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Blood vessels as a scaffold for neuronal migration

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ABSTRACT

Neurogenesis and angiogenesis share regulatory factors that contribute to the formation of vascular networks and neuronal circuits in the brain. While crosstalk mechanisms between neural stem cells (NSCs) and the vasculature have been extensively investigated, recent studies have provided evidence that blood vessels also play an essential role in neuronal migration in the brain during development and regeneration. The mechanisms of the neuronal migration along blood vessels, referred to as "vascular-guided migration," are now being elucidated. The vascular endothelial cells secrete soluble factors that attract and promote neuronal migration in collaboration with astrocytes that enwrap the blood vessels. In addition, especially in the adult brain, the blood vessels serve as a migration scaffold for adult-born immature neurons generated in the ventricular-subventricular zone (V-SVZ), a germinal zone surrounding the lateral ventricles. The V-SVZ-derived immature neurons use the vascular scaffold to assist their migration toward an injured area after ischemic stroke, and contribute to neuronal regeneration. Here we review the current knowledge about the role of vasculature in neuronal migration and the molecular mechanisms controlling this process. While most of this research has been done in rodents, a comprehensive understanding of vasculature-guided neuronal migration could contribute to new therapeutic approaches for increasing new neurons in the brain after injury.

1. Introduction

The regulation of cellular migration is fundamental not only to morphogenesis during development, but also to the maintenance and modification of adult tissues and organs. In the developing brain, immature neurons generated in the germinal zones migrate to their final destinations, in a manner tightly regulated by multiple cell-intrinsic and extrinsic mechanisms. Among them, common instructive cues and cross-talk signals between neurogenesis and angiogenesis play essential roles in establishing a complex and functional neuronal network that is supported by vascularization.

Even after the developmental period, neurogenesis still occurs in restricted brain regions. The ventricular-subventricular zone (V-SVZ) is the largest germinal zone in adult mammals. The V-SVZ-derived immature new neurons, called neuroblasts, migrate into the olfactory bulb under physiological conditions and toward a lesion in cases of brain injury, such as ischemic stroke. These processes are closely associated with angiogenesis and/or its regulatory factors. After the termination of migration, the neuroblasts differentiate into mature neurons and are integrated into the circuitry to modify or regenerate pre-existing neuronal circuits. In this review, we describe the latest findings on vasculature-guided neuronal migration. While most of this research has been performed in rodents, we also discuss the implications of these findings for therapeutic approaches involving neuronal regeneration.

2. Role of vasculature in cellular migration

Cells exhibit different migration modes depending on the cell type and context. Recent studies using time-lapse imaging techniques with transgenic mice and fish revealed a unique migrating mode in which cells move along blood vessels. In embryonic development, vasculature-guided migration has been reported for endothelial cells that form the lymphatic vascular system in the zebrafish trunk (Bussmann et al., 2010) and for oligodendrocyte precursor cells (OPCs) in mice (Tsai et al., 2016). In adult rodents after peripheral nerve transection, the Schwann cells enwrapping peripheral nerve axons de-differentiate and migrate along blood vessels toward the lesion, where they promote axonal regeneration (Cattin et al., 2015). Highly invasive and

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Abbreviations

Ang1	angiopoietin 1
BDNF	brain-derived neurotropic factor
CXCR4	C-X-C chemokine receptor type 4
ECM	extracellular matrix
GABA	gamma-aminobutyric acid
NSCs	neural stem cells
OPCs	oligodendrocyte precursor cells
RMS	rostral migratory stream
SDF1	stromal cell-derived factor 1
VEGF	vascular endothelial growth factor
V-SVZ	ventricular-subventricular zone

metastasizing tumor cells in malignant glioma and melanoma (Farin et al., 2006; Lugassy and Barnhill, 2007), and as described below, V-SVZ-derived neuroblasts also migrate along blood vessels in the brain. Although the molecular mechanisms regulating the association of these cells with blood vessels remain largely unknown, the vasculature appears to contribute to their active migration.

Blood vasculature supports cell migration in at least two ways: 1) by transporting oxygen and nutrients, and secreting soluble factors, which provide an appropriate microenvironment for cellular migration, and 2) by serving as a physical scaffold and providing adhesion-dependent signals for migration, as well as proliferation, differentiation, and survival to the cells. In adult animals, vasculature-guided migration is reported mainly in the brain, suggesting that brain-specific anatomical and/or functional properties, such as the presence of astrocytic endfeet that almost completely enwrap the blood vessels, might be involved in this migration. It is also possible that some environmental factors or conditions specific to the adult brain increase the need for the vascular support of migrating cells.

3. Vasculature-guided neuronal migration in the embryonic brain

During cortical development, excitatory neurons are produced by radial glia, embryonic neural stem cells (NSCs), in the ventricular zone of the dorsal telencephalon. The neurons then migrate radially along

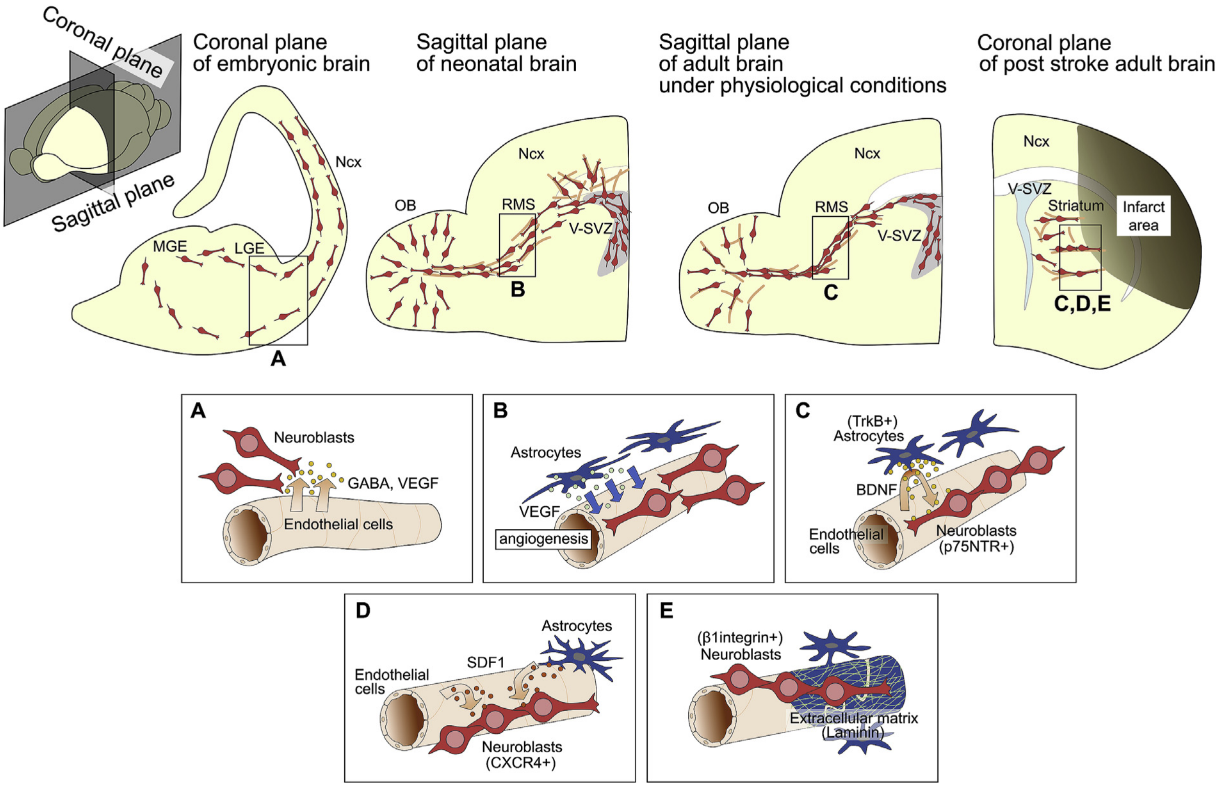

Fig. 1. Schematic illustration of neuronal migration along the vasculature.

(A) In the embryonic brain, GABAergic interneurons generated in the ventral telencephalon migrate tangentially toward the developing neocortex for a long distance along blood vessels. Diffusible factors secreted from vascular endothelial cells, such as GABA and VEGF, promote migration of the interneurons in close association with vascular networks.

(B) In the RMS in the developing neonatal brain, V-SVZ-derived neuroblasts migrate tangentially toward the OB through astrocytic tunnels referred to as glial tubes. Blood vessels running parallel to the RMS, which develop postnatally under the control of VEGF secreted by the RMS-forming astrocytes, assist the neuroblasts as migration scaffolds.

(C) In the adult RMS, endothelial cell-derived BDNF promotes neuronal migration toward the OB. RMS astrocytes modulate the local concentration of BDNF by capturing it with the high-affinity receptor TrkB, while neuroblasts express a low-affinity BDNF receptor p75NTR. This mechanism involving BDNF also regulates vasculature-guided neuronal migration in the striatum in the post-stroke brain.

(D, E) In the striatum in the post-stroke brain, SDF1 secreted from endothelial cells and reactive astrocytes promotes neuronal migration along blood vessels. The interaction of β1 integrin expressed in neuroblasts and laminin, an extracellular matrix protein composing the vascular basal lamina, facilitates neuroblast migration using vascular scaffolds.

MGE: medial ganglionic eminence; LGE: lateral ganglionic eminence; Ncx: neocortex; OB: olfactory bulb; RMS: rostral migratory stream; V-SVZ: ventricular-subventricular zone; GABA: gamma-aminobutyric acid; VEGF: vascular endothelial growth factor; BDNF: brain-derived neurotropic factor; SDF1: stromal cell-derived factor 1; CXCR4: C-X-C chemokine receptor type 4.

the long basal fibers of mother radial glia to reach their final destination (Kawauchi, 2015; Rakic, 2007). On the other hand, gamma-aminobutyric acid (GABA)ergic inhibitory interneurons originate in the ventral telencephalon and migrate tangentially toward the cortex over long distances (Marin, 2013; Guo and Anton, 2014) and are associated with blood vessels (Fig. 1A). The developing vasculature regulates the migration of these interneurons via diffusible signals, such as GABA and vascular endothelial growth factor (VEGF) secreted by vascular endothelial cells (Won et al., 2013; Barber et al., 2018; Li et al., 2018). Thus, both radial glia-dependent migration and vasculature-guided migration are involved in forming the cortical neuronal network.

4. Vasculature-guided neuronal migration in the adult brain under physiological conditions

Physiological neuronal migration has mostly been studied in the case of rodent olfaction (Fig. 1B). After birth, radial glia in the embryonic ventricular zone give rise to postnatal NSCs and ependymal cells in the V-SVZ within a week (Spassky et al., 2005). The V-SVZ is the largest neurogenic niche in the adult brain; at this site, NSCs produce intermediate progenitors that rapidly proliferate to generate a large number of neuroblasts continuously throughout life (Ihrie and Alvarez-Buylla, 2011; Ming and Song, 2011; Chaker et al., 2016; Lim and Alvarez-Buylla, 2016). The V-SVZ-derived neuroblasts migrate through a pathway called the rostral migratory stream (RMS) toward the olfactory bulb, and this migration is controlled by attractive or repellent diffusible guidance molecules, neurotransmitters, and cell-adhesion molecules (Wu et al., 1999; Nguyen-Ba-Charvet et al., 2004; Sawamoto et al., 2006; Bolteus and Bordey, 2004; Murase and Horwitz, 2002; Ng et al., 2005; Garzotto et al., 2008; Hu et al., 1996; Chazal et al., 2000; Yagita et al., 2009). In the olfactory bulb, the neuroblasts migrate radially toward the outer cell layers, where they differentiate into interneurons and are integrated into the neuronal circuitry involved in olfaction (Malvaut and Saghatelyan, 2016; Lledo and Valley, 2016).

Within this long journey of neuroblasts in the adult brain tissue, several unique migration modes have been described. The neuroblasts undergo a collective migration called "chain migration," in which they form a homotypic chain-like structure and slide over each other (Lois et al., 1996; Alvarez-Buylla and Garcia-Verdugo, 2002). The chains of neuroblasts are enwrapped by astrocytes that originate from radial glia in the V-SVZ and RMS (Alves et al., 2002). The formation of these astrocytic tubular structures, called glial tubes, is instructed by the neuroblasts, which secrete a diffusible protein, Slit1. This neuroblast-derived Slit1 controls the morphology and distribution of the surrounding astrocytes, which express its receptor, Robo2, to form the glial tubes; these glial tubes are necessary for the rapid, directional migration of the neuroblasts in the RMS (Kaneko et al., 2010).

In the neonatal RMS, astrocyte-derived VEGF controls the development of vasculature so that the vessels run parallel to the neuroblast chains (Bozoyan et al., 2012; Whitman et al., 2009) (Fig. 1B), and neuroblasts associate tightly with these vessels via a thin layer of astrocytic endfeet (Snapyan et al., 2009; Whitman et al., 2009). Furthermore, the vasculature-guided neuroblast migration is promoted by vascular endothelial cell-derived brain-derived neurotropic factor (BDNF) via a low-affinity receptor p75NTR. On the other hand, GABA released from neuroblasts induces the insertion of high-affinity TrkB receptors for BDNF on the astrocyte plasma membrane. Thus, astrocytes can trap extracellular BDNF to control neuroblast migration (Fig. 1C) (Snapyan et al., 2009). Taken together, astrocytes play important roles in the development and regulation of vasculature-guided neuroblast migration.

In the olfactory bulb, the neuroblasts detach from the chain and migrate individually toward the outer layer along blood vessels (Bovetti et al., 2007). In addition, only within the neonatal period, some of the neuroblasts migrate from the RMS radially toward the developing cortex through the corpus callosum, which also depends on vascular guidance (Le Magueresse et al., 2012). A similar association between migrating neuroblasts and vasculature is observed in the adult zebrafish brain (Kishimoto et al., 2011). Therefore, the migration of V-SVZ-derived neuroblasts in the postnatal brain is closely associated with blood vessels in diverse situations.

5. Vasculature-guided neuronal migration in the adult brain after injury

Under some pathological conditions such as ischemic stroke, the neuroblast production in the V-SVZ is upregulated. Some of these neuroblasts move toward the peri-injured area in the striatum, and differentiate into mature neurons that establish synaptic contacts with pre-existing ones (Arvidsson et al., 2002; Parent et al., 2002; Yamashita et al., 2006). To approach the lesion, the neuroblasts must migrate through the brain parenchyma, which contains complex neurite networks affected by insult-induced reactions, such as inflammation, gliosis, and dynamic tissue remodeling; these conditions are completely different from the microenvironment in the RMS. In this context, we found that activated astrocytes, referred to as reactive astrocytes, disturb the neuroblast migration toward an infarct area. Unlike the RMS, the neuroblasts cannot efficiently control the morphology of these astrocytes in the post-stroke striatum (Kaneko et al., 2018).

In the brain after stroke, neuroblasts migrating toward the injured area occasionally form chains, and contact blood vessels more frequently than those in the RMS (Ohab et al., 2006; Yamashita et al., 2006; Zhang et al., 2009; Kojima et al., 2010), suggesting that the vasculature is more important for V-SVZ-derived neuroblasts migrating in the non-permissive microenvironment after injury than for those migrating under physiological conditions. Endothelial cell-derived BDNF promotes vasculature-guided neuroblast migration in the ischemic striatum, and the local BDNF concentration is indirectly regulated by reactive astrocytes that capture the secreted BDNF (Grade et al., 2013), as is observed in the RMS (Snapyan et al., 2009). Therefore, BDNF mediates the vascular and astrocytic control of vasculature-guided neuroblast migration in the adult brain under both physiological and pathological conditions.

Ischemic stroke strongly induces vascular remodeling around the lesion and in the V-SVZ. The secreted factors Netrin1, VEGF, and Angiopoietin 1 (Ang1) are known to promote both angiogenesis and neuroblast migration in the brain after injury (Cayre et al., 2013; Ohab et al., 2006; Li et al., 2009; Wang et al., 2007). Stromal-derived factor (SDF)1 secreted by endothelial cells and ependymal cells in the V-SVZ controls the activity and vascular adhesion of NSCs, and increases the motility of neuroblasts (Kokovay et al., 2010). After ischemic stroke, SDF1 secreted from vascular endothelial cells and reactive astrocytes in the injured area acts as a chemoattractant for neuroblasts through its receptor, CXCR4 (Ohab et al., 2006; Thored et al., 2006; Robin et al., 2006; Kojima et al., 2010) (Fig. 1D). SDF1/CXCR4 signaling also regulates the vascular-guided migration of OPCs in the embryonic brain (Tsai et al., 2016).

In addition to diffusible factors, molecules regulating the contact of neuroblasts with blood vessels to increase their migration efficiency were recently revealed. Vascular basement membrane contains many extracellular matrix (ECM) proteins, such as type 4 collagen, laminin, and fibronectin, which are produced by endothelial cells, vessel-enwrapping pericytes, and astrocytes (del Zoppo and Milner, 2006; Daneman and Prat, 2015). The integrins are transmembrane receptors that mediate cell adhesion to the ECM, which is involved in the migration of various cell types (Sun et al., 2016; Paul et al., 2015). In the adult V-SVZ, NSCs and their progenies including neuroblasts express β1-class integrins, which bind to multiple ECM proteins (Emsley and Hagg, 2003; Belvindrah et al., 2007; Shen et al., 2008). While the integrin interaction with basement membrane laminin is critical for holding NSCs in a vascular niche (Shen et al., 2008; Tavazoie et al., 2008), it is also involved in the chain migration of neuroblasts in the

RMS (Emsley and Hagg, 2003; Belvindrah et al., 2007). Furthermore, β1 integrin is required for the chain formation and vasculature-guided migration of neuroblasts toward a lesion in the post-stroke brain (Fujioka et al., 2017) (Fig. 1E). The laminin-integrin-dependent adhesion of neuroblasts to a scaffolding substrate facilitates their migration *in vitro* (Fujioka et al., 2017), suggesting that neuroblast attachment to the vasculature should be controlled for efficient neuroblast migration. Therefore, although the relationship between chain formation and vascular-guided migration remains to be clarified, β1 integrin may be involved in orchestrating these two migration modes.

6. Conclusions and perspectives

The transplantation of laminin-containing artificial scaffolds promotes neuroblast migration from the V-SVZ toward a lesion in neonatal and adult mouse brain (Ajioka et al., 2015; Fujioka et al., 2017). Therefore, it is possible that artificial scaffolds that mimic the vascular structure and components are useful for promoting neuroblast migration and regeneration. Although the precise mechanism is still unknown, we found that enhancing the migration of V-SVZ-derived neuroblasts transplanted into the striatum of post-stroke mice (by overexpressing Slit1) enabled the neuroblasts to get close to the injury and induced functional recovery (Kaneko et al., 2018). Consistent with these findings, some genetic or pharmacological interventions and the transplantation of artificial scaffolds that promote neuroblast migration induce neurological improvement after brain insults (Jinnou et al., 2018; Nih et al., 2018; Ohab et al., 2006). The vasculature is an essential component in organ regeneration, serving as a supplier of oxygen and nutrients, a gatekeeper of cellular metabolism-sustaining homeostasis, and an inducer of angiogenesis and neurogenesis by the secretion of angiocrine factors (Rafii et al., 2016; Ramasamy et al., 2015). In addition, as presented in this review, the vasculature promotes neuroblast migration by secreting soluble factors and providing scaffolds in the adult brain under physiological and pathological conditions. Considering the importance of scaffolds for cell survival and differentiation (Bao et al., 2018; Muncie and Weaver, 2018), the vasculature may further affect the fate of differentiating neuroblasts in the damaged brain.

The basic structure of the brain vasculature and the vascular-guided neuroblast migration after stroke are similar in rodents and humans. However, the regenerative capacity of neurons varies depending on the species, and is especially limited in humans due to the large size and complex structure of the brain, and to the lower neurogenic function of the neural stem/progenitor cells in the V-SVZ (Parolisi et al., 2018; Paredes et al., 2016). A comprehensive understanding of the roles of vasculature in neuronal regeneration and their underlying mechanisms may contribute to new therapeutic approaches for brain injuries.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.03.001.

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