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Neurovascular development in the embryonic zebrafish hindbrain

Florian Ulrich [a], Leung-Hang Ma [b], Robert G. Baker [b], Jesús Torres-Vázquez [a,*]

[a] Department of Developmental Genetics, Skirball Institute of Molecular Medicine, 540 1st Avenue, 4th floor, lab 14, New York City, New York 10016, USA
[b] Department of Physiology and Neuroscience, New York University Medical Center, 550 1st Avenue, 4th floor, room 458, New York City, New York 10016, USA

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ABSTRACT

The brain is made of billions of highly metabolically active neurons whose activities provide the seat for cognitive, affective, sensory and motor functions. The cerebral vasculature meets the brain's unusually high demand for oxygen and glucose by providing it with the largest blood supply of any organ. Accordingly, disorders of the cerebral vasculature, such as congenital vascular malformations, stroke and tumors, compromise neuronal function and survival and often have crippling or fatal consequences. Yet, the assembly of the cerebral vasculature is a process that remains poorly understood. Here we exploit the physical and optical accessibility of the zebrafish embryo to characterize cerebral vascular development within the embryonic hindbrain. We find that this process is primarily driven by endothelial cell migration and follows a two-step sequence. First, perineural vessels with stereotypical anatomies are formed along the ventro-lateral surface of the neuroectoderm. Second, angiogenic sprouts derived from a subset of perineural vessels migrate into the hindbrain to form the intraneural vasculature. We find that these angiogenic sprouts reproducibly penetrate into the hindbrain via the rhombomere centers, where differentiated neurons reside, and that specific rhombomeres are invariably vascularized first. While the anatomy of intraneural vessels is variable from animal to animal, some aspects of the connectivity of perineural and intraneural vessels occur reproducibly within particular hindbrain locales. Using a chemical inhibitor of VEGF signaling we determine stage-specific requirements for this pathway in the formation of the hindbrain vasculature. Finally, we show that a subset of hindbrain vessels is aligned and/or in very close proximity to stereotypical neuron clusters and axon tracts. Using endothelium-deficient *cloche* mutants we show that the endothelium is dispensable for the organization and maintenance of these stereotypical neuron clusters and axon tracts in the early hindbrain. However, the cerebellum's upper rhombic lip and the optic tectum are abnormal in *clo*. Overall, this study provides a detailed, multi-stage characterization of early zebrafish hindbrain neurovascular development with cellular resolution up to the third day of age. This work thus serves as a useful reference for the neurovascular characterization of mutants, morphants and drug-treated embryos.

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Introduction

Blood vessels deliver oxygen, nutrients, hormones and immunity factors throughout the body to enable homeostasis and survival (Attwell et al., 2010; Koehler et al., 2009). The embryonic brain is vascularized by invading sprouts that launch from extra-cerebral vessels (reviewed in Mancuso et al., 2008). Cerebral vascularization is particularly critical because the brain is the organ that requires the largest blood supply and consumes most of the body's glucose due to the neurons' unusually high metabolic rate (Begley and Brightman, 2003; Rolfe and Brown, 1997). In addition, the brain requires protection from the entry of immune cells and serum proteins. The cerebral endothelium is unique in its expression of glucose transporters and, together with microglia, astrocytes and pericytes, it maintains the unique extracellular environment required for CNS function through the blood brain barrier (Engelhardt, 2006; Simpson et al., 2007). Accordingly, changes in cerebrovascular structure and/or function resulting from congenital vascular malformations, brain tumors, ischemic stroke, certain neurodegenerative diseases and disintegration of the blood brain barrier are usually disabling and can often be fatal (Carmeliet and Tessier-Lavigne, 2005; Kim and Lee, 2009; Segura et al., 2009; Taoufik and Probert, 2008). Hence, there is great interest in understanding the cellular and molecular mechanisms that shape the anatomy and modulate the functional properties of the cerebral vasculature during development and disease.

Most of our knowledge about vascular development in the CNS comes from the study of mouse, quail and chick embryos. These studies have implicated Vascular Endothelial Growth Factor (VEGF), Wnt, Integrins and GPCR receptors as key molecular players in this process (Dejana and Nyqvist, 2010; Lammert, 2008; McCarty et al., 2005; Milner and Campbell, 2002). The process of brain

* Corresponding author. Fax: +1 212 263 7760.
E-mail addresses: florian.ulrich@med.nyu.edu (F. Ulrich), Leung-Hang.Ma@nyumc.org (L.-H. Ma), robert.baker@nyumc.org (R.G. Baker), Jesus.Torres-Vazquez@med.nyu.edu (J. Torres-Vázquez).

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Table 1
Abbreviations for vascular and neuronal structures used in this paper. Vascular nomenclature as in (Isogai et al., 2001). Neuronal nomenclatures as in (Metcalfe et al., 1986).

a) Endothelial structures	
AA1	Mandibular arch
ACV	Anterior cardinal Vein
ACeV	Anterior cerebral Vein
Ang	Angioblasts
BA	Basilar artery
BCA	Basal communicating artery
CtA	Central artery
DCV	Dorsal ciliary vein
DLV	Dorsal longitudinal vein
DMJ	Dorsal midline junction
ec	endocardium
LDA	Lateral dorsal aorta
MCeV	Mid-cerebral vein
MsV	Mesencephalic vein
MtA	Metencephalic artery
NCA	Nasal ciliary artery
OV	Optic vein
PCS	Posterior comm. segment
PCeV	Posterior cerebral vein
PHBC	Primordial Hindbrain Channel
PICA	Primitive internal carotid artery
PMBC	Primordial midbrain channel
PNVP	Perineural vascular plexus
PPrA	Primitive prosencephalic artery
b) Neuronal structures	
ne	Neurectoderm
cb	Cerebellum
chb	Caudal hindbrain
cns	central nervous system
com	Commissure
cp	Cerebellar plate
ep	Epiphysis
fb	Forebrain
gc	Glial curtain
hb	Hindbrain
llf	Lateral longitudinal fascicle
mb	Midbrain
mhb	Mid-/hindbrain boundary
mlf	Medial longitudinal fascicle
ne	Neurectoderm
nV	Fifth cranial nerve (trigeminus)
nVI	Sixth cranial nerve (abducens)
nIX	Ninth cranial nerve (glossopharyngeal)
nX	Tenth cranial nerve (vagus)
ob	Olfactory bulb
op	Olfactory placode
ot	Optic tectum
r	Rhombomere
rms	Rostral migratory stream
SVZ	Sub-ventricular zone
t	Telencephalon
te	Tectum
tv	Tectal ventricle
url	Upper rhombic lip
v3	3rd ventricle
v4	4th ventricle
c) Reticulospinal neuron nomenclature	
Ma	Mauthner neuron
Ca	Caudal
Mi	Middle
Ro	Rostral
D	Dorsal
V	Ventral
M	Medial
L	Lateral

vascularization begins when vascular precursors from the paraxial mesoderm form a Perineural Vascular Plexus (PNVP) that envelops the brain and spinal cord (Bautch and James, 2009; Stenman et al., 2008). Subsequently, PNVP-derived angiogenic sprouts penetrate into the neurectoderm at stereotypic positions along the dorso-ventral axis. Once these sprouts are inside they grow towards the ventricular (inner) surface, where they branch perpendicularly to their original growth path and connect to neighboring vessels forming the Periventricular Vascular Plexus — PVVP (Bautch and James, 2009; Kuhnert et al., 2010; Vasudevan et al., 2008).

A key aspect of the cerebral vasculature is its interplay with both neurons and glia. Examples include the vascular niches of neural stem cells found in the adult mammalian brain (Goldberg and Hirschi, 2009; Li et al., 2006; Shen et al., 2008; Tavazoie et al., 2008); the specialized neurovascular units that constitute the blood brain barrier (Abbott et al., 2006); the coupling of neurogenesis and angiogenesis (Bautch and James, 2009; Lyden et al., 1999; Teng et al., 2008; Yang et al., 2010); and the alignment of ingressing vessels with radial glia (Gerhardt et al., 2004). In addition, blood vessels are also employed by neuronal precursors as cellular substrates for their migration. This process of "vasophilic migration" occurs in the adult mammalian brain (reviewed in Saghatelyan, 2009).

For example, in the murine forebrain immature neurons originating at the subventricular zone (SVZ) reach the center of the olfactory bulb (OB) via the rostral migratory stream (RMS) (Altman, 1969). Time-lapse imaging of sagittal forebrain slices shows that neuroblasts migrate through the RMS by moving along vessels, apparently guided by Brain-Derived Neurotrophic Factor (BDNF) provided by endothelial cells (Peretto et al., 2005; Snapyan et al., 2009; Whitman et al., 2009). Vasophilic migration also occurs within the OB as a mechanism by which neural progenitors arrive to injured regions after ischemic stroke (Bovetti et al., 2007; Kojima et al., 2010). Finally, it is likely that in the brain, like in other parts of the body, subsets of blood vessels and nerves run parallel to each other forming distinct regions of neurovascular congruence (Bates et al., 2002; Bearden and Segal, 2005; Benoit et al., 1999; Bentley and Poole, 2009; Capela and Temple, 2002; Dray et al., 2009; Furukawa et al., 2008; Kummer and Haberberger, 1999; Louissaint et al., 2002; Makita et al., 2008; Martin and Lewis, 1989; Mukouyama et al., 2002; Palmer et al., 2000; Segura et al., 2009; Smoliar et al., 1999; Vieira et al., 2007). Neurovascular congruence is coordinated by angioneurins, a diverse set of secreted and transmembrane protein families that includes VEGF, Semaphorins (Semas), Netrins, Slits, Ephrins/Eph, and chemokines, which function by regulating the survival, adhesion, differentiation and migration of cells of the vascular and nervous systems (Adams and Eichmann, 2010; Kokovay et al., 2010; Sciume et al., 2010; Zacchigna et al., 2008a). Neurovascular congruence arises in two ways. First, the neural and vascular subunits develop independently of each other, implying the existence of common guidance cues for both tissues. In these cases, defective formation or deletion of one of the two tissues does not preclude the proper formation of the other. For example, the quail forelimb displays peripheral nerves and blood vessels with congruent patterns. However, aneural forelimbs display normal vascular patterns and nerves are properly formed in both hyper- and hypo-vascularized forelimbs (Bates et al., 2002, 2003).

Alternatively, there is codependent relationship between the congruent vascular and neural components, with one of the two tissues guiding the development of the other. For example, peripheral nerves and arteries run parallel to each other in the skin of the embryonic mouse hindlimb. Their congruence is orchestrated by distinct nerve-provided signals: an unidentified vascular "aligning" cue and VEGF, which induces arteriogenesis of the aligned capillaries (Mukouyama et al., 2002, 2005). Conversely, the vasculature can guide nerves. Vascular smooth muscle cells express Artemin and Endothelin to align sympathetic axonal projections with them (Honma et al., 2002; Makita et al., 2008).

The embryos of most vertebrate model systems have a large brain and offer limited physical and optical access to the cerebral vasculature. As a result, the process of brain vascular development must be studied in these models using techniques that provide only

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