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Perivascular instruction of cell genesis and fate in the adult brain

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Abstract

The perivascular niche for neurogenesis was first reported as the co-association of newly generated neurons and their progenitors with both dividing and mitotically quiescent endothelial cells in restricted regions of the brain in adult birds and mammals alike. This review attempts to summarize our present understanding of the interaction of blood vessels with neural stem and progenitor cells, addressing both glial and neuronal progenitor cell interactions in the perivascular niche. We review the molecular interactions that are most critical to the endothelial control of stem and progenitor cell mobilization and differentiation. The focus throughout will be on defining those perivascular ligand-receptor interactions shared among these systems, as well as those that clearly differ as a function of cell type and setting, by which specificity may be achieved in the development of targeted therapeutics.

Neural stem cells (NSCs) and more restricted neuronal and glial progenitor cells are dispersed widely throughout the adult vertebrate brain^{1–3}. Long after fetal development, multipotent NSCs continue to reside in the forebrain ventricles of experimental animals and humans alike^{4,5}, whereas committed neuronal progenitor cells also remain in both the subependyma of the lateral ventricles^{6–9} and the subgranular zone of the hippocampal dentate gyrus^{10,11}. In adult mammals, active neurogenesis persists in each of these regions, an extensive subject that has recently been reviewed elsewhere¹². In addition, a larger pool of glial progenitor cells pervades adult tissue parenchyma (reviewed in ref. 13). All of these progenitor populations persist in adult humans and, as such, all are potential therapeutic targets (reviewed in ref. 14).

As stem cell progeny depart their localized niches of stem cell maintenance, they commit to more restricted lineages, at which point they are still mitotic, but subject to senescence¹⁵. Accordingly, lineage-restricted neuronal progenitor cells of the forebrain subependyma and hippocampus serve as transit-amplifying cells^{16,17}, as do glial progenitor cells of the white matter, which are similarly able to divide and yield phenotypically restricted daughters, and yet are incapable of sustained self-renewal¹⁸. Many recent studies have investigated those features that both define and distinguish the stem cell microenvironment from that of transit-amplifying progenitors (reviewed in ref. 19). These studies have revealed that, in both the mammalian ventricular wall^{20,21} and hippocampus²², as well as in the neurogenic regions of the avian brain²³, the local microvascular bed is important for providing a permissive environment for NSC expansion, neuronal differentiation and parenchymal migration. This

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review will focus on the anatomy and molecular constituents of the perivascular niche for adult neurogenesis, as a means of defining those processes by which addition of new neurons to adult brain tissue occurs naturally, and by which it might be enabled heterotopically.

The perivascular niche for neurogenesis

The normal perivascular environment of the brain includes endothelial cells, smooth muscle pericytes and fibroblasts, as well as microglia, glial progenitors and astrocytic endfeet. The combinatorial interactions among these cells and their region-specific responses to local signaling cues provide a rich set of perivascular microenvironments by which newly generated cells may be serially engaged by both endothelial and non-endothelial cytokines at distinct stages during their mitogenesis, differentiation and parenchymal recruitment^{23–27}.

The perivascular niche for neurogenesis was first described in the adult mammalian hippocampus as the anatomically contiguous co-association of newly generated neurons with dividing endothelial cells²². A direct role for endothelial mitogens in driving this process was then demonstrated *in vitro*, providing initial evidence that the co-association of endothelial cells with dividing NSCs might be causal²⁸. These studies followed earlier reports that angiogenesis preceded neuronal recruitment in an avian model of hormonally modulated neuronal addition, the songbird vocal control nucleus HVC²⁹. In this model of noncontiguous angiogenesis and neurogenesis, endothelial expansion was found to result in the production of vascular neurotrophins that both directed the recruitment of newly generated neurons to the angiogenic vascular bed and supported their differentiation and survival²³. Together, these studies led to the concept of a perivascular niche for neurogenesis, in which neural stem and progenitor cells serially receive instructive and permissive cues from the local microvasculature, enabling both their proliferative expansion and tissue invasion. This concept has proven to be applicable to the development of multiple organ systems, where tissue-defined vascular beds have been found to direct cell fate, proliferative expansion³⁰ and tumor invasion³¹.

Perivascular agents serially support neuronal development

In the adult mammalian brain, neuronal production is typically restricted to a few discrete regions of subependymally derived granule cell neurogenesis³. In each venue, stem cell mobilization and progenitor cell expansion appear to occur in tight co-association with the local capillary microvasculature. In the hippocampus, Palmer and Gage first reported the contiguous co-association of angiogenesis and neurogenesis in the subgranular zone of the adult dentate gyrus²², suggesting that endothelial cells and neural progenitor cells were either responding to a common mitogenic signal or that the dividing cells of one phenotype generated mitogens that were able to trigger the synchronous mitotic expansion of the other. Several groups subsequently reported that the proliferative expansion of hippocampal endothelial and neuronal progenitor cells is co-regulated by vascular endothelial growth factor (VEGF), such that hippocampal neurogenesis might, in effect, be co-regulated with angiogenesis^{22,32–34} (Fig. 1). Notably, another possibility is that newly generated neurons and endothelial cells both derive from a common stem cell with both neural and hemangioblastic lineage competence³⁵, a still-controversial concept that was recently revived by demonstrations of endothelial generation from malignant glioma cells³⁶.

As in the hippocampus, subependymal capillaries in the wall of the lateral ventricles may serve to regulate both the mitotic activity of neural stem and progenitor cells, and the differentiation of their neuronal progeny^{20,21,24}. Brain microvascular endothelial cells support the differentiation and survival of newly generated neuroblasts in explants of the adult striatal ventricular wall, by serving as rich sources of secreted brain-derived

neurotrophic factor (BDNF)²⁴. The mitotic expansion of cultured NSCs can also be supported by endothelial cells²⁸, and subsequent neuronal parenchymal invasion and progenitor expansion can be supported by this subependymal capillary network²⁰ (Fig. 2). Similarly, the potentially causal relationship between angiogenesis and neuronal addition in the adult songbird brain has also been examined, as testosterone treatment triggers both angiogenesis and neuronal addition to the principal song control nucleus, HVC²³. Testosterone induces the local production of VEGF in HVC, and the resultant VEGF-mediated induction of local angiogenesis is followed by the recruitment of newly generated neurons from the overlying ventricular zone to the mitotically active capillary bed.

Adult neurogenic regions can therefore exhibit contiguous mitotic angiogenesis and neurogenesis, as in the hippocampus, contiguous but mitotically quiescent endothelial support of neuronal progenitor cell expansion, as in the ventricular subependyma, or noncontiguous regulation of neuronal recruitment via endothelial chemotactic and neurotrophic cytokines, as in the HVC and in mammalian neurogenic regions. In broad terms, each of these model systems of adult neurogenesis exhibits a critical need for perivascular elements in providing instructive cues for neuronal production and migration. Chief among these perivascular signals for stem and progenitor cell expansion are activators of several important neural mitogenic pathways that include purinergic signaling, nitric oxide signaling, and both VEGF-dependent and pigment epithelium-derived factor (PEDF)-dependent signaling, each of which appear to act in concert with non-perivascular cytokines to coordinate NSC division and self-renewal. In addition, after initial asymmetric division to yield transit-amplifying progenitors, a different set of agents that promote neuronal differentiation and survival then become more germane. These include BDNF, acting in concert with matrix-derived signals encountered by newly generated neurons on their transit from the subependyma to the perivascular niche (Fig. 2). We will discuss each of these regulatory steps in turn.

Perivascular purinergic signaling in the neurogenic niche

Signaling by the P2Y class of purine receptors (P2YRs) contributes to NSC self-renewal³⁷. In particular, ADP can signal through P2YR1, P2YR2 and P2YR4 to drive the self-renewing expansion of both murine and human NSCs. Several groups have identified perivascular astrocytes and possibly pericytes in neurogenic regions as critical sources of the CD39L1 nucleotide triphosphate dinucleotide phosphorylase (NTPDase-2), an ectonucleotidase that degrades ATP to ADP, thereby making ADP available to activate P2YR signaling. In particular, high concentrations of CD39L1 in neurogenic regions of the adult rodent brain have been identified³⁸, and ectonucleotidase activity is present in high concentrations in the vascular beds subserving both the sub-ependymal and subgranular zones, the two major neurogenic niches of the adult forebrain³⁷. P2YR1 in particular is expressed by NSCs, which release ATP. On the basis of these observations, we can postulate that ATP release by neural stem and progenitor cells, coupled with regionally restricted expression of the CD39L1 NTPDase-2 by the subependymal and subgranular zone vascular beds, may provide purine nucleotides to purine receptive progenitors at levels sufficient to establish an autonomous paracrine network favoring perivascular expansion.

These data suggest that perivascular purinergic signaling may be critical for the self-renewing expansion of subependymal neural progenitor cells. Indeed, purinergic signals may dictate the proliferative expansion not only of neurogenic NSCs, but of glial progenitor cells, which may be similarly responsive to extracellular purine nucleotides^{39,40}.

Perivascular nitric oxide signaling regulates cell genesis

Nitric oxide (NO) signaling is a critical regulator of both angiogenesis and neurogenesis. In light of the frequency of NO-producing cells in stem cell niches, the role of NO in regulating angiogenesis in a number of systems and the concurrence of neuronal mitogenesis in some NO-producing regions of the adult brain, NO has been proposed to be an important regulator of cell genesis in the perivascular niche^{41,42}. A series of initial reports highlighted the role of NO as a tonic repressor of adult neurogenesis by showing that the nitric oxide synthase (NOS) inhibitors L-NAME and 7-NI increased neurogenesis in both the rodent dentate gyrus and subventricular zone^{41,43–45}. Similarly, it was noted that NO donors suppressed the proliferation of cultured NSCs, and were identified as doing so by the inhibition of the epidermal growth factor receptor (EGFR)-dependent PI3K/Akt signaling⁴⁶. Interestingly, although NO acts to suppress NSC expansion, NSCs themselves release NO, which may in turn feed back on the vascular bed to induce the production of both BDNF and VEGF⁴⁷. This observation introduces the possibility of reciprocal interactions by which mobilized NSCs can modulate their own niche for neurogenesis, thereby potentiating BDNF-mediated neuronal differentiation and postmitotic neurotrophic support (Fig. 2).

In addition to acting directly on receptive G protein-coupled receptors in both NSCs and non-neural vascular components, NO can also modify signaling through receptor tyrosine kinases, which are critical modulators of NSC expansion. As a case in point, EGF has been identified as a potent mitogen for NSCs; it appears to be largely of glial origin *in vivo*. Yet NO can induce the reversible S-nitrosylation of the EGFR, and may thereby suppress EGF-dependent NSC expansion⁴⁸. Notably, such nitrosylation-based receptor inactivation is a redox state-dependent event and, as such, it may serve to link the fate decisions of NSCs to tissue oxidation state. These observations may have especially broad implications for the influence of ischemia on the role of the perivascular niche in neural stem mobilization.

In that regard, although most *in vivo* pharmacological studies have indicated that NO acts to tonically suppress neurogenesis in the normal adult brain, its effects may be vastly different under conditions of hypoxic ischemic stress, especially given the number of concurrently active signaling systems modulated by NO. Thus, although most earlier studies emphasized that NO serves to inhibit both NSC expansion and neuronal production, a number of recent studies have stressed the cell type, dose and context dependence of NO's effects^{41,42,49–52}. For instance, several studies have indicated that, in the unperturbed CNS, neuronal NOS, and hence neuronally derived NO, may suppress NSC expansion by potentiating their neuronal differentiation in a BDNF-dependent manner through the NO-triggered release of BDNF by NO-receptive NSCs⁴². On the other hand, a recent report noted that under conditions of hypoxic stress, inducible NOS (iNOS)-generated NO can potentiate stem cell proliferation in a p21Ras/MAPK-dependent manner⁵¹. Interestingly, this report implicated iNOS in the excessive and heterotopic hippocampal neurogenesis that has been noted in response to seizure activity. Taken together with independent observations that NOS activity promotes stem cell expansion in hypoxia⁵⁰ and gliomas^{53,54}, these findings might lead one to postulate that the ambient oxygen tension might modulate the cellular effects of NO such that its role in the normal adult perivascular environment may differ from that in the more hypoxic environments of ischemic tissue and tumors. Clearly, further dissection of the relative roles of NO as released by the different constituents of the perivascular niche, considering the distinct thresholds for NOS-mediated NO production by each of the three NOS isoforms, NOS1–3, and the relative effects on hypoxic ischemia and other pathological redox states, is needed before we can fully describe NO's actions in the perivascular niche for neurogenesis.

Endothelial support of NSC expansion and differentiation

The secreted glycoprotein PEDF (also known as serpin-F1), previously recognized as having anti-angiogenic actions in the retina⁵⁵, was further identified as a subependymal vascular signal for NSC expansion⁵⁶. A series of subsequent studies demonstrated that PEDF acts to promote stem cell self-renewal via potentiating Notch-dependent transcription, at least in part by relieving the nuclear receptor co-receptor-mediated repression of Notch-responsive promoters⁵⁷. The critical role of Notch signals in maintaining adult NSC pools has been well described⁵⁸ and may be further potentiated in the perivascular niche by the endothelial expression of Dll4, a notch ligand that is selective to vascular beds^{59,60}. As such, PEDF defines a niche signal biasing the symmetric division of NSCs, thus potentiating their undifferentiated expansion to the detriment of neuronal differentiation. In so doing, PEDF's actions may prove to be complementary to those of purinergic signals, which appear to drive symmetric stem cell expansion while concurrently suppressing neuronal differentiation³⁷.

In contrast with perivascular mitogens, such as the purines and PEDF, endothelial BDNF appears to be critical for the induction of neuronal differentiation by stem cell progeny following their asymmetric division to give rise to transit-amplifying daughters²⁴. As such, it is important for regions of NSC expansion to exclude BDNF, and to therefore limit its availability to areas of desired neuronal differentiation and maturation. In the normal adult ventricular wall, parenchymal striatal BDNF is excluded from the subependymal stem cell population by a dense layer of subependymal astrocytes expressing truncated *trkB*⁶¹, which may act as a scavenger receptor to prevent BDNF's reception by periventricular NSCs. However, on their transit from the ventricular wall, stem cell progeny quickly encounter perivascular BDNF, which in turn potentiates their neuronal differentiation and maturation²⁷. This sequence is also suggested by the pattern of receptor expression by NSCs and their transit-amplifying progeny (type B and C cells, respectively)³; although both express the low-affinity neurotrophin receptor p75 (ref. 62), only lineage-restricted migratory neuroblasts (type A cells) appear to express the high-affinity BDNF receptor *trkB*^{63,64}. Indeed, p75 expression may define the potentially neurogenic fraction of subependymal cells⁶². The absence of *trkB* expression in NSCs and early transit-amplifying neuronal progenitors and its subsequent appearance only on later-stage neuroblasts suggests that BDNF's actions *in vivo* may be principally directed toward neuronal differentiation and postmitotic survival. Similarly, analysis of nestin-GFP transgenic mice has shown that *trkB* expression by newly generated hippocampal granule neurons develops with their postmitotic maturation⁶⁵; cycling stem and progenitor cells in the subgranular zone of the dentate gyrus express little *trkB*. Although the largely postmitotic effects of BDNF on neuronal maturation and survival was predicted by earlier studies *in vitro*^{9,66,67}, only recently has the critical role of endothelial cells in providing that BDNF become appreciated.

Vascular chemokines as directional modulators of migration

Although subependymally situated capillary vessels appear to strongly potentiate NSC expansion and initial neuronal mitogenesis, once daughter cells depart the subependymal niche, the parenchymal perivascular bed becomes a source of both trophic support and migratory cues for the newly generated neuroblasts. These perivascular signals for neuroblast immigration are both contact dependent and humoral. In regard to the former, a host of matrix constituents that include tenascin, laminin and its family members, the heparan sulfates and the chondroitin sulfate proteoglycans have all been identified as perivascular substrates for neuronal migration. Several groups have focused on laminin and have reported that the transit-amplifying daughter cell progeny of NSCs express $\alpha\beta 1$ integrin, which serves as a laminin receptor, and may permit neuronal progenitors to migrate into the brain parenchyma^{20,68}.

In the rostral migratory stream, the rostral extension of the ventricular subependyma, this association of newly generated neuroblasts with the adluminal surfaces of capillaries is maintained; neuroblasts migrate along a physical scaffold of longitudinally oriented capillary endothelial cells^{26,69}. In this microvascular network, humoral signals for neuronal differentiation and survival become an integral part of the perivascular niche. Endothelial BDNF in particular appears to act as both a chemoattractant and survival factor for new neuronal migrants²⁷, recruiting them to the local microvascular bed and supporting their survival as they transit to the BDNF-rich internal granular layer of the olfactory bulb. Notably, the serial attraction and support of newly generated neurons by microvascular endothelial-derived BDNF proceeds in a manner akin to that by which local endothelial BDNF attracts newly generated neurons to the adult HVC of canaries. As such, endothelial BDNF-directed neuronal immigration may prove to be a conserved mechanism of neuronal addition to neurogenic regions of both the adult mammalian and avian brain. Indeed, the location of microvascular beds rich in endothelial-derived BDNF may predict that those regions are permissive for neuronal addition in adulthood.

In addition to BDNF, a broad set of endothelial and pericytic cytokines have been associated with the direction and support of adluminal perivascular migration by newly generated neuroblasts. CXCR4 and CXCR7 have been especial targets of interest, as these SDF1/CXCL12 receptors are expressed on newly generated neuroblasts, both in development and in the adult. In a recent study, Temple and colleagues⁷⁰ demonstrated that the subependymal capillary bed expresses high levels of SDF1/CXCL12, which may attract CXCR4-expressing neuroblasts to leave the subependyma, while concurrently triggering their upregulation of $\alpha 6\beta 1$ integrin. This integrin isoform mediates the migration of these neuroblasts along the laminin-rich adluminal walls of the parenchymal microvasculature, whereupon the new neuronal migrants achieve access to endothelial BDNF and its attendant differentiative and trophic support (Fig. 2).

Niche interactions regionally specify neurogenesis

Neuronal addition to the adult brain entails serial events that are orchestrated by both spatially and temporally distinct signals to which neuroblasts are exposed as they traverse distinct compartments that together comprise the neurogenic niche. Thus, in both the avian and mammalian adult ventricular wall, the persistence of neurogenesis reflects the unique interaction of the periventricular environment and its constituent phenotypes with the subventricular microvascular bed, which together may provide the combinatorially specific array of signals that both permit and potentiate neurogenesis. The ventricular wall itself is comprised of both ependymal cells and subependymal astrocytes, each of which may provide unique neurogenic signals that act together to provide a permissive environment for neuronal production. These signals include the regionally delimited provision by ependymal cells of the BMP inhibitor noggin, which permits NSC daughters to escape a BMP-driven glial fate and instead differentiate as neurons⁷¹. Such ependymal cell-derived neurogenic signals may be induced by the interactions of these cells with the ventricular cerebrospinal fluid (CSF) with which they are in contact; CSF contains a panoply of humoral signals, such as Sonic Hedgehog and insulin-like growth factor 2, that may directly activate subependymal cells through their primary cilia, which traverse the ependymal layer to contact the ventricular CSF^{72–74}.

Yet the periventricular provision of a permissive environment for NSC expansion and neurogenesis may also be the product of unique combinatorial interactions between ependymal and subependymal cells and the subventricular microvasculature. For instance, the provision by ependymal cells of a neurogenic environment might be triggered by the subependymal cells as a product of their concurrent interactions with the CSF apically, and

the local subependymal vasculature basally. Indeed, it seems likely that the combinatorial integration of signals from both CSF and the perivascular niche, in tandem with a reciprocal interaction with adjacent ependymal cells, might dictate the geographic restriction of adult neurogenesis to discrete regions of the adult ventricular wall. Surprisingly, despite many years of elegant studies of the anatomy of the adult mammalian subependyma^{75,76}, relatively few studies have investigated the paracrine interactions among cells in the adult ventricular wall, the combinatorial nature of which defines the regional specificity of neurogenesis and gliogenesis.

Neuronal addition in the adult songbird brain

In the adult songbird brain, neurogenesis persists in several regions of the forebrain responsive to gonadal steroids, including the forebrain vocal control nucleus HVC^{1,29}. In adult canaries, testosterone-induced neurogenesis in HVC was uniformly preceded by a marked increase in endothelial cell division and angiogenesis²⁹. BDNF is known to be generated by microvascular endothelial cells²⁴ and to have a role in directing the neuronal differentiation of subventricular zone progeny^{66,67,77}. Testosterone has been shown to trigger the production of VEGF by large neurons in HVC; VEGF then acts through VEGF receptor 2 to stimulate the mitotic expansion of HVC capillaries²³. The expanded endothelial cell population then serves as a source of secreted BDNF, which acts to support the recruitment of newly generated neurons from the overlying ventricular zone (Fig. 3). Pharmacological inhibition of VEGF receptor 2 blocks both HVC angiogenesis and neuronal addition²³, whereas local overexpression of BDNF without either androgen treatment or antecedent angiogenesis is sufficient to restore both HVC neuronal addition and song⁷⁸. Thus, testosterone-induced neuronal addition in the HVC appears to require antecedent androgen-stimulated angiogenesis, with the release of BDNF by the expanded HVC microvascular bed. As such, the songbird HVC exemplifies the paracrine support of neuronal recruitment by a noncontiguous microvascular bed, which then attracts new neuronal migrants to the perivascular niche in which those neurons can mature and integrate.

A paradoxical feature of androgen-induced HVC angiogenesis has been its rapid rate of onset; in testosterone-treated females, endothelial proliferation begins within 2–3 days of treatment, even though VEGF mRNA levels are not detectably elevated until 4 days after treatment²³. The rapidity of the capillary response to androgen treatment suggested that HVC angiogenesis might be subject to additional mechanisms of androgen-linked control, which might in turn regulate HVC neuronal addition. In that regard, during both development and tumor invasion, angiogenesis is facilitated by the activity of matrix metalloproteases (MMPs), particularly the gelatinases MMP2 and MMP9, which act to release matrix-bound angiogenic cytokines⁷⁹. Testosterone has been shown to induce perivascular production of MMPs in HVC and potentiate neuronal addition⁸⁰ by rapidly and specifically inducing perivascular gelatinase activity in HVC. Notably, testosterone-treated birds given a gelatinase inhibitor exhibited marked reductions in endothelial cell division, accompanied by substantially diminished HVC neuronal recruitment⁸⁰. These experiments revealed endothelial MMP2 to be a critical regulator of cytokine access in the perivascular niche; its upregulation appeared to be necessary for the progression of both angiogenesis and neuronal addition, likely through the release of matrix-bound cytokines critical to both processes. In adult songbirds, the early androgenic induction of endothelial MMP2 thus comprises an important regulatory checkpoint for neuronal addition to HVC. In adult mammals, an analogous process of erythropoietin-triggered release of MMP2 and MMP9 appears to be necessary for the perivascular immigration of neuroblasts into the neostriatum after hypoxic ischemia⁸¹. As such, the endothelial production of matrix metalloproteinases may be critical for the perivascular provision of a permissive environment for neuronal immigration in avian and mammalian brain alike.

Coordination of angiogenesis and neurogenesis in disease

The perivascular space may provide a critical niche for the mobilized expansion and differentiation of new cells recruited in response to injury or disease, as well as a conduit for their directed migration. A number of studies have documented both the mobilization of NSCs after ischemia and the subsequent migration of newly generated neurons into affected regions^{82–84}. Notably, the neuronal migrants typically follow adluminal migratory paths and appear to require the perivascular space for both migratory and neurotrophic support^{25,85}. Similarly, the striatal capillary bed appears to provide the principal migratory route by which new neuroblasts invade the adult striatum in response to BDNF overexpression⁸⁶.

Yet despite this robust phenomenology documenting the use of perivascular routes for neuronal penetration into, and transit through, adult brain parenchyma, little is known of the specific signals that mediate this process. In a similar vein, the molecular signals that trigger the initial expansion of NSCs in response to injury remain unclear. In both cases, however, many of the ligands and pathways implicated in homeostatic NSC turnover are likely to be involved. For instance, in response to injury or ischemia, damaged astrocytes may cooperate with the local vascular endothelium to mobilize the resident progenitor pool: astrocytes release substantial bursts of ATP in response to injury that initiate inter-glial calcium waves, which in turn trigger further ATP release in the astrocytic syncytium⁸⁷. In the perivascular niche of the adult subependyma, this advancing wave of interstitial ATP release might be expected to encounter a subependymal capillary bed unique for its high-level expression of CD39L1, which would in turn be expected to catalyze the rapid local production of ADP^{37,38}. As a P2YR1 agonist, the resultant interstitial burst of ADP would be expected to potentiate NSC expansion. Similarly, a number of potent angiogenic factors able to co-regulate NSC expansion, such as VEGF, EGF, FGF2 and NO, have been found to be locally upregulated in response to both ischemia and injury, and might be expected to link angiogenesis with the neurogenic responses to these insults⁸⁸.

Neuroimmune modulation of the perivascular niche

A number of studies have focused on the specific effects of both stress and inflammation on hippocampal neurogenesis, and have emphasized the role of inflammatory mediators in modulating both NSC turnover and neuronal mitogenesis. Local inflammation within brain parenchyma is often angiocentric, and the effects of inflammation on the perivascular niches for both neurogenesis and gliogenesis may be profound.

The effects of inflammation on both progenitor mobilization and the perivascular modulation thereof have been well-studied in radiation injury, which is associated with both diminished stem and progenitor cell turnover and substantial local inflammation. In particular, radiation-induced decrements in hippocampal neurogenesis have been shown to be products of post-radiation inflammation, which is largely perivascular⁸⁹. Post-radiation dentate granule neurogenesis could thus be restored in part by treatment with the nonsteroidal anti-inflammatory medication indomethacin⁹⁰. As such, the cellular mechanisms by which perivascular inflammation can influence neuronal and glial cell genesis in the CNS comprise highly attractive targets for future investigation.

The perivascular niche for gliogenesis

Normal glial progenitor cells of the adult forebrain parenchyma, as well as their neoplastic derivatives, may also reside and selectively expand in a perivascular niche. Indeed, the endothelial provision of a perivascular niche for gliogenesis has become of great interest in regard to glial turnover and fate in the adult white matter, in which a number of potential ligand-receptor systems have been identified that may comprise targets for modulating

astrocytic and oligodendrocytic recruitment. Sim and colleagues⁹¹ first established the gene expression repertoire of adult glial progenitor cells and identified a number of ligand-receptor relationships that suggested specific vascular ligands of potential importance to the homeostatic maintenance of glial and oligodendrocyte progenitors. Foremost among these was the pleiotrophin–receptor tyrosine phosphatase- β/ζ (RTPZ) system. *PTPRZ1*, the gene encoding receptor tyrosine phosphatase- β/ζ , is selectively expressed by adult glial progenitors⁹¹, whereas its primary ligand, pleiotrophin, may be generated both autogenously and by endothelial cells⁹². Pleiotrophin has been shown to stimulate stem cell expansion in a number of tissues, including tumors, in whose genesis and anaplastic progression it has been implicated⁹³. Thus, endothelial pleiotrophin, and its consequent suppression of glial progenitor cell–borne RTPZ, might be expected to result in the perivascular mobilization of glial progenitor cells, providing a route for the induction of glial progenitor cell expansion by activated vascular beds.

Endothelial cells actively support the maintenance of oligodendrocyte precursor cells⁹⁴, and perivascular endothelin has been shown to directly modulate gliogenesis and glial progenitor fate, acting directly through endothelin B receptors expressed by parenchymal GPCs⁹⁵. Notably, the perivascular niche for gliogenesis may be a critical target of ischemic disease and hypoxic stress. The exposure of endothelial cells to sublethal levels of oxidative stress abrogates their support of oligodendrocyte precursor viability⁹⁴. This intriguing result provides a potential mechanistic basis for the delayed loss of oligodendrocytes and their precursors following insults ranging from transient hypoxia to radiation injury, which share brief, but profound, oxidative stress as a feature and that have long been co-associated with delayed vascular injury.

Coordinate regulation of angiogenesis and gliomagenesis

The perivascular niche for gliogenesis is also of particular interest in that it may share molecular homologies with the vascular microenvironment in which gliomagenesis and tumor invasion proceed³¹. Indeed, a number of recent studies investigating the molecular basis for the vascular support of glioma progression have expanded our understanding of endothelial-progenitor interactions in normal adult tissue; the respective fields of neuro-oncology and adult neurogenesis are now ripe for cross-fertilization. Many of the pathways that are important for the perivascular support of neurogenesis and gliogenesis are similarly critical for the perivascular support of gliomagenesis. For instance, endothelial NOS–derived NO has recently been reported to regulate the expansion of platelet-derived growth factor–dependent glioma cells via the potentiation of Notch signaling⁵³. Similarly, purinergic signaling, which may provide important mitogenic signals in the perivascular niche for neurogenesis, may similarly regulate the perivascular expansion of glioma cells⁹⁶. Locally derived perivascular VEGF signaling, as a coordinate regulator of both endothelial and glioma expansion⁹⁷, is yet another example of a mitogenic mechanism that is used by NSCs and glioma cells alike. In this regard, the use of anti-angiogenic agents such as bevacizumab in malignant glioma highlights the value of targeting these perivascular niche–selective pathways: although bevacizumab was originally developed as a means to slow the provision of VEGF by tumor cells to the local vasculature, it is now clear that its effects on tumor expansion may derive as much from impeding reciprocal endothelial signals to tumor cells and their progenitors⁹⁸.

In broad terms, by understanding the role of the perivascular niche in supporting neuronal production and migration in adult brain tissue, we may hope to better define strategies for inducing heterotopic neuronal production and directing recruitment to sites of need. Indeed, recent studies have raised the possibility of inducing neuronal addition to otherwise non-neurogenic regions of the adult brain by using viral gene transfer to overexpress BDNF and

noggin, key components of the perivascular and subependymal niches, broadly throughout the adult ventricular wall^{99,100}. Thus, by more precisely defining the cell-cell interactions and molecular determinants thereof among the constituents of the perivascular niches for neurogenesis and gliogenesis, we may hope to better control the generation, destination and phenotypic instruction of new cells from endogenous stem and progenitor cells in the adult CNS.

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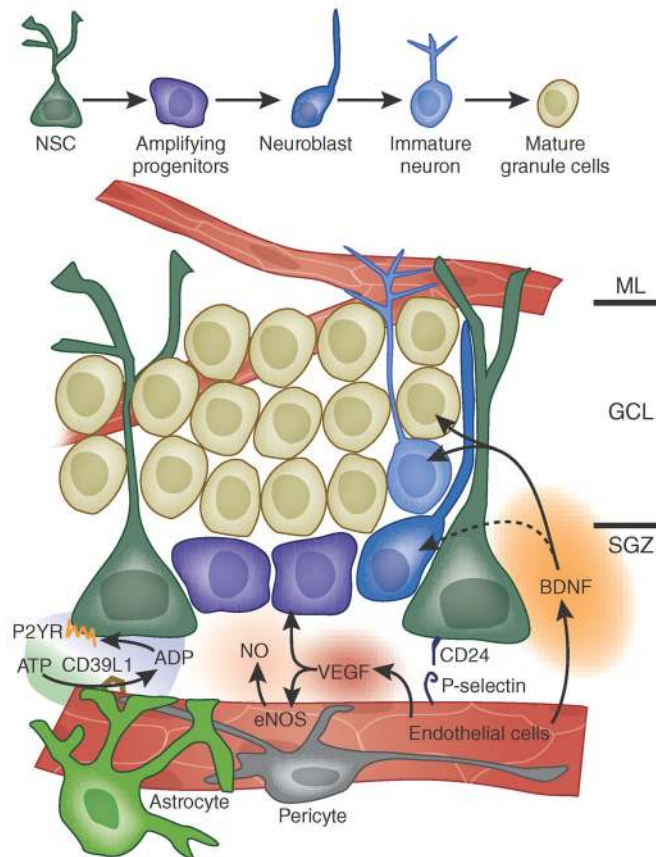


Figure 1.

Perivascular interactions within the subgranular zone of the adult mammalian hippocampus. This cartoon illustrates the architecture of the subgranular zone and dentate granule layer of the adult hippocampus and shows the relationships of hippocampal NSCs to transit-amplifying progeny and their neuronally restricted progeny. Only those interactions identified as being specifically between the microvascular bed and hippocampal stem and progenitor cells are noted; many mitogens and differentiation agents of nonvascular origin have otherwise been defined in the hippocampus. The subgranular zone of the dentate gyrus manifests a cellular hierarchy that is similar to that of the ventricular subependyma. Major molecular interactions, as cited in the text, include the provision of ATP to vascular NTPDase-2/CD39L1, with generation of ADP that interacts with P2YRs expressed by the stem cell pool, vascular VEGF, which interacts with both endothelial and neural precursor receptors, CD24 and its endothelial P-selectin receptors, both endothelial NOS (eNOS) and precursor-derived neuronal NOS (nNOS), with their derived NO and targets thereof, and endothelial BDNF and its neuronal receptors. GCL, granule cell layer; ML, molecular layer; SGZ, subgranular zone.

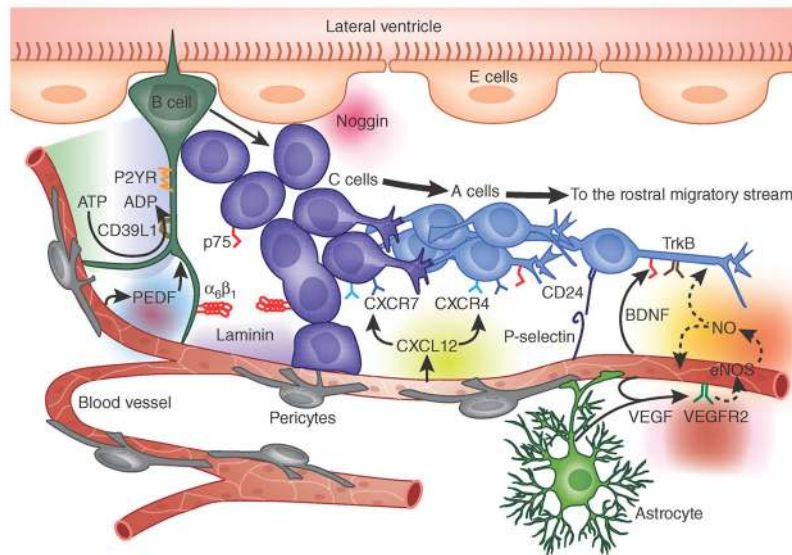


Figure 2. Perivascular interactions with the adult mammalian subependyma. This cartoon illustrates the architecture of the striatal ventricular wall and shows the relationships of subependymal NSCs (B cells, according to the nomenclature of Alvarez-Buylla^{3,19,75}) to transit-amplifying progeny (C cells) and their neuronally restricted progeny (A cells). Major molecular interactions, as cited in the text, include the provision of ATP to vascular NTPDase-2/CD39L1, with generation of ADP that interacts with B and C cell P2YRs, vascular VEGF and PEDF, which interact with cognate B cell receptors, B cell CD15 and C and A cell CD24 with their endothelial P-selectin receptors, endothelial SDF1/CXCL12 with its A cell receptors CXCR4 and CXCR7, endothelial BDNF with both its B and C cell p75 and A cell trkB receptors, endothelial laminin with its C and A cell $\alpha_6\beta_1$ integrin receptor, and both endothelial eNOS and neural precursor-derived nNOS, and their derived NO with cellular targets thereof.

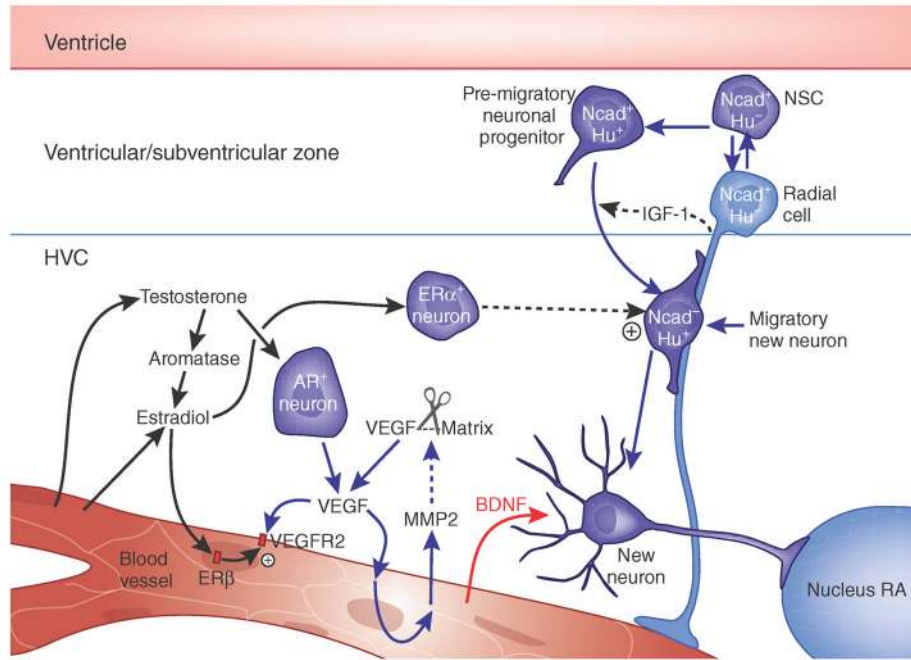


Figure 3.

Angiogenesis and neurogenesis in the adult songbird brain. Testosterone-induced neuronal addition to the adult songbird vocal control center, HVC, requires the androgenic induction of VEGF, followed by VEGF-stimulated matrix metalloproteinase release and angiogenesis. The expanded vasculature acts as a source of BDNF, which supports the immigration of new neurons from the overlying ventricular zone^{23,77,78,80}. AR, androgen receptor; ER, estrogen receptor; Nucleus RA, the HVC target nucleus robustus archistriatalis.