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Mechanisms of cellular plasticity in cerebral perivascular region

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Abstract

Brain vasculature acts in synergism with neurons to maintain brain function. This neurovascular coupling, or trophic coupling between cerebral endothelium and neuron, is now well-accepted as a marker for mapping brain activity. Neurovascular coupling is most active in the perivascular region, in which there are ample opportunities for cell-cell interactions within the neurovascular unit. This trophic coupling between cells maintains neurovascular function and cellular plasticity. Recent studies have revealed that even adult brains contain multiple stem cells of various lineages, which may provide cellular plasticity through the process of differentiation among these stem cell populations. In this chapter, we provide an overview of the process by which neurovascular components contribute to cellular plasticity in the cerebral perivascular regions, focusing on mechanisms of cell-cell interaction in adult brain.

Keywords

perivascular region; neurovascular coupling; neurogenesis; oligodendrogenesis; neurovascular niche; oligovascular niche; neurovascular unit

1. Introduction

Trophic coupling between different brain cells plays an essential role in maintaining normal brain function. In this regard, the concept of the neurovascular unit is a useful depiction of brain physiology and pathophysiology. The neurovascular unit provides a conceptual framework in which cell-cell interactions between neuronal, glial, and vascular elements constitute a functional entity^{1–7}. One important phenomenon within the neurovascular unit is that of neurovascular coupling, wherein neural activity evokes local blood flow changes. Imaging techniques including PET, fMRI, and fNIRS utilize the cerebrovascular-neuron interaction as a principle mechanism to map brain activity (see Chapters 4–6).

Neurovascular coupling takes place most prominently in the perivascular region (the microenvironment surrounding the microvasculature). This perivascular pocket may also provide an opportunity for trophic coupling between other types of cells. For example, the

perivascular region gives rise to the neurovascular niche and gliovascular niche, wherein signaling pathways between cerebral endothelial cells and neuronal/glia precursor cells help mediate pockets of ongoing neurogenesis, gliogenesis and angiogenesis in adult brain^{8,9}. These intricate interactions are maintained during the remodeling phase after brain injury. Angiogenic signals are known to enhance neurogenesis after stroke^{8,10}. In turn, neuroblasts migrate along perivascular routes, and the process of neurogenesis enhances vascular re-growth¹¹. This cellular plasticity is an important mechanism in brain remodeling after injury.

Recent studies have revealed that even in the adult brain, mechanisms of cellular plasticity are retained to some extent. Adult brains possess stem cells from multiple lineages in the perivascular region, and coordination of self-renewal and differentiation in those stem cell populations maintains brain homeostasis. Notably, cell-cell trophic coupling may contribute to the cellular plasticity in the perivascular region, which plays an important role in repair responses in the adult brain after injury. In this chapter, we review mechanisms of cellular plasticity in the neurovascular unit, focusing on cell-cell interaction in the perivascular region.

2. Cellular plasticity and function of neurovascular unit components

The neurovascular unit is composed of neurons, glial cells (astrocytes, microglia, oligodendrocytes), and vascular cells (endothelial cells, pericytes). The dynamic interactions among these components regulate complex brain function, an example of which is that of adjustment of local blood flow by neural activity. Recent research advances have shown that these neurovascular unit components have diverse heterogeneity in their morphology, developmental origin, gene expression profile, physiological properties, function, and response to injury and disease^{12–17}. This diversity is a major contributor that underlies the cellular plasticity of neurovascular unit components in the adult brain.

Within the neurovascular unit, cell plasticity may come from differentiation of progenitor cells in the perivascular region. As noted, several kinds of progenitor cells reside even in the adult brain, and with trophic support by neighboring cells, they differentiate as needed for maintenance and/or remodeling of the relevant brain region. In this regard, neuronal stem/progenitor cells (NSPCs) play an essential role because they have the potential to differentiate and mature into all the subtypes of neurons and glial cells. They undergo both self-renewal and diversification into other types of cells; the former through symmetric proliferation and the later through asymmetric proliferation. The cellular plasticity exhibited by NSPCs during differentiation (i.e. neurogenesis and gliogenesis) is partly a response to intrinsic or extrinsic mechanisms, which trigger the pathways that determine the eventual cell fate. For example, NSPCs respond to inner or outer stimuli such as epigenetic regulation as in chromatin remodeling¹⁸, cellular signaling by cell-cell communication¹⁹ and the action of local trophic factors.

In this section, we briefly review the function of neurovascular components, focusing on cell differentiation mechanisms. Because mechanisms of adult neurogenesis and gliogenesis may mirror the cell differentiation steps observed during embryonic development, we also

overview intrinsic and extrinsic signaling mechanisms for cell differentiation during brain development.

2.1. Neurons

Radial glia (RG), which is the progenitor cell for neural/glial cells, is morphologically characterized by the projection of its processes from the ventricular zone (VZ) to the meningeal zone with apico-basal polarity during the embryonic stage of brain development. During this period, RG switches its role among three main functions: self-proliferation, neurogenesis and gliogenesis (astrogenesis). NSPCs, which are originally derived from RG, generate both neurons and astrocytes even in cell culture conditions²⁰. Thus far, several intrinsic signaling pathways, such as Notch, Wnt and JAK/STAT signaling, have been found to have the ability to maintain NSPCs in undifferentiated states during the self-proliferation phase. In addition, chromatin remodeling of DNA by methylation and histone modification has also been shown to contribute to the plasticity of neurons and glial cells during the developmental stage (Fig. 1).

Notch signaling is one of the major mediators of cell fate determination in cells of neural lineage. Notch signaling is mediated by the Notch receptors activated by ligand Jagged on the surface of the neighboring cells²¹. The targets are transcriptional factors Hes (Hes1 and Hes5), which inhibit the neural differentiation of NSPC. The Notch-mediated cell-cell interactions spread to surrounding cells to maintain the undifferentiated conditions in their surrounding, which is known as 'lateral inhibition'. Notch 1 knockout in mature neurons did not change the morphology but altered dendritic spines and disrupted long-term potentiation and long-term depression, leading to deficits in performing several memory tasks in mice²².

Phase-dependent activation of Wnt signaling is another critical regulator of neuronal cell fate. Binding of Wnt to its receptor Frizzled inhibits the degradation of β -catenin, which binds the T-cell factor to upregulate downstream genes. The importance of β -catenin in neurogenesis is illustrated by the fact that β -catenin deletion is associated with impaired neurogenesis from immature neuron progenitor cells²³. Among genes downstream of Wnt signaling, Ngn1 and Ngn2 are key regulators that are highly expressed transcriptional factors during the neurogenesis phase^{24,25}. Ngn regulates neurogenesis and gliogenesis in a complex way. Ngn strongly promotes neurogenesis to constitute the six layers of brain cortex in an order from deep to superficial layers, and Ngn negatively regulates JAK-STAT-mediated demethylation of the GFAP promoter region and inhibits NSPC differentiation into astrocytes²⁶. Ngn2-knock out mice exhibit prominent decrements in neurogenesis and gliogenesis²⁷. Although Wnt signaling upregulates the expression of Ngn during the neurogenesis phase, its effects on chromatin remodeling by histone-modification of the promoter region of Ngn in the later phase results in decreased neurogenesis and Wnt-induced chromatin remodeling blunts the sensitivity to Wnt signaling, leading to a shift from neurogenesis to gliogenesis²⁸. Since precise mechanisms as to how Ngn regulates neurogenesis/gliogenesis are still mostly unknown, elucidating phase- and region-dependent mechanisms of Ngn signaling in NSPC function is warranted for future studies.

Taken together, phase-dependent cellular signaling and epigenetic modification in the promoter region of genes related to neurogenesis and gliogenesis are key regulators involved

in the shift from neurogenesis to gliogenesis. Further studies will be needed to elucidate how these factors act synergistically to organize the process of neurogenesis by maintaining asymmetrical differentiation, and contribute to phase-dependent cellular plasticity.

2.2. Glial cells (astrocytes, oligodendrocytes, and microglia)

Astrocytes are mainly generated from three distinct areas in the brain: VZ, subventricular zone (SVZ) and the distributed localized area²⁹. RG in the VZ generates astrocytes in white matter during the gliogenesis phase. Glial progenitor cells in SVZ migrate to the cortical or subcortical layer of the brain and generate astrocytes in both gray and white matter. These newly generated astrocytes are morphologically categorized into two types - protoplasmic astrocytes in gray matter and fibroblastic astrocytes in white matter.

Several signaling pathways have been identified to modulate NSPC differentiation into astrocytes. As mentioned above, a central one is JAK/STAT signaling, in which JAK phosphorylates STAT1/3 and promotes the dimerization of STAT1/3 to up-regulate GFAP expression. Notch signaling is also an important regulator of GFAP gene expression both genetically and epigenetically. Notch intracellular domain (NICD)/CBF1 complex upregulates GFAP via direct binding to the GFAP promoter region. There are CpG methylated regions on the GFAP promoter to which Notch signaling-activated NFIA binds and prevents Dnmt1 from accessing the promoter region³⁰. This leads to demethylation of the promoter region and upregulation of GFAP expression.

Besides neurons and astrocytes, oligodendrocyte lineage cells are also generated from NSPCs. In general, oligodendrocytes are derived from so-called oligodendrocyte precursor cells (OPCs), which originate from NSPCs. However, there is ongoing debate as to whether oligodendrocytes should be generated from OPCs with fate-restricted lineage or not, since several studies have shown that OPCs retain context-dependent lineage plasticity in the differentiation period^{31,32}.

Historically, OPCs have been purified from rat optic nerves by immunopanning with antibody against A2B5 and identified as bi-potential oligodendrocyte-type2 astrocyte progenitor cells (O-2A cells)³³, which indicate that OPCs could differentiate into oligodendrocytes as well as astrocytes. In the postnatal period, OPCs appear in the SVZ and diffusely distributed to cover the entire parenchyma of the brain. Even in the adult CNS, OPCs have been found to comprise 2–8 % of all the cells^{34,35}. While majority of SVZ derived-OPCs can differentiate into oligodendrocytes, some may directly differentiate into protoplasmic astrocytes in gray matter. Actually, OPCs contribute to about 40 % of protoplasmic astrocytes in the gray matter of the ventral forebrain³⁶. In addition, when purified OPCs were transplanted into the glia-depleted mice, they were differentiated into both oligodendrocytes and astrocytes³⁷. Moreover, when transplanted into myelin basic protein (MBP)-depleted conditions, some OPCs were differentiated into GFAP positive cells, while others expressed MBP, a marker of mature oligodendrocytes³⁸. Astrocyte generation from OPCs is limited during the initial postnatal period. These data suggest that OPCs are capable of differentiating into different types of cells, depending on the condition of the surrounding environment³⁹.

Thus far, several key mechanisms have been identified in cell fate decisions for oligodendrocyte lineage cells. Olig2 is a critical transcriptional regulator, which directs OPCs to become oligodendrocytes during embryogenesis^{40–42}. In fact, in Olig2-deficient conditions, OPCs were directed to become astrocytes, and postnatal hypomyelination was observed in the neocortex and corpus callosum⁴³. Epigenetic regulation such as DNA methylation and histone modification associated with chromatin remodeling was also shown to be involved in cell specification for oligodendrocytes⁴⁴. Treatment with HDAC inhibitor or genetic ablation of HDAC1/2 in OPCs resulted in failure of differentiation in vivo^{45,46}. Several groups have confirmed that HDAC activities are required for efficient myelination⁴⁷. For example, HDACs act in conjunction with the transcription factor YY1 to start myelin gene expression by suppressing Id4 and Tcf4⁴⁸. Neuronal activity⁴⁹, microRNAs⁵⁰, and Notch signaling⁵¹ are also well-defined mechanisms for cell fate decisions in oligodendrocyte lineage cells. Working together, the factors and signaling pathways discussed here coordinately regulate oligodendrocyte generation during development.

Microglia, which originates from mesodermal yolk sac tissue during development^{52,53}, is a major cell type for the immune response in brain. After infiltrating into the brain during development, microglia reside and proliferate locally. In terms of cellular plasticity in the neurovascular unit, microglia plays a major role in synaptic pruning during development. The fractalkine receptor (CX3CR1), a marker of microglia⁵⁴, has been shown to be involved in the cytokine-mediated pathway in which synaptic plasticity would dynamically be formed by the interaction between neurons⁵⁵. Also, microglia responds to neurotransmitter released by neuronal activity and contributes to the synaptic pruning via fractalkine/fractalkine receptors (CX3CL1/CX3CR1) signaling^{56,57}. Genetic fate mapping studies using CX3R1-knockout mice have revealed deficits in multiple learning abilities as well as a remarkable reduction in glutamatergic synapse formation^{58,59}. The function of CX3R1 is partially dependent on microglia-derived BDNF activity. The homeostasis of microglia is dependent on CSF-1/CD115 receptor because its inhibition results in complete depletion of brain microglia⁶⁰. These findings support the idea that in addition to immune responses, microglia play an important role in maintaining neurovascular homeostasis including cellular plasticity in neurons.

2.3. Vascular cells (cerebral endothelial cells and pericytes)

Vascular cells constitute a major cellular element of the brain, and cerebral endothelial cells play a central role in the neurovascular unit. The cerebrovascular system was traditionally seen as a passive conduit for blood, however, recent research has revealed that the microvasculature plays an active role in maintaining brain homeostasis. Cerebral endothelial cells are differentiated from endothelial progenitor cells (EPCs). EPCs originate from mesodermal cells, and are responsible for vasculogenesis such as the formation of capillary network in the developing embryo. In addition, EPCs also contribute to angiogenesis – in the setting of remodeling and repairing of the capillary network^{61,62}.

In addition to its role as a conduit for blood flow, cerebral endothelial cells act as a source of multiple mediators to regulate neurovascular plasticity. Through secreting soluble factors,

cerebral endothelial cells control neuronal regeneration through the processes of proliferation, migration, and differentiation of NSPCs⁶³. Major mediators from cerebral endothelial cells are nitric oxide (NO)^{64,65}, *SXCL12* (SDF1), vascular endothelial growth factor (VEGF)⁶⁶, brain-derived neurotrophic factor (BDNF)⁶⁷ and pigmented epithelium-derived factor (PEDF). These endothelial-derived factors may act in concert with secreting factors from other neurovascular unit components to coordinate neurogenesis, neural plasticity and NSPC division during the developmental stage. For example, NO inhibits epidermal growth factor receptor (EGFR)-dependent PI3K/Akt signaling⁶⁸ and acts as a tonic repressor of neurogenesis *in vivo*. VEGF plays multiple functions in maintaining the fenestration permeability of the vessel⁶⁹, activity-induced neurogenesis⁷⁰ and synaptic plasticity such as enhancement of the long-term potentiation response⁶⁶. BDNF is reported to support the recruitment of newly generated neurons in SVZ⁷¹. PDGF acts to promote NSC renewal through potentiating Notch-dependent transcription⁷². Since cerebral endothelial cells play a central role in the neurovascular unit, future studies are needed to further investigate the mechanisms by which cerebral endothelial cells contribute to cellular plasticity within the neurovascular unit.

Within the neurovascular unit, pericytes play several unique roles. Pericytes are especially abundant in the brain vasculature. Similar to other neurovascular unit components, pericytes also interact with neighboring cells. For example, cerebral vasculature is covered with a 1:1–3 ratio between endothelial cells and pericytes^{73–75}, and pericytes are well known to regulate the integrity of blood-brain barrier^{76,77}. In addition, pericytes and endothelial cells reciprocally support each other in the perivascular area through the secretion of soluble factors. Platelet-derived growth factor-receptor β (PDGFR β) is a constitutive marker of pericytes, and endothelial cells secrete PDGF β to activate the recruitment and proliferation of pericytes. PDGF- β /PDGFR β knockout mice suffer from a deficiency pericytes in the brain as well as other organs such as kidney, heart and lung⁷⁸. On the other hand, pericytes secrete Angiopoietin-1, the receptor for which (Tie-1), is predominantly expressed in endothelial cells and promotes endothelial maturation and stability^{79,80}. In addition to endothelium-pericyte interactions, recent studies demonstrated that in the perivascular region, pericytes may also exchange soluble factors with OPCs to support their function⁸¹.

As discussed above, through secreting trophic factors, pericytes regulate cellular plasticity through their involvement in angiogenesis and oligodendrogenesis in the perivascular area. However, pericytes may contribute to cellular plasticity in a more direct way. Early studies have demonstrated that pericytes in the brain originate from mesenchyme cells that localize on the abluminal side of the endothelial cells⁸². Recent studies in turn have stressed that the pericytes exhibit stem-cell-like properties, which enable them to differentiate into a variety of cell types, such as osteoblasts, adipocytes, chondrocytes, vascular smooth muscle and skeletal muscle. In fact, under ischemic conditions, pericytes can be reprogrammed into neurons⁸³. As illustrated by these examples, the pericyte is an important cell in the regulation of cell plasticity in the perivascular region.

3. Neurovascular/Oligovascular niche mediates neurogenesis and oligodendrogenesis in the neurovascular unit

The components of the neurovascular unit coordinately affect cellular plasticity through self-renewal, cell fate, and synaptic plasticity, in processes that respond to stimulation by intrinsic and extrinsic factors (Figure 2). In this regard, cerebral endothelial cells play a central role in cellular plasticity because they produce the neurovascular and oligovascular niches to support neurogenesis and oligodendrogenesis.

3.1. Neurovascular niche

As noted in the introduction section, cell-cell interaction in the neurovascular niche is one of the major facets within the neurovascular unit. Cerebral endothelial cells and NSPCs are closely related in the perivascular region in the processes of neurogenesis and angiogenesis⁸. In this neurovascular niche, a number of trophic factors such as VEGF, BDNF, EGF and FGF2 are released from endothelial cells to upregulate NSPC expansion for neurogenesis. This is an important mechanism for adult neurogenesis in the adult brain. Additionally, after brain injury, cerebral endothelial cells respond to ischemic or traumatic stress by releasing necessary soluble factors that are important in the recovery of cellular functions.

In turn, NSPCs (and neurons) can regulate development of functional integrity in the neurovascular unit by secreting the factors such as VEGF that induce endothelial cell migration and guide vessel sprouting⁸⁴. For example, neuroblasts migrate along perivascular routes and the promotion of neurogenesis enhances vascular re-growth¹¹. Besides angiogenesis, neuronal activity also regulates blood flow in the local area of the brain (e.g. neurovascular coupling). This is mediated at least partly by the neuron-to-astrocyte signaling in which glutamate-mediated Ca^{2+} elevation in astrocytes promotes dilation of the arterioles⁸⁵ (see Chapter 2 by Nuriya and Hirase).

3.2. Oligovascular niche

Similar to the neurovascular niche, the oligovascular niche mediates interactions between cerebral endothelial cells and OPCs, mostly in cerebral white matter^{86,87}. OPCs are widely distributed even in adult brain^{88–90} and when guided to the injured site, they contribute to myelin repair after brain injury⁹¹. At the same time, cerebral endothelial cells may promote the survival and proliferation of perivascular OPCs⁸¹ via FGF-2 and BDNF⁹². VEGF-A may also be an important mediator in the oligovascular niche. VEGF-A is secreted from cerebral endothelial cells and its receptor (Flk-1) is expressed in OPCs⁹³. In vitro cell culture studies confirmed that endothelial-derived VEGF-A did promote the migration of OPCs⁹⁴. Notably, the trophic support from cerebral endothelial cells to OPCs may change under diseased conditions. Even sub-lethal level of oxidative stress could suppress the secretion of FGF-2/BDNF from cerebral endothelial cells, indicating that cerebral endothelial cells would not provide sufficient support to OPCs under diseased conditions⁹². Therefore, disruption of OPC-endothelium trophic coupling may hasten the progression of white matter-related diseases.

In turn, cells from the oligodendrocyte lineage may modulate the cerebrovascular system. For example, OPCs produce TGF- β , which maintains the tightness of BBB during development⁹⁵. However, under diseased conditions such as cerebral hypoperfusion in the adult brain, OPCs could damage the BBB by secreting matrix metalloproteinase-9⁹⁶. Importantly, patterns of cell-cell interaction in the oligovascular niche may change again during the chronic (repairing) phase after injury. After white matter damage, oligodendrocyte-derived MMP-9 would work on white matter remodeling by promoting angiogenesis⁹⁷. Taken together, these findings indicate that the oligovascular niche contributes to cellular plasticity in cerebral white matter.

4. Cell-cell interaction in disease

Cell-cell interaction in the perivascular region is an important mechanism for cellular plasticity, which maintains neurovascular homeostasis. Importantly, these cell-cell interactions may change under disease conditions – for example, disruption of cell-cell trophic coupling causes cellular damage, but at the same time, changes in neurovascular interactions after brain injury may promote neurovascular repair. Therefore, an understanding of cell-cell interaction in disease may lead to new therapeutic approaches for CNS diseases. In this section, we will briefly introduce some key findings related to changes in neurovascular components under pathological conditions.

In the acute phase after the cerebral ischemia, injured neurons release damage-associated molecular pattern proteins (DAMPs), leading to the secretion of deleterious mediators such as inflammatory cytokines (e.g. IL-1 β and TNF- α) and reactive oxygen species. These factors induce BBB breakdown and facilitate the infiltration of circulating monocytes, neutrophils and lymphocytes^{98,99}, which then accelerate post-ischemic inflammation, which may further damage the surviving neurons¹⁰⁰. Under ischemic conditions, CX3CL1/CX3CR1 signaling promotes microglial phagocytosis of apoptotic neurons, an important aspect of remodeling¹⁰¹. This response also promotes neurogenesis in the ipsilateral SVZ - residual NSPCs are activated to migrate to the ischemic lesion and to proliferate at that site¹⁰². This dual effect is also observed in other signaling proteins. For example, HMGB-1, which belongs to DAMP family, induces inflammatory/deleterious effects in the early phase of stroke, while it contributes to neurovascular remodeling by promoting neurogenesis and angiogenesis in the chronic recovery phase¹⁰³.

Other mechanisms of cell-cell interactions are also affected under conditions of stress. Deficits in axonal energy caused by metabolic disturbance in glial cells are closely related to neurodegenerative disease. Oligodendrocyte dysfunction may cause neuronal/axonal damage. Under normal conditions, oligodendrocytes supply lactate to neurons through monocarboxylate transporter 1 (MCT1)¹⁰⁴. However, in the setting of amyotrophic lateral sclerosis, oligodendrocytes exhibit MCT1 deficiency – a phenomenon observed both in a mouse model and in human subjects¹⁰⁵. This deficit would likely lead to a disruption of the trophic support from oligodendrocytes to neurons (axons).

Protein aggregation and degeneration in glial cells are also related to the progression of neuronal disease. Astrocytes take up and degrade A β protein, which is deposited in brains of

patients with Alzheimer's disease (AD) and thought to cause neuronal damage¹⁰⁶. Enhancing the autophagy-mediated proteolysis in astrocytes attenuate A β deposit¹⁰⁷, suggesting that astrocytes are important in A β clearance and that astrocyte dysfunction may accelerate the progression of AD pathology. In addition to A β protein, α -synuclein is another important protein in neurodegenerative diseases. α -synuclein deposits mostly in neuronal Lewy bodies, and α -synuclein-aggregated Lewy neurites are observed in brains of Parkinson's disease or dementia patients. On the other hand, in multiple system atrophy patients, α -synuclein deposits largely in oligodendroglial cytoplasmic inclusions¹⁰⁸. These findings suggest that mechanisms of α -synuclein clearance could be deranged in specific cell populations depending on the type of disease.

In general, pathological conditions disturb cell-cell trophic coupling, leading to neurovascular dysfunction. But, as briefly mentioned above, cell-cell interactions may recover to some extent during the chronic phase to promote compensative neurogenesis/angiogenesis/oligodendrogenesis. However, it still remains unknown how those cell-cell interactions contribute to barrierogenesis (i.e. re-sealing BBB) after brain injury. During development, cells in the perivascular region, such as pericytes and astrocytes, provide support to cerebral endothelial cells in BBB formation¹⁰⁹. Therefore, to reveal the mechanisms of cellular plasticity in the neurovascular unit, future studies are warranted to investigate the roles of pericyte-endothelium or astrocyte-endothelium trophic coupling in compensative barrierogenesis of BBB in adult brains.

5. Conclusion

The concept of the neurovascular unit has provided a basic framework for understanding brain physiology and pathology. As discussed in this chapter, cell-cell trophic coupling is important for the regulation of neurovascular function and preservation of brain homeostasis. In this regard, perivascular region may play an essential role because the neurovascular/oligovascular niche mediates the interaction of cerebral endothelial cells with other cells within the neurovascular unit to regulate cellular plasticity. Ultimately, cellular plasticity can be easily affected by neighboring microenvironments in both beneficial and detrimental ways, and therefore, a precise understanding of cell-cell interaction pathways is needed to develop efficient therapeutic treatments for CNS diseases.

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Figure 1.

Cellular signaling in neurogenesis and gliogenesis during brain development. Abbreviation: RG, radial glia; OPC, oligodendrocyte progenitor cell; GM, gray matter; WM, white matter; SVZ, subventricular zone.

Figure 2.

Interactive behavior in the neurovascular unit for systematic plasticity. Trophic factors are secreted from each neurovascular unit component to affect the function of its target cell. Abbreviation: A, Astrocyte; P, Pericyte; O, Oligodendrocyte or oligodendrocyte progenitor cell; N, Neuron; M, Microglia; E, Endothelial cell.