Published in final edited form as:

Regen Med. 2009 November ; 4(6): 879–897. doi:10.2217/rme.09.61.

Diverse roles of the vasculature within the neural stem cell niche

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Abstract

An interdependent relationship between the vascular and nervous systems begins during the earliest stages of development and persists through the mammalian lifespan. Accordingly, the process of adult neurogenesis involves the coordinated response of both systems to maintain a specialized microenvironment (niche) that tips the scale towards maintenance or regeneration, as needed. Understanding the nature and regulation of this balance will provide a foundation on which the potential for molecular-and stem cell-based therapies can be developed to treat prevalent CNS diseases and disorders. The vasculature is cited as a prominent feature within the adult subventricular zone and subgranular zone, known adult neural stem cell niches, helping to retain neural stem and progenitor cell potential. The vascular compartment within the neural stem cell niche has the unique opportunity to not only regulate neural stem and progenitor cells through direct contact with, and paracrine signaling from, endothelial and mural cells that make up blood vessels, but also integrates systemic signals into the local microenvironment via distribution of soluble factors from blood circulation to regulate stem cell niche behavior. Understanding the intricate role that the vasculature plays to influence neural stem cells in the context of niche regulation will help to bridge the gap from bench to bedside for the development of regeneration-based therapies for the CNS.

Keywords

adult neural stem cell; endothelial-derived factors; vascular endothelium

Only recently has the discovery of adult neurogenesis overturned the long-standing dogma describing the adult mammalian brain as a static organ. With the discoveries of postnatal neurogenesis and the existence of adult neural stem cells (NSCs) [1–4], a field once limited by the postnatal ‘static brain’ model is now breaking ground at a rapid pace. Although well characterized within the developing embryo, the concept of adult neurogenesis is still relatively new, gaining attention and capturing the interest of biologists and clinicians. The possible therapeutic benefits of treating neurological disorders and disease via adult stem cell-based therapies represent an open door to novel approaches and treatments. However, to truly harness the therapeutic potential of stem cell-based therapies, a solid understanding of the intrinsic and extrinsic mechanisms surrounding NSC regulation needs to be met.

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Financial & competing interests disclosure

KK Hirschi is supported by NIH R01 Grants EB-005173, HL77675 and HL096360, as well as NIH P20-EB007076 and P01-GM081627. JS Goldberg is supported by NIH grant T32 DK-064717. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Towards this goal, the identification of the vasculature as a prominent feature across several stem cell niches, as well as the most recent *in vivo* observations within the adult NSC niche [5,6], suggest that it plays an important role in niche regulation and maintenance. This idea of a neural–vascular inter-relationship is not a new one. In fact, the observation that nerves and vessels share similar distribution and branching patterns was made centuries ago, and the more recent reports of a shared cohort of signaling molecules, both for migration as well as regulation, further highlights this issue [7]. Additionally, this neurovascular relationship manifests itself through clinical phenotypes of some of the most prominent neurological disorders, such as stroke and Alzheimer’s disease, where a combination of vascular and neural defects account for brain degeneration [8,9]. It has become increasingly clear that the process of neurogenesis and NSC niche regulation is a complicated one, and that it most likely involves the balance of regulatory signals and molecules within the specialized microenvironment that ultimately leads to niche maintenance and/or regeneration. Of the proposed regulators of NSC, the vasculature represents an intriguing piece of the puzzle, both for understanding niche regulation at the molecular level, as well as discovering potential therapies for CNS disorders at the clinical level.

Defining the vasculature

Functions of the vasculature

Although blood vessels appear to have arisen after nerves evolutionarily [7], the vasculature is one of the earliest organ systems to appear developmentally [10]. In most tissues, blood vessel formation occurs in a closely coordinated manner with nerve development, and it is the interaction between blood vessels and nerves that consequently results in the formation of closed circuit neurovascular networks [11]. Through its vital role in establishing systemic blood circulation, the vasculature is responsible for distributing nutrients and oxygen, as well as a providing a means for metabolic waste removal [10,12]. Its ability to permeate almost all tissues allows for sufficient oxygen diffusion [13] and enables an intimate association with surrounding tissue environments. Additionally, the vascular endothelium remains highly metabolically active, and thus serves important physiological roles; these include, but are not limited to: regulating the proliferation and survival of surrounding cells, establishing systemic innate and adaptive immunity, maintaining hemostatic balance, trafficking of blood cells and blood-borne effectors, and controlling vasomotor tone and systemic blood pressure [14].

Within the brain, the critical balance between blood supply and energy consumption is meticulously kept. Therefore, the cerebral vasculature contains neurovascular control mechanisms that involve the coordinated interactions of neurons, glia and vascular cells to properly regulate cerebral blood flow under a variety of conditions [15]. This becomes increasingly important in blood–brain barrier (BBB) maintenance. The interactions between astrocytic endfeet, mural cells (vascular smooth muscle cells and pericytes) and endothelial cells are crucial in restricting the flux of harmful agents from the blood to neural tissue while being permissive to essential metabolic substances. In fact, astrocytes play a direct role in establishing the BBB by instructing endothelial cells to form tight junctions [16,17].

Composition of blood vessels in the brain

In general, the composition of blood vessels involves at least two distinct cell types: endothelial cells comprise the inner luminal lining of the vessel, while mural cells form the surrounding contractile layer [18]. Vascular smooth muscle cells form the outer wall of larger vessels and pericytes support capillary networks; both types of mural cells can penetrate through the basement membrane to form tight and gap junctions with the underlying endothelium [13]. An outer adventitial layer usually exists around the largest vessels, such as arteries, and is composed of fibroblasts, extracellular matrix (ECM) and perivascular nerves [15,18]. Given

the anatomical complexity of the brain, it is not surprising then that different microenvironments harbor different blood vessel types based on location and composition.

Arising from the circle of Willis (the circle of arteries supplying blood to the brain), large cerebral arteries branch out into smaller pial arteries and arterioles. These pial arteries travel along the surface of the brain across the subarachnoid space, giving rise to the first penetrating arteries and arterioles that carry with them the normal vascular composition (as outlined earlier) and are separated from the brain by the Virchow–Robin space (the perivascular space surrounding vessels as they enter the brain). Progression into the brain yields the disappearance of the Virchow–Robin space, allowing astrocytic end-feet to directly contact vascular cells through their basement membrane. However, as arterioles traverse even deeper into the brain, they become progressively smaller and lose portions of their smooth muscle layer, and are thus termed cerebral capillaries [15]. Essentially, these capillaries are tubes of endothelial cells that are variably surrounded by pericytes or pericyte processes and ECM. Indeed, it is this minimal composition of capillaries that allows for a unique interface facilitating communication with the underlying tissue environment. Owing to their thin walls and slow rate of blood flow, capillaries are remarkably engineered to minimize diffusion path length and optimize diffusion time [14]. The distribution of cerebral capillaries within the brain is relatively heterogeneous, owing to regional differences in blood flow and metabolic demands.

Phenotype & origin of mural cells in the brain

Interactions between endothelial cells and their surrounding mural cell counterparts are crucial for the maintenance of endothelial cell growth and function, as well as vessel structural integrity. In fact, disruption of endothelial–mural cell interactions can lead to severe and lethal cardiovascular defects, as well as diabetic retinopathy [19,20]. Although the origin of mural cells in the brain is still unclear, they are most likely regionally derived from surrounding mesodermal and/or neural crest precursors; perhaps line-age-tracing studies would provide useful insight regarding the origin and potential specialized functions of mural cells within the NSC niche. The type of mural cell coverage is relative to the vessel diameter, where vascular smooth muscle cells and pericytes associate with large and small vessels, respectively. For example, large cerebral arteries in the cortex are surrounded by multiple layers of vascular smooth muscle cells, while pericytes are distributed along microvessels within the subventricular zone (SVZ) and subgranular zone (SGZ). Whether pericytes and vascular smooth muscle cells have distinct origins is not known [21–23].

Concerning pericytes, specifically, several reports suggest a degree of multipotentiality based on *in vitro* differentiation schemes and progenitor marker expression [24,25]; however, *in vivo* evidence to support this is lacking. Serving a contractile role to regulate blood flow, physiologically pericytes are not stem cells in the adult brain, and should not be confused with other perivascular progenitor cell types. Of the markers used to identify pericytes, including smooth muscle α -actin, desmin, NG-2, PDGFR β , aminopeptidase A and N, and RGS5, none are entirely specific, and none recognize all pericytes [19]. Perhaps there is some degree of heterogeneity among pericytes, as mentioned earlier, and their phenotype reflects their origin and specialized functions within distinct microenvironments.

Ultrastructural characterization of endothelial cells

Heterogeneity among pericytes would not be surprising, given that the vascular endothelium is a highly heterogeneous tissue, with differences in vascular bed composition observed along the same vessel even at the same vascular site [26]. Indeed, it has been reported that the structure and function of endothelial cells are regulated temporally and spatially by systemic signals delivered through the bloodstream as well as paracrine signals produced locally within the tissue [27]. Therefore, among the endothelium of different vascular beds, the most common

morphological differences include cell size, shape, extent of mural cell coverage and degree of permeability [13].

The vascular endothelium is semipermeable, allowing for regulated transport of material into and out of the blood; however, the degree of basal permeability is physiologically regulated. For example, capillaries represent the major exchange vessel where the constant flow of molecules between the blood and underlying interstitium occurs. However, during times of acute and chronic inflammation, the endothelium has been reported to induce an increased permeability. This extraordinary ability among the endothelium to exercise control over the degree of permeability results from differential activity of transcytotic machinery, frequency of fenestrae (transcellular pores that contain a thin non-membranous diaphragm across their openings to allow for rapid exchange of molecules with the surrounding tissue) and properties of junctional complexes [14]. For example, fenestrated capillaries are usually found within endocrine organs, such as the adrenal gland, pituitary and pancreas, where they are believed to increase transport of long-range hormones between extravascular cells and blood through thin diaphragms covering pores of these capillaries [13].

Through the advent of electron microscopy, structural heterogeneity among endothelial cells has revealed two types of endothelium: continuous and discontinuous endothelium. These two types of endothelium differ in the degree of endothelial cell connectivity and the extent of surrounding basement membrane. In continuous endothelium, endothelial cells are tightly connected, surrounded by a continuous basement membrane, and are either fenestrated or nonfenestrated. Discontinuous endothelium, however, are characterized by gaps, a poorly formed basement membrane and larger fenestrae. While nonfenestrated continuous endothelium are found in regions under strict control of diffusion (e.g., the arteries, veins and capillaries of the brain involved in BBB maintenance), fenestrated discontinuous endothelium are localized to regions characterized by increased filtration and transendothelial transport [14]. Regulation of vascular fenestrations seems to involve VEGF, as inhibitors of VEGF signaling pathways within the pancreas and kidney (where fenestrated vessels are normally found) decrease the presence of fenestrated endothelium [28,29]. Conversely, ectopic expression of VEGF induces the presence of fenestrae in vessels not normally fenestrated [30]. In situations where the rapid exchange of molecules with the surrounding tissue is deleterious, as is the case within the brain where strict control over of the BBB is vital, compensation through increased expression levels of regulatory transporters, such as glucose transporter 1, L-type amino acid transporter 1 and excitatory amino acid transporters 1–3, is achieved [31].

Morphological and structural characterization has revealed three types of junctions present within endothelial cells: tight junctions (also referred to as zone occludens), adherens junctions (also referred to as zone adherens) and gap junctions [32,33]. Tight junctions are usually localized to the apical region of intercellular clefts to seal the endothelial cell layer and form a barrier to facilitate specific transport between endothelial cells. This partial fusing of apposed neighboring plasma membranes also helps to maintain cell polarity between the luminal and abluminal side of endothelial cells [34,35]. Occludens, the primary component of tight junctions, are transmembrane proteins that associate with the cytosolic proteins zonula occludens-1 and -2 [14]. On the other hand, adherens junctions are composed of cadherins, with VE-cadherin being prominent within the endothelium. Traditionally thought to serve as adhesion molecules, cadherins use their cytoplasmic tail as an anchor to interact with a network of intracellular cytoplasmic proteins. However, recent evidence indicates that cadherins also serve signaling roles through the catenin-based actin microfilament network [36].

Environmental influence on endothelial cell potential

It is now clear that spatial and temporal differences in the extracellular environment influence the structure, interactions and function of endothelial cells, further lending to endothelial cell heterogeneity. For example, increases in blood flow lead to concomitant changes in hemodynamic forces acting on the vessel wall. These can be in the form of shear stress, a tangential frictional force acting in the direction of blood flow on the surface of endothelial cells and pressure stretch, which acts perpendicularly to the vessel wall and affects endothelial cells as well as mural cells [37]. Towards these mechanical stimuli, endothelial cells display precise and defined biochemical responses, ranging from instantaneous electrochemical responses to more delayed changes in gene expression. Specifically, increases in shear stress cause an increase in nitric oxide release through the rapid activation and upregulation of endothelial nitric oxide synthase gene expression [38]. Through activation of membrane receptors and mechanosensitive ion channels, shear stress also promotes endothelial cell survival by instructing the release of endothelial cell factors that inhibit coagulation, migration of leukocytes and mural cell proliferation [37,39,40]. There is also emerging evidence that certain site-specific properties of endothelial cells are epigenetically regulated and retained despite removal from their microenvironment. When cultured human endothelial cells isolated from different vascular sites are subjected to DNA microarray analysis, differences in the transcriptional profiles between arterial and venous endothelial cells, and between macrovascular and microvascular endothelial cells were revealed, suggesting that maintenance of endothelial cell phenotype may not be solely dependent on extracellular-derived signals [41].

Even from a functional perspective, the endothelium has been described to display a ‘division of labor’ [42,43]. For example, postnatal endothelial cells are normally quiescent, with an average lifespan of more than 1 year, while the endothelium of the corpus luteum and uterus physiologically undergo drastic cyclical periods of dramatic endothelial cell proliferation [44].

Although complex at times, the diverse potential among endothelial cells is quite beneficial. Throughout evolution, the endothelium has acquired distinct fitness advantages conferring this adaptive ability to conform to the needs of underlying tissues and surrounding microenvironment. For example, the drastically different environments within the inner medulla of the kidney and pulmonary alveoli, being hypoxic/hyperosmolar and well oxygenated, respectively, have been shown to sustain functional endothelial cell residence [14]. The ‘flexibility’ of the endothelium to adapt to its tissue microenvironments is certainly an advantage in the brain, where it plays distinctly different roles in maintaining the BBB in the cortex, yet allowing permeability within NSC niches.

Components of the stem cell niche

Vascular component of a functional stem cell niche

With the introduction of the ‘stem cell niche’ concept in 1978, Shofield described the potential for the existence of an extracellular environment that would be able to maintain a stem cell in its undifferentiated, proliferating state [45]. In fact, through the years, this concept has not changed, and documentation of specialized niche microenvironments supporting lifelong self-renewal and production of differentiated cells can be found throughout the literature [46,47]. Therefore, within a given tissue, the niche can be defined as an anatomical microenvironment or compartment providing signals to control stem cell proliferation, fate specification and protection. These signals provide structural and trophic support, temporal and spatial information, and physiological cues [48].

Comparisons of various stem cell niches across a variety of organisms reveal several shared components believed to contribute to niche potency and function. In general, diffusible signals in conjunction with cell–cell and cell–ECM interactions are responsible for niche maintenance [46,47,49,50]. With respect to tissue specificity, the vasculature, and in particular the endothelium, is reported to be an integral component of many stem cell niches [51]. Blood vessels not only serve as signaling conduits, facilitating local and long-distance systemic transmission of molecules, their recruitment of inflammatory and circulating cells to the niche adds another dimension to their already diverse functional repertoire [48]. Accordingly, blood vessels are also used as migratory scaffolds for neural progenitor cells [52], and the intimate association between stem cells and endothelial cells has been reported to regulate stem cell self-renewal and differentiation [53,54]. Integrins and laminins, known endothelial cell-derived secreted adhesion and ECM proteins, respectively [55], act as stem cell anchors [56] to increase proximity to self-renewal and survival signals [57,58].

Within the hematopoietic system, endothelial and hematopoietic cells are thought to share a common precursor, and from the earliest embryonic stages forward, there exists extensive interaction between these two cell types. During development, as hematopoietic colonies form in the yolk sac and aorta–gonad–mesonephros region [59,60], hematopoietic stem cells (HSCs) emerge and bud from the vascular lumen, indicating that HSCs are derived from the endothelium. In fact, genetic labeling experiments confirm that cells with HSC activity can be derived from the endothelial cell layer [61].

Not only do embryonic endothelial cells isolated from hematopoietic regions support HSCs *in vitro*, sinusoidal endothelial cells within the adult bone marrow also influence HSC function [62,63]. For example, along the endosteal surface of trabecular bone within the bone marrow, HSCs reside within close proximity to both osteoblasts and endothelial cells lining the blood vessels [64–66]. Similarly, spermatogonia stem cells as well as undifferentiated spermatogonia preferentially localize to vascular networks [51].

Endothelial cells have also been reported to modulate stem cell activity in the CNS. Anatomically, observations by several groups have placed NSCs in close proximity to blood vessels, suggesting a role for cooperative interaction. Multiple coculture experiments demonstrate that endothelial cells significantly affect the composition of embryonic NSC cultures. For example, the presence of endothelial cells in NSC cocultures seems to increase stem cell self-renewal through the Notch1 effector Hes1 [54]. Studies of the higher vocal center (HVC) within the adult songbird brain indicate that the endothelium in this region stimulates recruitment and functional integration of newly born neurons during HVC seasonal expansion. Specifically, the upregulation of VEGF expression after testosterone administration stimulates local angiogenesis, which in turn increases brain-derived neurotrophic factor (BDNF) production from newly formed vessels that promote migration of ventricular zone neurons [67]. Thus, vascular cells play a critical role in regulating stem cell activity in multiple stem cell microenvironments, including the NSC niche.

Architecture of the adult neural stem cell niche

There are thought to be two germinal regions of the adult brain that function as NSC niches, enabling continuous generation of new neurons. Representing the largest neurogenic region within the adult brain is the SVZ, a four to five cell diameter thick layer [68] residing within the lateral walls of the lateral ventricles. As the predominant source of adult neurogenesis, SVZ neural progenitors migrate through the rostral migratory stream to the olfactory bulb where they have been reported to differentiate into at least five interneuron subtypes, as well as oligodendrocytes of the corpus callosal white matter, albeit to a lesser extent [69,70]. In fact, it is estimated that 30–60,000 new neurons may be generated in the rodent olfactory bulb per day [71,72]. The second neurogenic region is the SGZ, which is located within the dentate

gyrus of the hippocampal formation. SGZ progenitors migrate short distances to the granule cell layer to differentiate into granular neurons [73].

To fully address the concept of niche regulation, we must first examine the cellular architecture. In lieu of recent findings characterizing the SVZ microenvironment we will focus on the cellular architecture of the SVZ (depicted in Figure 1). In this region, there are five distinct cell types that help maintain a specialized niche microenvironment and confer its unique regenerative properties: putative NSCs (type B cells), transit-amplifying cells (type C cells), neuroblasts (type A cells), ependymal cells and a specialized vascular endothelium [5,74]. The multiciliated ependymal cells form a single cell layer lining the ventricle, acting as a physical barrier separating the brain parenchyma from the cerebrospinal fluid [49]. Although a topic of debate, recent reports using transgenic approaches suggest that the ependyma generate neurons *in vivo* and behave like adult NSCs; certainly, further delineation of the role of the ependyma in neurogenesis is needed [75,76]. NSCs, also referred to as stem cell astrocytes, owing to similar marker expression and morphology that is closely reminiscent to that of radial glia within the developing embryo, reside just under the ependymal layer and at times innervate between ependymal cells to extend a single apical process that contacts the cerebrospinal fluid of the ventricle. While NSCs are relatively quiescent, transit-amplifying cells represent the most proliferative progenitor type and remain localized to the SVZ [49,74]. On the other hand, neuroblasts migrate as chains rostrally through the rostral migratory stream where they differentiate into inhibitory interneurons of the olfactory bulb [74,77,78]. Most recently, the presence of a specialized vasculature within the SVZ has been reported to not only be different from non-neurogenic regions of the brain, but also different from SGZ vasculature [5]. Recent reports demonstrate that NSCs and transit-amplifying cells lie significantly closer to the SVZ vasculature, both in proximity and frequency of direct contact, which are even more dramatic in niche regeneration models [5,6]. Additionally, NSCs extend a long basal process terminating on blood vessels in the form of specialized endfeet that may facilitate responses to changes in the perivascular ECM [79]. Therefore, the presumptive natural lineage progression from stem cell to more differentiated progenitor is as follows: NSCs give rise to transit-amplifying cells that then differentiate to migrating neuroblasts.

Vascular environment within the SVZ & SGZ

It is clear that the SVZ and SGZ both present a functional neurogenic environment to maintain NSCs in a poised and undifferentiated state, ready to react to changes in the local microenvironment [2,80]. As regulatory processes within the NSC niche can be controlled via secreted neurotrophic and angiogenic factors, such as Wnts, Shh and TGF- β [81], it is evident that both neural and non-neural cell types play vital roles in maintenance [49]. For example, interaction between endothelial cells and specialized astrocytes provide a unique neurogenic niche, as demonstrated by the detection of *in vivo* 'hot spots' located in close proximity to capillaries [1,49,52]. Rather than being randomly distributed throughout the brain, NSCs are concentrated around blood vessels, allowing constant access to circulating signaling molecules and nutrient metabolites [82,83]. It has been shown that components of complement signaling are present on transit-amplifying cells and neural progenitors *in vivo*, and that circulating complement factors promote both basal and ischemia-induced neurogenesis [84]. Additionally, vascular-secreted factors promote neuroblast proliferation and survival [85] and serve as migration scaffolds [86,87] to damaged areas poststroke through the expression of stromal cell-derived factor (SDF)-1 and angiopoietin (Ang)-1 [88]. In fact, it has been proposed that NSCs reside within a vascular niche in which endothelial cells regulate NSC self-renewal [52,54, 67,89]. This interaction with the vascular endothelium may in fact be a vital component of a functional neurogenic niche, as radiation-induced disruption of endothelial cell-SGZ precursor cell interaction results in a loss of neurogenic potential. Additionally, this loss of neurogenic

potential after transplantation from a nonirradiated mouse into an irradiated host further demonstrates the importance of this endothelial association [90].

Specifically within the SGZ, nestin (a marker associated with NSCs) expressing radial astrocytes are localized to areas near blood vessels [73], and there exists an anatomical relationship between proliferating hippocampal neural progenitors and proliferating endothelial cells [52,91,92]. Furthermore, in contrast to the SVZ where angiogenic sprouting and division of endothelial cells seems to be absent [5], surges of endothelial cell division within the SGZ are spatially and temporally related to clusters of neurogenesis [52]. The high levels of VEGF and VEGFR2 [52], as well as the shared responsiveness to similar growth factors (e.g., neurotrophins, neuropilins, semaphorins and ephrins) [93–95], strongly suggest that angiogenesis and neurogenesis are coupled within the SGZ of the hippocampus. A mechanism illustrating this bidirectional communication has been proposed within the HVC of the songbird brain, where testosterone-induced upregulation of VEGF and VEGFR2 in neurons and astrocytes, respectively, increases angiogenesis. The newly generated capillaries produce BDNF that subsequently promote the recruitment and migration of newly born neurons [67]. Situations where exercise-induced angiogenesis in the hippocampus see increases in NGF and BDNF [96] protein levels also lead to robust increases in neurogenesis [97–99].

The SVZ represents a slightly different vascular environment, harboring a more stable vascular bed as compared with the SGZ. In other areas of the brain, where the BBB is strictly maintained by endothelial cell tight junctions, pericyte coverage and astrocyte endfeet that restrict transport of molecules from the blood to the brain parenchyma, new evidence presents the notion that there exists a modified BBB within the SVZ. The observation that certain sites along SVZ blood vessels lack astrocyte endfeet and endothelial cell tight junctions, as revealed by aquaporin-4 and zonula occludens-1 immunostaining, respectively, demonstrate major structural differences in this vascular endothelium relative to other areas of the brain, where gaps in astrocyte endfeet coverage are not observed. Long-term bromodeoxyuridine (BrdU) labeling allows the identification of presumed resident NSCs relative to the highly proliferative and migratory transit-amplifying cells and neuroblasts, respectively. Not only do the majority of BrdU⁺ label-retaining cells and transit-amplifying cells reside significantly closer and make direct contact to the vasculature more frequently compared with the other SVZ cell types under homeostatic conditions, these associations are further increased during regeneration after antimitotic cytosine- β -D-arabinofuranoside treatment [5,6]. Furthermore, transit-amplifying cells can contact the vasculature at sites lacking astrocyte endfeet and pericyte coverage, possibly facilitating signaling and communication. Certainly, fluorescent tracer experiments have proposed that differences in the ultrastructural composition of SVZ blood vessels may be responsible for the detection of sodium fluorescein after perfusion into the blood; however, access to the SVZ from the cerebral spinal fluid cannot be dismissed.

Integrin $\alpha 6 \beta 1$ has been proposed to partially mediate the adhesion between neural stem/progenitor cells (NSPCs) and the vascular endothelium through the binding of laminins that are highly localized around SVZ blood vessels. *In vitro* and *in vivo* experiments using the GoH3 integrin antibody to specifically block integrin $\alpha 6 \beta 1$ binding to laminin have demonstrated a crucial role for this interaction in attachment and spreading of NSPCs that can even effect proliferation rate [6].

Endothelial cell regulation of adult NSCs & NSPCs

Whether it is through secreted factors and cytokines, or direct contact *in vivo* or within the confines of the coculture system, endothelial cells exert their influence over NSCs to regulate fate specification, differentiation, quiescence and proliferation. Certainly, some of the earlier experiments involving SVZ explants cocultured with endothelial cells reveal increased neurite

outgrowth and maturation along with enhanced neuronal migration, thus establishing a crude role for endothelial cell regulation of neural cells [100]. It has also been reported that NSCs can respond to pro-angiogenic factors [101–103], and that these factors promote the proliferation of NSPCs, neurogenesis, synaptogenesis, axonal growth and neuroprotection [11]. Studies in tumor and stroke models have also uncovered neural regulatory roles for endothelial cells. For example, endothelial cells can protect stem cells and tumor cells from radiation damage [104,105], and in preclinical models where NSPCs isolated from stroke boundary are cocultured with cerebral endothelial cells, a significant increase in neural progenitor cell proliferation, neuronal differentiation and capillary tube formation are observed [106]. Through the release of certain growth factors, such as PEDF or VEGF, endothelial cells can regulate self-renewal and differentiation of NSPCs [89,107]. Mock treatment of NSCs with serum rich endothelial growth media induces NSC differentiation into neurons and astrocytes [108], and coculture of adult NSCs with endothelial cells results in self-renewal and symmetric cell division, generating increased numbers of nestin⁺ precursors to enhance subsequent neurogenesis [54].

A recent cytokine-expression profile of human umbilical vein and cerebral microvascular endothelial cells revealed a large number of chemokines, growth factors, adhesion molecules and ECM proteins being expressed [109]. However, levels of these signaling molecules varied under stimulating and nonstimulating conditions, as well as endothelial cell type, highlighting the diverse signaling potential that exists even among endothelial subtypes. Studies of adult neurogenic niche regulation have identified a limited number of growth factors and secreted molecules thus far, with the origins of some still unidentified. Owing to the scope of this article, the focus will be on signaling molecules shown to affect NSPCs that are likely to be vascular endothelium derived (Table 1 & Figure 1).

The vascular-derived molecules shown to locally regulate the adult NSC niche include leukemia inhibitory factor (LIF), BDNF, VEGF, PDGF, PEDF and laminins [6,67,110–112]. However, there are additional factors reported to influence NSPC behavior that have the potential to be derived from the NSC niche vasculature, although they have not demonstrated to be, and they are FGF-2, EGF, IL-6, stem cell factor (SCF), IGF-1, TGF- β , bone morphogenic proteins (BMP), SDF-1, collagen IV, Eph/ephrins, angiotensin, erythropoietin and prolactins.

Effectors known to be derived from endothelium within the NSC niche

VEGF

Reported to be required for hippocampal neurogenesis in the adult rat [107], endothelial cells, ependymal cells and the choroid plexus secrete VEGF at neurogenic sites, serving as a survival factor to stimulate NSPC self-renewal. Neurospheres as well as reactive astrocytes have been shown to express VEGF-A [113,114], and infusion into the lateral ventricle acts as a trophic survival factor for NSPCs and increases neurogenesis most likely through the VEGFR2/Flk-1 receptor [54,115,116]. Although VEGF-A is reported to have a direct role in signaling during development [52,91,115], evidence also supports an indirect role when secreted by ependymal cells, through the stimulated release of BDNF from endothelial cells [54,67]. Specifically, in experiments comparing the numbers of primary Ki-67⁺ adult neural precursors in Nestin^{cre}Flk1^{+/-} and Nes^{cre}Flk1^{-/-} 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 similar sizes and consist of similar numbers of cells [116]. Therefore, VEGF-A signaling may exert control over NSCs through regulating survival, which should be further explored, especially given that an autocrine role for VEGF-A in HSC survival has been demonstrated.

BDNF & IGF

Brain-derived neurotrophic factor is an endothelial secreted factor that induces the differentiation of astrocyte precursors [110,117], and *in vivo* has been shown to influence proliferation and differentiation of NSPCs in adult neurogenic regions [67,100]. *In vivo* experiments suggest that VEGF-induced secretion of BDNF from HVC capillary vasculature in the songbird brain results in newly born neuron recruitment. The amount of BDNF being secreted in this region is quite remarkable; canary brain endothelial cells secrete an average of 1 ng BDNF/10⁶ cells/24 h [67,118], and a recent study of BDNF secretion from adult-derived human brain endothelial cells revealed a similar amount of 1 ng/10⁶ cells/24 h [100]. *In vitro*, BDNF release from endothelial cells support SVZ-derived neuron outgrowth, survival and migration [100]. Although we cannot discount the fact that astrocytes also secrete BDNF, it has been reported that astrocytic BDNF may be sequestered at the cell surface, in part mediated by the truncated gp95 extracellular domain of the TrkB (a receptor for BDNF), preventing its release into the surrounding space [100]. Additionally, it has been suggested that BDNF acts in a positive feedback loop to reduce proliferation and increase neuroblast differentiation through the release of nitric oxide by NSPCs [119,120]. BDNF has also been reported to mediate exercise-induced cognitive enhancement within the hippocampus [121]. Studies of exercise-induced neurogenesis in the dentate gyrus have linked the roles of IGF-1 and BDNF together. It has been shown that exercise stimulates uptake of IGF-1 from the bloodstream into the hippocampus, where it is necessary for the observed increase of BrdU⁺ hippocampal neurons as well as the increased levels of BDNF mRNA and protein [122,123]. The neurogenic effect of IGF-1 seems to be mediated in part through estrogen signaling, where estrogen antagonists reduce neurogenesis within the dentate gyrus [124]. Previously shown to have pleiotropic effects on brain cells, new evidence suggests that IGF-1 may also play a role in neurodegenerative diseases, such as Alzheimer's disease and stroke, where levels of circulating IGF-1 are altered [125]. Thus, further investigation of the role of IGF-1 in regulating neurogenesis will provide insights of clinical importance.

PDGF & SCF

PDGF is known to be a vascular-derived growth factor, and its role within the CNS is to regulate oligodendrocyte precursor cell number. Interestingly, PDGF is implicated in brain tumor formation, where activation of its signaling pathway is present in more than 80% oligodendrogliomas and 50–100% of astrocytomas. Thus, identifying which cells respond to PDGF is crucial. In the SVZ, type B putative NSCs have been shown to express PDGFR α , and become activated in the presence of PDGF [111]. Accordingly, PDGF is reported to have mitogenic and differentiation actions on neural progenitor cells [126–128]. After intracerebroventricular infusion of PDGF, astrocyte-derived periventricular hyperplasias are formed, and increases in oligodendrogenesis are observed at the expense of olfactory bulb neurogenesis. Conversely, conditional ablation of PDGFR α in the SVZ decreases oligodendrogenesis while having little effect on neurogenesis [111]. Thus, PDGF may play a role in maintaining the balance between neurogenesis and oligodendrogenesis.

SCF (also known as Kit ligand) has been reported to be expressed by a variety of cell types including vascular endothelial cells [129,130]. Previous reports indicate that within the CNS, SCF/Kit 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 NSPCs is 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 [131–133].

PEDF

Being the first soluble factor shown to selectively activate type B NSCs, PEDF seems to contribute to stem cell maintenance within the neurogenic niche. Immunocytochemical staining for PEDF in the adult mouse brain indicates that 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 [89,134,135]. Aside from acting as a brake on cell cycle progression by promoting NSC self-renewal without affecting proliferation [136], recent evidence suggests an additional role in renewing symmetric divisions. BrdU-labeled mice treated with PEDF increase the number of BrdU⁺GFAP⁺ cells, and injection with a C-terminal-blocking peptide to PEDF reveals no significant change in the number BrdU⁺GFAP⁺ cells compared with vehicle-injected controls. Taken together, these data suggest that PEDF may not be a survival factor for NSCs, but rather plays a role in activating NSCs by stimulating self-renewal. Given that PEDF is also a potent regulator of angiogenesis [89,136,137], the link between neurogenesis and angiogenesis within the NSC niche is further strengthened, and interdependent regulation by PEDF should be further explored.

Laminin & collagen IV

Expressed on the outer surface of blood vessels, these extracellular molecules play roles in both adhesion and signaling. Collagen IV inhibits proliferation of rat NSPCs and promotes differentiation into neurons [112]. Most recently the importance of the laminin–integrin interaction within the SVZ highlights a role for laminins in migration, spreading and proliferation of NSPCs [6].

Endothelial-derived effectors potentially generated from NSC niche vasculature

FGF-2

In vivo, FGF-2 is primarily detected at sites of vessel branching within the basal lamina of blood capillaries, as well as in the endothelium of tumor 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, the latter acting through intracellular signaling mechanisms [138]. While endothelial cells can secrete this potent angiogenic factor [139] to regulate endothelial cell proliferation, migration and differentiation, type B NSCs respond to [82,140–143] and express the corresponding receptor [111,144,145]. Within the CNS, FGF-2 has been shown to affect neurogenesis and proliferation of cortical progenitors [146–148]. In fact, FGF-2 knockout mice display a decrease in olfactory bulb size, presumably owing to decreased output from neurogenic regions. Although FGF-2 can promote NSC proliferation, it does not act alone to maintain their self-renewal, and must work with other factors to accomplish this [54]. Aside from inducing VEGF expression in endothelial cells, FGF-2 can prime neural precursor responsiveness towards EGF [143].

EGF

Although the origin of EGF remains unidentified within the adult NSC niche, recent reports suggest possible sources of EGF expression and secretion to be endothelial in nature. Affymetrix microarray analysis has revealed that human dermal microvascular endothelial cells express EGF, and that this expression is further upregulated in coculture with head and neck squamous cell carcinoma cells [149]. 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

endothelial cells [109]. Within the SVZ, receptors for EGF are predominantly expressed by the type C transit-amplifying cells. Intraventricular infusion causes transit-amplifying cell proliferation while arresting neuroblast production, and *in vitro* transit-amplifying cells are stimulated to generate neurospheres and revert to a more 'stem-like state' [144].

BMPs & LIF & IL-6

The astrocytic glial compartment within the SVZ produces high levels of BMP2 and -4, however, not exclusively. Recently, it has been demonstrated that brain endothelial cells (BECs) can act as potential sources of BMPs. mRNA transcripts for BMP2 and -4 were found in the adult bEnd.3 endothelial cell line, as well as in primary brain endothelial cells. Furthermore, BMP4 protein was also detected in these BECs [150]. Shown to counteract neurogenesis *in vitro* and *in vivo* [151–153], BMP signaling increases astrocyte formation, possibly through activation of transcriptional regulators of Smads to control cell-cycle exit. Indeed, when embryonic and adult NSPCs are cocultured with BECs, the canonical BMP/Smad pathway becomes activated to reduce proliferation and induce NSPC cell-cycle exit in the presence of EGF and FGF-2 [150]. LIF and IL-6 belong to the cohort of endothelial secreted factors that promote self-renewal of adult NSCs [154], and when synergized with BMP factors, promote self-renewal of embryonic stem cells through activation of gp130-mediated STAT signaling to induce astrogenesis [154,155].

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

Stromal cell-derived factor-1 (also referred to as CXCL12) is a chemokine previously shown to direct the migration of leukocytes during inflammation. Similarly, during nervous system development of the dentate gyrus, SDF-1 signaling via its receptor, CXC chemokine receptor (CXCR)4, provides migratory cues to direct recruitment of NSPCs from the lateral ventricle to the nascent dentate gyrus. It is interesting to note that SDF-1 is expressed by endothelial cells associated with blood vessels as well as neurons, and SDF-1/CXCR4 expression persists into adulthood within the dentate gyrus. Neuroblasts expressing CXCR4 migrate towards and are attracted to activated endothelial cells of cerebral vessels that secrete SDF-1 α [156–160]. While neurospheres express CXCR4, human cerebral endothelial cells have been shown to secrete growth-related oncogene- α , also a ligand for CXCR4 [161]. Recent reports also suggest shared receptor/cytokine signaling between NSCs and the vasculature concerning growth-related oncogene- α /CXCR4 and Ang-1/Tie2 [7,162]. Ang-1 can be expressed by endothelial cells, as well as mural cells, and seems to be upregulated poststroke. While having a general neuroprotective effect on the nervous system, it has been shown to directly regulate stem cell differentiation and migration through Tie2 and CXCR4 receptors [157,159,163–165].

TGF- β

Reported to induce VEGF expression by vascular endothelial cells and gliomas [166,167], TGF- β serves to be an important neurogenic growth factor. While produced in a latent form in mesenchymal and epithelial cell types, endothelial cells and mural cells have also been shown to produce a latent form of TGF- β that can be activated in endothelial cell-mural cell cocultures [168–170]. Because TGF- β 1 knockout mouse models demonstrate a reduced potential for neuron survival [171], and transgenic mouse models overexpressing TGF- β 1 under control of the glial fibrillary acidic protein promoter show a reduction in NSC/precursor proliferation [172], it is believed that TGF- β 1 has no impact on NSC/NPC identity or on differentiation. Rather, it is believed to affect proliferation potential, as demonstrated by an arrest in G0/G1 phase of the cell cycle [173]. In cell culture, NSCs and progenitors express TGFRI, II and III, and TGF- β 1 decreases the expansion of these cells in a dose-dependent manner.

Eph/ephrins

The Eph/ephrin molecules belong to a family of receptor tyrosine kinases and associated transmembrane ligands, respectively, that have established roles in vascular development. However, more recent data suggest a role for Eph receptor and ephrin ligand interaction within the CNS, and that 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 [174]. 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 NSCs. Additionally, ephrin-B2/3 are also localized to SVZ astrocytes. By contrast, ephrin-A2 is predominantly expressed on transit-amplifying cells and neuroblasts [175,176]. 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 [177]. 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 [2, 175,176].

Circulating effectors that potentially regulate the NSC niche

Erythropoietin & prolactin

Acting as transportation conduits, blood vessels facilitate hormone circulation through the body, bestowing upon them the potential to affect all cells in tissue-specific environments. Of these circulating hormones, erythropoietins and prolactins are reported to have an effect 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 [178]; however, the responsiveness to prolactin within the dentate gyrus is negligible, owing to diversity even among adult NSC niches [4, 178]. Although erythropoietin synthesis can be activated in astrocytes and neurons [179–181], 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 endothelial cells and within caveoli [182,183], and systemic administration of erythropoietin has been shown to penetrate the BBB as an intact molecule [184]. 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 [185], and erythropoietin-activated endothelial cells promote the migration of neuroblasts through the secretion of matrix metalloproteinase-2 and -9 [187]. Thus, further investigation of the penetrance and potential function of erythropoietin in the adult NSC niche is warranted.

Clinical relevance

This relationship between the vascular and nervous systems presents itself early in development and persists throughout adulthood. The vasculature maintains some of the most important neural microenvironments to prevent aberrant regulation leading to the onset of neurovascular disease. Thus, dysregulation or degeneration of one of these interdependent systems can lead to the onset of prevalent CNS diseases and disorders.

Cancer

Within the brain there is mounting evidence substantiating the existence of a cancer stem cell–vascular niche complex [187], which may explain why some of the most aggressive brain tumors are highly angiogenic [188–190]. Under normal conditions where the BBB is strictly maintained, tumor vessels have been shown to lack a functional BBB [191]. Coculture experiments plating primary human endothelial cells with CD133⁺nestin⁺ cancer stem cells reveal a role for endothelial cell maintenance of cancer stem cell proliferation and self-renewal. In contrast to CD133[−] tumor cells that generally remained separate from vascular-like structures, CD133⁺ cells quickly form intimate contacts with endothelial tubes. Additionally, after 2 weeks in coculture, tumor spheres increase in size and are five-times larger than spheres cocultured with control cells. *In vivo*, growth of orthotopic brain tumor xenografts are maintained by preculturing the brain tumor cells with primary human endothelial cells, and increasing the number of capillaries within these brain tumors seems to augment the number of self-renewing and multipotent cells contained within the tumor. Thus, endothelial cells appear to propagate brain tumor survival *in vivo* [187].

CNS disorders & disease

Aside from the heart, it is interesting to note that diseases affecting the brain's vasculature are responsible for more deaths than circulatory disorders of any other organ [191]. For example, the majority of Alzheimer patients suffer from microvascular degeneration and cerebral amyloid angiopathy [192,193], with cerebral micro-infarcts and cerebral amyloid angiopathy-related intracerebral hemorrhages affecting 35 and 10% of patients, respectively. Furthermore, amyloid- β can directly affect the cerebral vasculature, leading to vasoconstriction, reduced blood flow and increased vascular resistance, causing endothelial cell damage [94]. Supporting the notion that Alzheimer's disease is actually a vascular disorder, there is surprisingly little evidence demonstrating that amyloid independently causes neurotoxicity or neurodegeneration of synapses, metabolism or decreases in neurons [8,9]. Amyotrophic lateral sclerosis has also been suggested to harbor a vascular disease component. Decreased levels of VEGF are responsible for spinal-cord perfusion defects and chronic ischemia that primarily affect α -motor neurons in the ventral horn that lead to adult-onset motor neuron degeneration and paralysis [194]. In fact, in humans carrying low-expression gene variations of VEGF who are at increased risk for amyotrophic lateral sclerosis [195], VEGF administration has been partially successful in protecting and preconditioning neurons against hypoxic stress [196, 197].

Another CNS disease involving vascular defects is Moya-moya, in which irreversible blockage of primary blood vessels to the brain leads to stroke and seizures owing to the lack of efficient blood and oxygen delivery [198]. Although the few treatments for Moya-moya disease are relatively invasive, promoting *de novo* angiogenesis could provide a better alternative [199]. Finally, this neurovascular relationship of CNS disorders and disease may be most definitively illustrated through stroke and ischemic brain damage. Ischemia-induced brain damage induces both angiogenesis and neurogenesis [86,88,91,191,200–205]. While poststroke neuroblasts migrate along vessels and astrocytes [87,161] to sites of active angiogenesis within the ischemic boundary [86,88,206], blocking this angiogenesis *in vivo* significantly reduces the level of newly born neuroblast migration [88]. Certainly, data from *in vitro* studies also suggest a neurovascular relationship, wherein cocultures of cerebral endothelial cells with NSPCs harvested from ischemic and nonischemic boundaries respectively, significantly increase proliferating NPC numbers [205].

Conclusion

Given their diversity, both in structure and function, their early appearance and critical role in embryonic development, and their ubiquitous presence within all tissues, it is not surprising that blood vessels far exceed the normal functions of nutrient and oxygen transport. The somewhat plastic nature of vascular cells allows them to be reciprocal modulators of their surrounding environment, not only by responding to extracellular cues, but translating them into signals that serve to direct and instruct neighboring cells. This unique ability of vascular endothelium has been proposed for some time, and now with the rapid advancement of imaging and molecular technology their role(s) in stem cell maintenance and niche regulation is beginning to be revealed. Understanding the cellular mechanisms underlying neuronal regeneration, and the important role for the vasculature therein, both under normal homeostasis and disease conditions, will enable the development of more specific and targeted therapies aimed at promoting neurovascular repair and regeneration.

Executive summary

Vascular endothelium

- Normal role of the vasculature is to establish proper blood circulation that allows for the distribution of oxygen and nutrients to tissues, as well as metabolic waste removal.
- The vascular endothelium is highly metabolically active to allow physiological regulation of proliferation, survival, innate and adaptive immunities, homeostatic maintenance, blood cell trafficking and control of vasomotor tone.
- Heterogeneity among the endothelial cell compartment results from diversity in structure and composition; this leads to differences in cell size, shape, extent of mural cell coverage and permeability.

Endothelial cell regulation of neural stem cell niche

- Endothelial-secreted factors documented to affect aspects of adult neural stem cell niche regulation include: leukemia inhibitory factor, brain-derived neurotrophic factor, bone morphogenic proteins, FGF-2, IGF-1, VEGF, PEDF, TGF- β , EGF, IL-8 and PDGF.
- Blood vessels also provide access to circulating systemic factors, including sex hormones, glucocorticoids, erythropoietins and prolactins.
- Blood vessel extracellular matrix basal lamina may also regulate adult neural stem cells through interactions via collagen IV and laminins.

Future perspective

- Because many CNS disorders exhibited disrupted neural and vascular systems, fully examining the inter-relationship between these two systems will be critical for developing more effective and targeted approaches to CNS disorders.

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Figure 1. Proposed endothelium-derived regulators of the adult neural stem cell niche*

Vascular endothelium-derived factors known to regulate the adult NSC niche can originate from the endothelial cell itself, the circulation or the ECM surrounding the blood vessel.

*Referring to the subventricular zone.

Ang: Angiopoietin; BDNF: Brain-derived neurotrophic factor; EC: Endothelial cell; ECM: Extracellular matrix; GRO: Growth-related oncogene; LIF: Leukemia inhibitory factor; NSC: Neural stem cell; SCF: Stem cell factor; SDF: Stromal cell-derived factor.

Table 1

Summary of endothelium-derived factors that regulate neural stem/progenitor cells.

Endothelium-derived factor	Effect on NSPCs			Ref.
	Proliferation	Survival/self-renewal	Differentiation	Migration
VEGF	✓			[54,67,115,116]
FGF-2	✓		✓	[82,140–143,146–148]
EGF	✓	✓		[109,144,149,150]
BMPs	✓			[152–154]
LIF		✓		[155,156]
IL-6		✓		[155,156]
BDNF	✓		✓	[54,100,119,120]
IGF-1	✓		✓	213–125]
PDGF	✓		✓	[111,126–128]
SCF		✓		[131–133]
PEDF		✓		[89,134–137]
SDF-1			✓	[157–161]
GRO- α			✓	[162]
Angiopoietin			✓	[158,160,164–166]
TGF- β	✓			[172–174]
Collagen IV	✓		✓	[112]
Laminin	✓			[6]
Erythropoietin	✓			[183–187]
Prolactin	✓		✓	[4,179]
Eph/eprins	✓			[2,175–178]

BDNF: Brain-derived neurotrophic factor; BMP: Bone morphogenetic protein; GRO: Growth-related oncogene; LIF: Leukemia inhibitory factor; NSPC: Neural stem/progenitor cell; SCF: Stem cell factor; SDF: Stromal cell-derived factor.