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Interaction of the nervous system and vascular system is required for the proper assembly of the neocortex

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A B S T R A C T

Mammalian neocortical development encompasses an entire set of events that leads to the generation of excitatory and inhibitory neurons from neural progenitors in the dorsal and ventral telencephalon, including cell proliferation, production of migratory precursors and their progeny, differentiation, and integration into circuits. During these processes, the developing neocortex acquires its vasculature by angiogenesis, a process consisting of proliferation of endothelial cells in existing blood vessels or vascular plexuses, and leading to formation of new blood vessels. Recent studies have suggested that neocortical angiogenesis progresses in a spatially and temporally restricted manner to construct a specialized vascular niche that supports ongoing neurogenesis during neocortical development. Here we review that periventricular blood vessels selectively influence neocortical progenitors behavior and neurogenesis, highlighting how CNS angiogenesis is utilized to construct neocortical cytoarchitecture.

1. Introduction

Vascular networks and neural networks enable elaborate physiological functions, and these two types of major networks interact by “neuro-vascular wiring”. This neuro-vascular wiring is evidenced by anatomical associations and reciprocal homeostatic interactions. Therefore, neuro-vascular plays a central role in exhibiting and supporting our physiological functions. However, our knowledge of the interaction of the nervous system and the vascular system remains limited. The neocortical function essentially relies on the balance between excitation and inhibition, which is served by excitatory glutamatergic projection neurons and inhibitory gamma-aminobutyric acid (GABA)ergic interneurons. Recent studies have suggested that the vasculature close to the neurogenic niche contributes a variety of factors that impact neural progenitors to generate and differentiate both projection neurons and interneurons.

Here we review the current understanding of how neuro-vascular wiring regulates neocortical development. We will focus on the mechanisms by which neural and vascular systems interact, particularly, we focus on the cooperative systems needed to develop blood vessels stereographically in the developing neocortex (Fig. 1), the mechanisms controlling the expansion and differentiation of neural stem and progenitor cells (NSPCs), and cellular dynamism and molecular signaling that are involved in the establishment and maintenance of neuro-vascular wiring, to explore the mechanisms of the mammalian neocortical cytoarchitecture in complex structures that control high-order functions.

2. Neural development during neocortical development

During embryonic development of the mammalian neocortex, a multitude of cellular events (cell division, migration, differentiation, and synaptogenesis) must all occur with precise spatio-temporal control to result in an animal with normal cognitive function. Many disorders, including cortical dysplasia, Down syndrome, autism, and cerebral palsy demonstrate how congenital or environmental perturbations of embryonic events can lead to mental retardation and cognitive disability (LoTurco and Bai, 2006; Sun and Hevner, 2014). Despite the critical nature of these prenatal events, the molecular and cellular mechanisms of neocortical development are far from fully understood.

Histogenesis of the developing neocortex begins soon after neural tube closure as the neuroepithelial cell population exponentially expands through symmetrical ventricular zone (VZ) cell divisions. This early expansion generates the required number of founder cells immediately prior to the onset of neurogenesis, which begins on embryonic day (E) 11 in mice. Neuroepithelial cells become radial glial cells (NSPCs), which have a long process that extends to the pial surface, in the VZ of the dorsal telencephalon and undergo asymmetric cell divisions to generate neurons. Indeed, the majority of glutamatergic projection neurons are thought to originate in the dorsal VZ (Noctor

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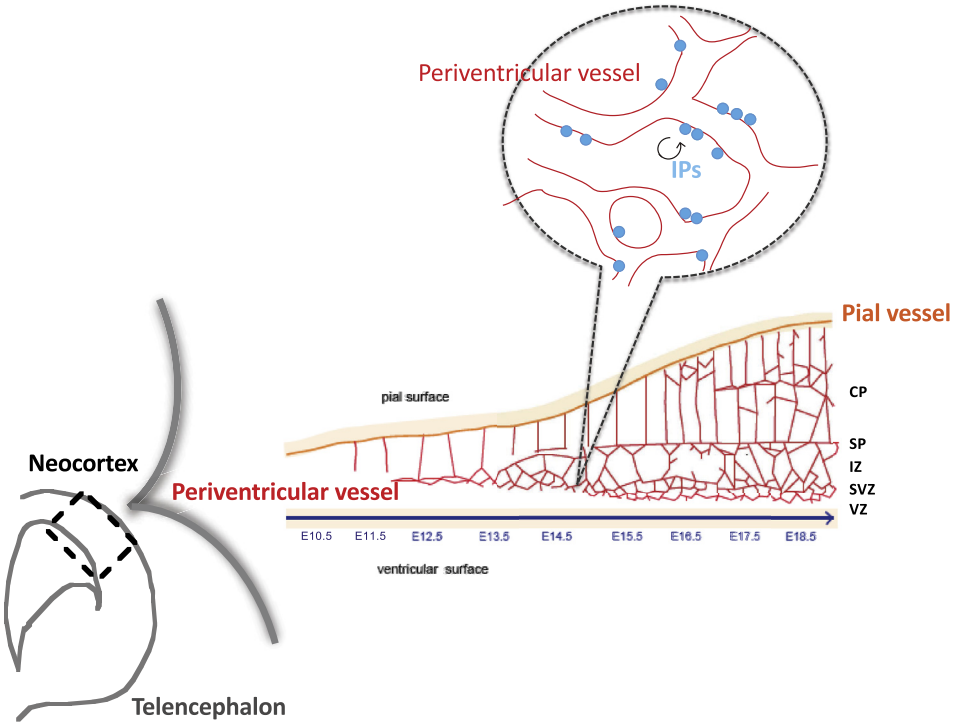

Fig. 1. Angiogenesis progresses in an extremely regular pattern during neocortical development. Antecedently arranged pial vessels (orange) encompassed the entire telencephalic pial surface as early as E9, whereas periventricular vessels (red) originated from a basal vessel on the telencephalic floor of the basal ganglia primordium and developed in an orderly, ventral-to-dorsal gradient after E11.5, and expanded its vascular plexus in the neocortical parenchyma (VZ, SVZ, IZ, SP, and CP) around E12.5 to E17.5, consistent with an expansion of the differentiation of neural progenitors. Periventricular vessels attract newborn intermediate progenitors (IPs, blue) in the developing neocortex and induce their division in the vicinity of vessels.

et al., 2001; Rakic, 1988). During development of the mammalian neocortex, newborn neurons undergo multiphasic radial migration processes to reach their final position within the cortical plate (CP). During this process, post-mitotic immature neurons, which originate from NSPCs and remain in the VZ before transforming into post-mitotic cells with multipolar morphology, and move out of the VZ and migrate radially toward the pial surface through the SVZ (subventricular zone), IZ (intermediate zone), and the CP (Inoue et al., 2014; Inoue et al., 2015; Inoue et al., 2017; Iwai et al., 2018; Mizutani, 2018; Noctor et al., 2004; Tabata and Nakajima, 2003).

On the other hand, most cortical GABAergic interneurons originate from ganglionic eminences (GEs) in the ventral telencephalon (Rakic, 1995). These GABAergic interneurons migrate tangentially toward the dorsal telencephalon along the marginal zone (MZ) or SVZ/IZ from their origins (Fig. 2). The origins and routes of tangential migration of telencephalic GABA neurons are well established (Corbin et al., 2001; Marín and Rubenstein, 2001; Parnavelas, 2000). However, many missing links remain and the mechanisms that underlie GABA neuron tangential migration are not fully understood. The establishment of neocortical cytoarchitectures is essential for brain functions, and the function of the neocortex essentially relies on the balance between excitatory glutamatergic projection neurons and inhibitory GABAergic interneurons. Recent studies have suggested that these two classes of neurons are strictly controlled by the vascular niche.

3. Vascular development during neocortical development

Besides the neural system, the other major cellular component of the developing neocortex is the vascular system. The central nervous system (CNS) acquires its vasculature by angiogenesis, a process consisting of proliferation of endothelial cells in existing blood vessels or vascular plexuses, and leading to the formation of new blood vessels. Notions of cerebral vascularization often depict CNS angiogenesis as a passive process driven primarily by the demand for oxygen and to meet the metabolic needs of growing neuronal populations (Risau, 1997; Kurz, 2000). They treat the developing endothelial network as a homogenous population.

Based on the anatomical location, growth pattern, and developmental regulation, the telencephalic vasculature has been suggested to comprise of two categories: pial vessels and periventricular vessels (Fig. 1). The neural tube, acting as a vessel patterning nexus, directs the formation of the pial vessels that encompass it. The pial vessels do not display developmental gradients and are present circumscribing the entire telencephalon by E9. On the other hand, the periventricular vessels of the basal ganglia primordium actively develop in the ventral telencephalon and form an elaborate network that progressively propagates into the dorsal telencephalon by E11.5 (Hiruma et al., 2002).

During early development, oxygen (O_2) levels, which are low in the embryo, control important events, such as the formation of the placenta, vascular system, and skeleton (Maltepe et al., 2005; Simon and Keith, 2008). After birth, O_2 demands, consumption and flow vary amongst organs, affecting its dissolved concentrations, despite the fact that they are usually much lower than values expected in the atmospheric air (Panchision, 2009). Blood vessels can exert their effects in the stem cell niche via delivery of oxygen or nutrients (Cleaver and Dor, 2012; Ramasamy et al., 2015).

Hypoxia and the hypoxia-inducible transcriptional factor HIF-1α have been reported to be involved in NSPCs proliferation and differentiation (Mazumdar et al., 2010; Li et al., 2014). In contrast, the functional role of vessels and the possible function of HIF-1α during neocortical neurogenesis have been less clear. A recent study reported that initial vessel ingrowth in the developing neocortex coinciding with an increase in tissue oxygenation and reduced levels of HIF-1α was associated with a reduction in NSPCs expansion and the transit to its differentiation (Lange et al., 2016). Additionally, it has been suggested that NSPCs expand more and differentiate less when low oxygen levels in the early developmental stage fail to increase during further neocortical development, thereby indicating that blood vessels regulate neurogenesis by supplying oxygen (Lange et al., 2016). These new findings of the mechanisms governing neocortical angiogenesis and the role of endothelial cells in neuronal networks may lead to new perspectives on telencephalic regionalization and histogenesis principles.

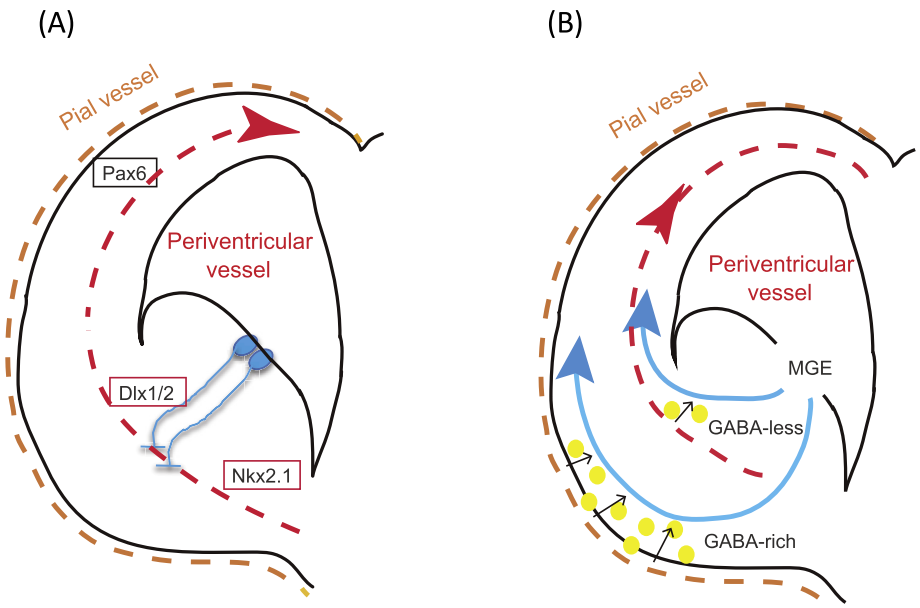

Fig. 2. GABAergic interneurons are strictly controlled by the vascular niche. Neocortical development requires the orchestrated migration of post-mitotic neurons from both the dorsal and the ventral germinal ventricular zones (VZ) to the overlying cortical plate (CP). A direct association between the neuronal phenotype and the migration pattern within the cortex was observed during the neocortical cytoarchitecture, with excitatory projection neurons arranged radially from the dorsal VZ and inhibitory interneurons migrated tangentially from the ventral VZ (B; blue). The periventricular vessel (red)-anchored ventral radial glial cells (A; blue) are progressively generated around E14.5 (A). Periventricular vessels in the ventral region express ventral transcriptional factors, Dlx1/2 and Nkx2.1, while those in the dorsal region express dorsal transcriptional factor, Pax6. The migrating periventricular vessels (B; red allow head) and GABAergic interneurons migrating from the ventral to the dorsal region (B; blue allow heads) follow the same in migratory route, and periventricular endothelial cells migrate at least a day in advance of the GABA neurons (B). The different levels of GABA secretion (B; yellow) by periventricular and pial vessels (orange) show critical functions in attracting and promoting neuronal migration (B).

4. The vascular niche influences neural progenitor expansion

It is generally accepted that different modes of cell division influence the expansion of progenitor cells and the eventual size and complexity of the post-mitotic cell population (Davis and Temple, 1994; Franco et al., 2012; Mizutani et al., 2007; Noctor et al., 2001; Rakic, 1995; Takahashi et al., 1996; Walsh and Cepko, 1993). Histogenesis of the developing neocortex begins soon after neural tube closure as the NSPCs population expands exponentially due to symmetrical VZ progenitor cell divisions. This early expansion generates the required number of neuroepithelial cells immediately prior to the onset of neurogenesis, which begins on E11 in mice. With the onset of neurogenesis, neuroepithelial cells transform into radial glial cells (NSPCs), which are located in the VZ. NSPCs divide asymmetrically to self-renew and produce either a glutamatergic projection neuron or an intermediate progenitor (IPs) daughter cells in the SVZ which divides symmetrically to generate neurons (Gal et al., 2006; Malatesta et al., 2000; Miyata et al., 2001; Noctor et al., 2001; Sessa et al., 2008). The third, relatively recently discovered type of progenitors, outer radial glia cells (oRGs), are located in the SVZ/IZ (Wang et al., 2011). In some species, including humans, this third germinal zone in the neocortex is greatly expanded and separated into outer and inner SVZ layers (Smart et al., 2002). The inner SVZ is different because it includes numerous oRGs that retain their basal process but lose their apical contact and more prolific IPs. This major expansion of the SVZ niche is thought to underlie much of the evolutionary expansion of the neocortex. oRG undergo self-renewing divisions to generate more oRGs and are able to produce IPs. Interestingly, the abundance of oRGs is greater in gyrencephalic species and correlates with the higher complexity of their cytoarchitecture (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011).

The mechanisms regulating cell fate specification in the mammalian brain are poorly understood. In particular, almost nothing is known about how these different NSPCs subtypes are generated, nor how their different characteristics are regulated on a signaling level. Signals from the stem cell niche regulate the expansion or differentiation of these progenitor subtypes. In various developing organs, blood vessels are an essential component of “the stem cell niche” that regulates the balance between progenitor/precursor expansion and differentiation (Bautch, 2011; Bjornsson et al., 2015; Ramasamy et al., 2015). During neocortical development, the periventricular vessels, originating from a basal vessel on the telencephalic floor of the basal ganglia primordium, actively develop and form an elaborated network that progressively propagates into the neocortex around E11.5 (Fig. 1).

Hence, the synchronized developmental timing between the neural system and vascular system raises the intriguing possibility that these vessels regulate progenitor behavior and neurogenesis. Transcriptome analysis shows that brain endothelial cells secrete numerous factors (Daneman et al., 2010a), periventricular vessels have a unique transcriptome that differs from those at the pial vessels (Won et al., 2013), and further mining of such information will be valuable to understand the distinctive properties of the vascular niche. It is known that vascular endothelial cells promote embryonic NSPCs self-renewal and neurogenesis (Shen et al., 2004). Further, periventricular vessels attract newborn IPs in the developing neocortex and induce their division in the vicinity of vessels (Fig. 1), suggesting that the vascular niche preferentially regulates basal progenitors in SVZ, rather than apical progenitors in the VZ (Javaherian and Kriegstein, 2009). Additionally, brain endothelial cells express high levels of the Notch ligands, such as Jagged 1, Jagged 2, and Dll4 (delta-like 4), compared with the surrounding brain tissue (Daneman et al., 2010a), which may bind at Notch receptors on contacting with NSPCs (Thomas et al., 2013). Both anti-angiogenic factors, such as Dll4, and pro-angiogenic factors, such as Angiopoietin-2 and Tie-2 receptor ligand, stimulate NSPCs proliferation *in vitro* (Androutsellis-Theotokis et al., 2010). During neocortical development, pericytes are primarily involved in promoting blood-brain barrier maturation (Daneman et al., 2010b) and, thereby, indirectly affect neurogenesis by limiting the blood-borne factors available to NSPCs.

On the other hand, various reports have demonstrated that neural progenitors reside in a hypoxic niche (Lee et al., 2001). Accordingly, oxygen tension regulates the balance between NSPCs maintenance and differentiation (Mohyeldin et al., 2010; Simon and Keith, 2008). Under normoxia, the HIF-1α subunit is continuously degraded by the ubiquitin-proteasome pathway, whereas under hypoxia the degradation pathway is circumvented. As a consequence, HIF-1α accumulates in the cytoplasm and translocates to the nucleus where it heterodimerizes with HIF-1β, leading to the transcription of HIF-1 target genes (Semenza, 2006). As the brain grows and simple diffusion becomes insufficient to deliver oxygen, HIF-1α is induced by low oxygen levels

to increase vascular development, in part through expression of VEGF (Lee et al., 2009). Interestingly, the Notch intracellular domain interacts with HIF-1α, and HIF-1α is required for Notch-responsive promoters upon Notch activation under hypoxic conditions (Gustafsson et al., 2005). A recent study showed that HIF-1α deletion impairs hippocampal Wnt-dependent processes, including NSPCs proliferation, differentiation, and neuronal maturation (Mazumdar et al., 2010). NSPCs help stabilize the nascent blood vessels by modulating canonical Wnt signaling, and disruption of NSPCs causes vessel regression (Ma et al., 2013). A more recent study showed that by modulating maternal oxygenation, fetal brain oxygen levels are robustly affected, subsequently leading to a modification in cortical neurogenesis. Increased fetal tissue oxygen tension during mid-neurogenesis results in an accumulation of proliferative cells in regions more basal to the SVZ at the expense of proliferative cells within the SVZ (Wagenführ et al., 2015), and indicates that oxygen tension initiates the expansion of the oRGs by inducing self-renewing divisions to augment brain complexity. In contrast, endothelial cells have also heterogenous properties in different areas, and acquire specialized functional properties in local environments (Nolan et al., 2013; Vanlandewijck et al., 2018). As such, these findings suggest that the vascular niche is an excellent candidate to generate neural progenitor heterogeneity, and by extension to be differentially utilized by distinct progenitor subtypes.

5. The vascular niche influences neural migration and differentiation

It is known that the development of telencephalic periventricular vascular networks predates or synchronizes development of neuronal networks. Thus, the periventricular networks are temporally and spatially well positioned to construct the dorsal telencephalon and guide tangential migration of GABAergic neurons from the ventral telencephalon (Fig. 2). Recent studies have suggested that periventricular endothelial cells have intrinsic programs that can significantly regulate neural migration and differentiation. For example, telencephalic angiogenesis progresses along a ventral-to-dorsal gradient under significant intrinsic regulation by homeobox transcription factors Dlx1/2, Nkx2.1, and Pax6 (Fig. 2A), which also regulate development of telencephalic neuroepithelial domains and post-mitotic neurons, raising the possibility that neurogenesis and angiogenesis in the neocortex may be linked mechanistically (Vasudevan et al., 2008). The direction of the periventricular endothelial cell gradient matches the direction of GABA neuron migration from the basal to the dorsal telencephalon, but with respect to timing, the angiogenesis gradient is in advance by about a day (Fig. 2B). A close physical association between the periventricular vascular network and GABA neurons has been reported (Won et al., 2013). This intimate vessel-GABA neuron contact is observed frequently, and nearly 84% of randomly selected GABA neurons were located within 5 μm of periventricular vessels in the E13 forebrain (Won et al., 2013). Additionally, migrating interneurons of the deep and superficial streams respond selectively to different levels of GABA secreted by periventricular and pial endothelial cells (Fig. 2A). A recent study has shown that radial glial progenitors in the ventral telencephalon (Tan et al., 2016), responsible for producing interneurons, progressively grow radial glial fibers anchored to periventricular vessels (Fig. 2A). Interneurons undergo an initial radial migration along the radial glial fiber after their generation from ventral progenitors and then a tangential migration to reach the neocortex (Tan et al., 2016). There are two general tangential migratory routes for MGE-derived interneurons, including a superficial route along the MZ and a deep route in the SVZ/IZ (Fig. 2B). Interestingly, the deep interneuron migratory stream appears around E12.5 and becomes the superficial route after E14.5. This temporal switch from the deep to the superficial migratory route correlates with the appearance of the vessel-anchored radial glial cells in the MGE (Tan et al., 2016), suggesting that the migratory route is controlled by the vascular niche. Furthermore, disruption of this association by selective removal of integrin β1 in radial glial progenitors leads to a decrease in progenitor division, a loss of interneurons, and defective synaptic inhibition in the neocortex (Tan et al., 2016), suggesting that the interaction between ventral neural progenitors and periventricular vessels is important for proper production and function of neocortical interneurons. A recent study has shown that NSPCs in the ventral region selectively associate with periventricular vessels. This association is robust and is actively maintained as progenitors divide, and loss of vessel association affects interneuron production and function (Tan et al., 2016). In addition, although VEGF is not normally produced by endothelial cells, during telencephalic development it is, and selective deletion of VEGF from endothelial cells perturbs cerebral cortical neurogenesis, cytoarchitecture, and axon tract formation (Li et al., 2013), indicating that the physiological function of endothelial VEGF is to regulate neocortical histogenesis. These recent reports suggest that neocortical angiogenesis progresses in a spatially and temporally restricted manner to construct a specialized vascular niche that supports ongoing neural migration and differentiation during neocortical development.

6. Future prospects

Patterning of blood vessels markedly varies among tissues. The diversity and plasticity of vascular networks are considered an important system to exert the tissue functions. Therefore, clarification of the diversity and similarity of vascular networks is important to shed light on the developmental systems of cytoarchitecture. In the CNS, dense vascular networks containing arteries and veins are formed on the organ surface (the pia mater of the brain), whereas only capillary blood vessels are distributed inside tissue parenchyma. In our recent studies (unpublished data), the vascular density in tissues was very accurately maintained during neocortical development (Fig. 1). Therefore, it is assumed that the surrounding blood vessels supply a specific vascular niche to precisely control cytoarchitecture.

Clarification of the physiological significance of vascular networks enabling development of tissues is expected not only to lead to breakthroughs concerning the developmental events of brain tissues, but also to advance various applied researches. Specifically, if the biological vascular design can be simulated, it may contribute to establishing *in vitro* differentiation induction techniques for pluripotent stem cells. Therefore, further research is warranted to make important discoveries regarding novel perspectives on neocortical histogenesis principles and will lead to discoveries with unprecedented implications for regenerative medicine and the treatment of several neurological diseases (Mansour et al., 2018).

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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.2019.104481.

Disclosures

The authors have no competing financial interests to declare.

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