitogenic and differentiation actions on neural progenitor cells [179-181], and synergy with bFGF has been reported to enhance neurosphere generation [178]. After intracerebroventricular infusion of PDGF-AA, astrocyte-derived periventricular hyperplasias are formed, and increases in oligodendrogenesis are observed at the expense of olfactory bulb neurogenesis. While EGF infusion elicits a similar proliferative response in the SVZ, staining for PDGFRα and EGFR reveals expression in distinct populations, suggesting that they label stem cells and transit-amplifying progenitors, respectively. Conversely, conditional ablation of PDGRα in the SVZ decreases oligodendrogenesis while having little effect on neurogenesis [178]. Thus, PDGF signaling may play a role in maintaining the balance between neurogenesis and oligodendrogenesis.

5.2.4. SCF

SCF, also known as Kit ligand, has been reported to be expressed by a variety of cell types including vascular EC [182, 183]. Previous reports indicate that within the CNS, SCF/Kit-ligand signaling influences oligodendrocyte precursors prior to differentiation towards a myelinated phenotype. Although Kit belongs to the same class of tyrosine kinase receptors as PDGF receptors, their effects on NSPC are different. In $nestin^+$ NSCs isolated from embryonic rat cortex, more than 93% express SCF. More recent studies demonstrate that SCF acts as a chemoattractant and survival factor for NSPCs during early stages of differentiation while having no effect on proliferation or differentiation [184-186].

5.2.5. PEDF

PEDF is secreted by a variety of cell types, and can interact with the ECM, most notably collagen-I [187-189]. Being the first soluble factor shown to selectively activate type B NSC, PEDF seems to contribute to stem cell maintenance within the neurogenic niche. In the adult

mouse brain, expression is restricted to endothelial and ependymal cells, suggesting that PEDF is in fact a niche-derived signal. Accordingly, Western blot analysis on conditioned media from cultures indicate that PEDF is specifically secreted by endothelial and ependymal cells [144, 190, 191]. Aside from acting as a brake on cell cycle progression by promoting NSC self-renewal without affecting proliferation [192], recent evidence suggests an additional role in renewing symmetric divisions. Interestingly, PEDF has been implicated in regulating certain aspects of Notch signaling by modulating the NFκB pathway. The role of Notch signaling in NSC maintenance is well characterized [193], and NSC treated with PEDF upregulate Notch effectors Hes1 and Hes5, as well as the Sry-related HMG box-transcription factor Sox2 [194]. In cells with low levels of Notch signaling, PEDF enhances Notch-dependent transcription by relieving repression of Notch-responsive promoters by the transcriptional co-repressor N-CoR, thereby potentiating symmetric cell division [195]. Additionally, BrdU-labeled mice treated with PEDF display an increase in the number of $BrdU^{+}GFAP^{+}$ cells, and injection with a C-terminal blocking peptide to PEDF reveals no significant change in the number of $BrdU^{+}GFAP^{+}$ cells compared with vehicle-injected controls. Taken together, these data suggest that PEDF may not be a survival factor for NSC, and may instead serve to activate NSC by stimulating self-renewal [194].

5.2.6. Nitric Oxide (NO)

A variety of mechanisms have been proposed for NO regulation of NSPC, perhaps accounting for conflicting studies suggesting opposing roles on NSPC proliferation. Early reports demonstrated a role for NO in the repression of adult neurogenesis, as exposure to NOS inhibitors L-NAME and 7-NI increased neurogenesis in the dentate gyrus and SVZ [165, 166, 196, 197]. However, its effects seem to depend on the signaling pathway involved. Potentially through NO-induced S-nitrosylation of the EGFR [198], NO inhibits PI3K/Akt signaling to suppress NSPC proliferation, both in culture and *in vivo* [199]. However, bypassing the EGFR induces proliferation through activation of p21Ras, leading to an increase in activation levels of c-Myc, p90RSK and Elk-1, and subsequent reduction in $p27^{Kip1}$ [200]. BDNF may be involved in this process as well, as its stimulatory effect on neuronal differentiation is blocked by L-NAME. Interestingly, NSC express and release NO, suggesting a feedback mechanism whereby NSC-produced NO induces production of BDNF from the vascular bed [201]. EC also produce NO via eNOS, and a decrease in SVZ cell proliferation and migration post-stroke is observed in eNOS-deficient mice. Interestingly, BDNF levels are also reduced in $eNOS^{-/-}$ ischemic mice, and BDNF treatment rescues the decrease in neurosphere formation, proliferation, and neurite outgrowth in cultured $eNOS^{-/-}$ neurospheres [202].

5.2.7. Vascular ECM: Laminins, collagens, fractones

The ECM is an integral component of the NSC niche, regulating signaling by providing, storing, and compartmentalizing growth factors and cytokines indispensable for proliferation, differentiation and adhesion. Within the SVZ, a unique basal lamina, rich in laminins, collagen-1 and collagen IV, extends from perivascular cells as 'fractones' [203]. Each fractone consists of a base, attached to the perivascular cell, a stem that crosses the SVZ, and bulbs that

terminate just underneath the ependymal layer [204]. The branched configuration of fractones has been suggested to enable sequestration and subsequent presentation of growth factors and other signaling molecules to stem cells and progenitors to regulate their proliferation, activation, and differentiation within the niche [205].

Other important ECM molecules secreted by niche cells are laminin and fibronectin, both of which have been implicated in neural stem cell growth, differentiation, and migration. In addition to promoting neuroepithelial proliferation and differentiation during development, they also function as permissive substrates, supporting the migration of cerebellar neural precursors *in vitro* and neural progenitors through the RMS *in vivo* [206]. Most recently, the importance of laminin–integrin interactions within the SVZ support a role in migration, spreading and proliferation of NSPC [37]. Several *in vitro* studies have highlighted a critical role for β1-integrin in mediating multiple effects of ECM on NSC in a temporally and spatially controlled manner. For example, genetic ablation of β1-integrin results in reduced neural progenitor proliferation, increased cell death, and impairment of cell migration on different ECM substrates [207]. In β1-integrin-deficient neurospheres, β1-integrin signaling is not required for NSC maintenance, and instead seems to cooperate with growth factor signaling to regulate progenitor number [208]. *In vivo*, the role of laminins in migration and recruitment are critical, as injection of intact laminin and peptide infusion mimicking the E8 domain of the laminin α chain dramatically redirect neuroblast migration towards the site of administration. Interestingly, inhibiting the α6 or β1 subunits with antibodies also recapitulates the migratory defect without causing neuroblast death [209].

Collagen IV and chondroitin sulfate proteoglycans (CSPG) are also present in the microenvironment, and have been demonstrated to exert control over proliferation, leading to differentiation. While collagen IV inhibits proliferation of rat NSPCs and promotes differentiation into neurons [210], treatment of neurospheres or telencephalic ventricles with enzymes degrading CSPG glycosminoglycans leads to a reduction in cell proliferation and self-renewal of radial glia; interestingly, the increase in astrocyte formation is at the expense of neuronal differentiation [211]. Additionally, sulfation of chondroitin sulfate polymers *in vitro* modulates the activities and effects of various growth and morphogenetic factors that control NSC proliferation, maintenance, and differentiation [212].

5.3. Other putative endothelial-derived niche effectors

5.3.1. FGF-2

FGF-2 (aka (b)FGF) is detected in the endothelium of tumor capillaries *in vivo*, as well as at sites of vessel branching within the basal lamina of capillaries. *In vitro* studies suggest significant amounts of FGF-2 can also localize to the ECM in cell culture. Normally found to be extracellular, FGF-2 is reported to modulate cell function in an autocrine manner, and depending on the molecular weight isoform, may or may not be secreted; secreted FGF acts through intracellular signaling mechanisms [213]. While EC can secrete this potent angiogenic factor [214] to regulate proliferation, migration and differentiation, type B NSC respond to [113, 215-218] and express the corresponding receptor [178, 219, 220]. Within the CNS, FGF-2

has been shown to affect neurogenesis and proliferation of cortical progenitors [220-222]. Interestingly, FGF-2 infusion increases adult SVZ proliferation while decreasing the number of newly born neurons, suggesting that FGF-2 serves to maintain SVZ self-renewal [223]. In fact, *Fgf-2* knockout mice display a decrease in olfactory bulb size, presumably owing to attentuated output from neurogenic regions. Although FGF-2 can promote NSC proliferation, it does not act alone to maintain self-renewal, and must work with other factors to accomplish this [37]. In addition to inducing VEGF expression in EC, FGF-2 can prime neural precursor responsiveness towards EGF [218].

5.3.2. EGF & Betacellulin

While the specific cell type(s) expressing and secreting EGF remains unidentified within the adult NSC niche, several reports suggest an EC orgin. Affymetrix microarray analysis has revealed that human dermal microvascular EC express EGF, and that this expression is further upregulated in coculture with head and neck squamous cell carcinoma cells [224]. Similarly, an antibody-based human cytokine array has demonstrated that EGF is expressed and secreted by dermal microvascular endothelial cells with or without VEGF stimulation, suggesting basal expression of EGF within some EC [146]. Within the SVZ, receptors for EGF are predominantly expressed by the type C transit-amplifying cells apposed to capillaries. Furthermore, EGFR expression can be further induced by SDF-1 and PEDF [34, 85, 225, 226]. Intraventricular infusion of EGF increases the number of type B NSC contacting the ventricle [219], and leads to transit-amplifying cell proliferation while arresting neuroblast production. *In vitro,* EGF stimulates neurosphere generation from transit-amplifying cells, and is said to cause reversion to a more 'stem-like' phenotype [219]. Curiously, transit-amplifying cells with elevated EGFR signaling also show non-cell autonomous defects in Notch signaling, leading to elevated Numb levels in the stem compartment [227].

Recently, another member of the EGF family, BTC, has been shown to play a critical role in SVZ regulation. mRNA transcripts for *BTC* are detectable in EC, and immunofluorescent analysis reveals protein expression in EC of microcapillaries and in the choroid plexus, with the latter demonstrating greater expression. After intraventricular infusion, NSC and neuroblast compartments are expanded, promoting neurogenesis both in the olfactory bulb and the dentate gyrus. Defects in neuroblast regeneration are observed post cytosine-β-arabinofuranoside (Ara-C) infusion in *Btc*-null mice in comparison to wild-type littermates. Although related to EGF, its effects in the SVZ are slightly different, and it has been suggested that its ability to act on distinct receptors expressed on NSC and neuroblasts, EGFR and Erb4 respectively, may account for these differential effects.

5.3.3. BMPs & LIF & IL-6

In addition to high levels of BMP2 and BMP4 production in astroglia within the SVZ, it has been demonstrated that brain EC can act as potential sources of BMP. mRNA transcripts for *BMP2* and *BMP4* were found in the bEnd.3 endothelial cell line, as well as in primary brain EC. Furthermore, BMP4 protein was also detected in these brain EC [228]. Shown to counteract neurogenesis *in vitro* and *in vivo* [229-231], BMP signaling increases astrocyte formation,

possibly through activation of transcriptional regulators of Smads to control cell-cycle exit. Indeed, when embryonic and adult NSPC are cocultured with brain EC, the canonical BMP/Smad pathway becomes activated to reduce proliferation and induce NSPC cell-cycle exit in the presence of EGF and FGF-2 [228]. LIF and IL-6 belong to the cohort of endothelial-secreted factors that promote self-renewal of adult NSC [232], and when synergize with BMP factors to promote self-renewal of embryonic stem cells through activation of gp130-mediated STAT signaling, which induces astrogenesis [232, 233].

5.3.4. SDF-1 & growth-related oncogene-α & angiopoietin

A chemokine previously shown to direct migration of leukocytes during inflammation, SDF-1/CXCL12 signaling via its CXCR4 receptor also provides migratory cues for NSPC recruitment from the lateral ventricle to the nascent dentate gyrus during CNS development; interestingly, SDF-1/CXCR4 expression by EC and neurons persists in the adult dentate gyrus. In the SVZ, neural cells express CXCR4 while ependymal cells and vascular EC express SDF-1 [226]. Neuroblasts expressing CXCR4 migrate towards and are attracted to activated EC of cerebral vessels that secrete SDF-1α [234-238]. While neurospheres express CXCR4, human cerebral EC have been shown to secrete growth-related oncogene-α, also a ligand for CXCR4 [239]. More recently, evidence of progenitor homing to SVZ EC in a SDF1/CXCR4-dependent manner has been demonstrated, where SDF1 upregulates EGFR and α6-integrin in activated NSC and transit amplifying cells, thereby enhancing activation state and the binding to laminin on resident vessels. SDF1 was also shown to increase the motility of migrating neuroblasts towards the olfactory bulb [34, 226].

Recent reports also suggest shared receptor/cytokine signaling between NSC and the vasculature concerning growth related CXCR4/oncogene-α and Ang-1/Tie2 [240, 241]. Ang-1 can be expressed by EC, as well as mural cells, and seems to be upregulated poststroke. While also having a general neuroprotective effect on the nervous system, it has been shown to directly regulate stem cell differentiation and migration through the Tie2 and CXCR4 receptors [235, 237, 242-244].

5.3.5. TGF-β1

Latent TGF-β1 is secreted by EC, pericytes, glia and neurons. Reported to induce VEGF expression by vascular EC and gliomas [245, 246], TGF-β1 serves as an important neurogenic growth factor. Produced in a latent form in mesenchymal and epithelial cell types, EC and mural cells have also been shown to produce a latent form of TGF-β1 which can be activated in endothelial cell-mural cell cocultures [247, 248]. Because *Tgf-β1* knockout mouse models demonstrate a reduced potential for neuron survival [249], and transgenic mouse models overexpressing *Tgf-β1* under control of the GFAP promoter show a reduction in NSCP proliferation [250], it is believed that TGF-β1 has no impact on NSP identity or on differentiation. Rather, it is believed to affect proliferative potential, as demonstrated by an arrest in the G0/G1 phase of the cell cycle [251]. In cell culture, NSC and progenitors express TGFβRI, II and III, and TGF-β1 decreases the expansion of these cells in a dose-dependent manner [252].

5.3.6. Ephs and ephrins

Belonging to a family of receptor tyrosine kinases and associated transmembrane ligands, Ephrins and Eph receptors have established roles in vascular development. However, more recent data suggest both a role for Eph receptor and ephrin ligand interaction within the CNS, and this interaction can occur between endothelial and nonvascular tissues. For example, during development, the close proximity of EphB3/4 on intersomitic vessels with ephrin-B1/B2 of somites seems to imply bidirectional communication [253]. Within the SVZ, EphA7 seems to localize to ependymal cells and astrocytes. Interestingly, the cells immunoreactive for EphA7 also express nestin, a marker associated with NSC. Additionally, ephrin-B2/3 is localized to SVZ astrocytes. By contrast, ephrin-A2 is predominantly expressed on transit-amplifying cells and neuroblasts [254, 255]. Although ephrin-B2 is not cell type exclusive within the SVZ, it has been shown to selectively mark arterial endothelium in the adult, as well as surrounding smooth muscle cells and pericytes [256]. While EphA7 and ephrin-A2 negatively regulate NSPC proliferation, EphB1–2/EphA4 and ephrin-B2/3 direct neuroblast migration and directly or indirectly regulate NSPC proliferation. Interestingly, infusion of antibody-clustered ephrin-B2-Fc or EphB2-Fc into the lateral ventricle increases SVZ proliferation, suggesting that B-class ephrins and Ephs may promote proliferation [254, 255, 257]. A correlation between EphB2 and Notch signaling has also been proposed, wherein EphB2 acts downstream of Notch to maintain ependymal identity under homeostatic conditions, while regulating conversion to astrocytes after injury [258].

5.4. Circulating effectors:

5.4.1. Erythropoietin & prolactin

Systemic transport of erythropoietins and prolactins via blood circulation has been demonstrated to have effects within the CNS. Prolactin, in cooperation with TGF-α, promotes SVZ proliferation and neuronal differentiation. It has been proposed that prolactin serves as an important contributor to the increase in neurogenesis during pregnancy [259]; however, the responsiveness to prolactin within the dentate gyrus is negligible [259, 260]. Although erythropoietin synthesis can be activated in astrocytes and neurons [261-263], it is also possible that circulating erythropoietin, from the kidneys, can cross the BBB to exert neuroprotective effects. Significant amounts of the erythropoietin receptor are localized to the surface of EC and within caveoli [264, 265], and systemic administration of erythropoietin has been shown to penetrate the BBB as an intact molecule [266]. These observations certainly suggest that erythropoietin can reach the brain; however, the precise mechanism mediating this transport is unknown. Erythropoietin has been shown to stimulate NSPC production and prevent apoptosis during embryonic development. Additionally, it serves as a paracrine neuroprotective mediator of ischemia in the brain [267], and erythropoietin-activated EC promote the migration of neuroblasts through the secretion of MMP-2 and 9. [268]. Thus, further investigation of the penetrance and potential function of erythropoietin in the adult NSC niche is warranted.

6. Conclusions

Its remarkable ability to penetrate throughout the entire body to regulate and respond to distinct microenvironments simultaneously has truly earned the vasculature the term of 'master regulator'. It plays a crucial role in embryonic and adult neurogenesis, where its secretion and/or systemic circulation of growth factors, serves to regulate the growth and behavior of stem and progenitor cells. Although a handful of signaling molecules have been identified thus far, it is likely that there are many more unidentified effectors that influence NSC behavior. From a neuro-regenerative perspective, identifying factors responsible for modulating specific stem cell behaviors is crucial, whether the goal is preventing further tissue loss or potentiating endogenous repair mechanisms. Towards this goal, stem cell-based therapies offer the intriguing possibility of accomplishing both. Therefore, understanding the intrinsic and extrinsic mechanisms responsible for modulating NSPC behavior will be critical for the development of more targeted therapies. As mounting evidence points to a strong interdependent relationship between neurogenesis and the vasculature, therapies aimed at targeting both compartments hold great promise.

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