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Molecular and Cellular Mechanisms of the Neurovascular Link

Goal

Our research group aims to understand the molecular mechanisms of vascular and neurodevelopment and the communication between both networks within the central nervous system.

Background

Despite their distinct functions, the nervous and vascular systems share many more similarities and common principles than previously anticipated. Recent research has demonstrated that both networks develop using similar molecular mechanisms and guidance cues and that communication between them is essential for proper formation and function of each of them. These observations bring up the new concept of an existing **Neurovascular link**. The Neurovascular link highlights the significance of a shared-tight molecular regulation between the vascular and the nervous system and underlines the importance of studying both systems together and not as separate entities. Moreover, identifying the cellular and molecular mechanisms of neuro-vascular communication is essential to understand how both systems develop and function within such complex organs as the brain or spinal cord, as well as to intervene in pathological situations.

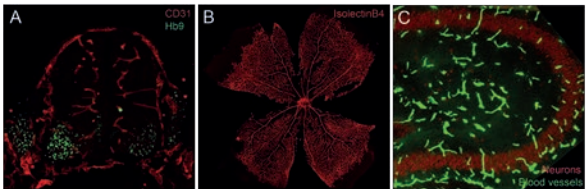

Figure 1. Model systems to study neuro-vascular communication during CNS development,
A) *Image of a spinal cord cross-section from a E11.5 mouse embryo where blood vessels are labeled with the endothelial cell marker CD31 (red) and motor neurons with the HB9 marker (green).*
B) *Whole mount image of a mouse retina from postnatal day 6 where blood vessels are labeled with IsolectinB4 (red).*
C) *Image of a developing mouse hippocampus at postnatal day 10 (blood vessels shown in green and neurons in red).*

Research Highlights

While other embryonic tissues undergo primary vascularization, it is unique that only the central nervous system (CNS) becomes secondarily vascularized by sprouting angiogenesis from a surrounding vascular plexus. Another exclusive feature of the CNS vasculature is the formation of a blood brain barrier (BBB) that restricts the passage of substances between the circulating blood and the cerebrospinal fluid and is essential for neuroprotection. Acquisition of BBB properties occurs concomitantly with developmental CNS vascularization. However, despite the fundamental and critical importance, it is surprising that very little is known about the molecular mechanisms that specifically control CNS vascularization. We are therefore interested in studying the signals that the developing nervous system sends to the growing vasculature in order to control CNS angiogenesis. As model systems we use the devel-

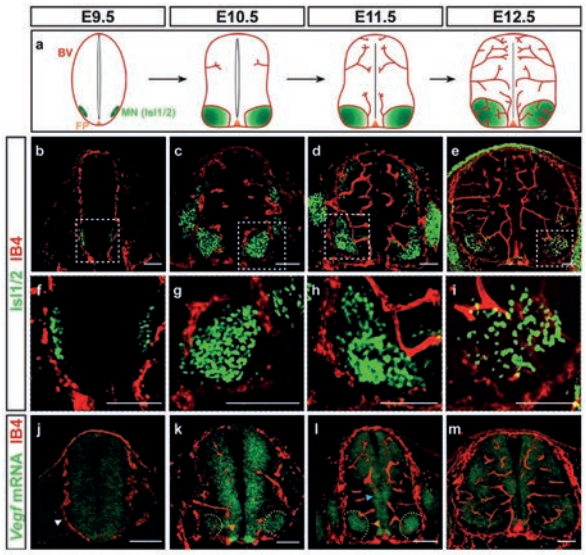

Figure 2. Motor neurons control blood vessel patterning for a specific time window during spinal cord development

A) *Scheme of SC vascularisation during mouse development (E9.5 till E12.5), showing blood vessels (BV, red), the floor plate (FP, orange), and the MN columns (green).* ***B-E)*** *Representative images of SCs at the developmental stages indicated, showing labelled endothelial cells (IB4+) and post-mitotic MNs (Isl1/2+).* ***F-I)*** *Higher magnifications of insets in (B-E). Note blood vessels stay outside the Isl1/2+ domain till E12.5.* ***J-M)*** *Representative images of blood vessel staining (IB4+) in the SC combined with ISH for Vegf from E9.5 till E12.5 in mice. At E9.5 (J), Vegf is uniformly expressed in the entire SC. From E10.5 till E12.5 (K-M) Vegf expression becomes restricted to specific neuronal domains (yellow dotted lines: MN columns; orange arrowheads: FP; blue arrowhead: neuronal progenitors).* ***N-Q)*** *Representative images of ISH for Vegf combined with immunostaining for MNs (Isl1/2+) confirming that Vegf expression is highly localised and increased in MN columns from E10.5 onwards. Insets show higher magnifications of MN columns.*

oping mouse CNS (brain, spinal cord and retina) (Figure 1). In addition, we have established in the lab the use of chicken embryos, as they are easily accessible and allow the performance of large genetic screenings in a short period of time.

Our results of the past three years show that the prototypic pro-angiogenic factor vascular endothelial growth factor (VEGF) is expressed in neuronal progenitors, the floor plate and motor neurons in the developing spinal cord. However, the sole presence and expression of VEGF cannot explain the process of spinal cord vascularization as precisely those regions where VEGF is highly expressed remain avascular during a developmental time window (Figure 2). We found that spinal cord motor neurons utilize an autocrine mechanism in order to titrate their own VEGF and thus control the amount of VEGF that the surrounding blood vessels can sense. Like that they prevent blood vessel invasion into the areas where they are located for a specific time frame. The role of other neuronal populations, as well as the signaling mechanisms involved, for CNS vascularization is currently being investigated. Likewise, we are further characterizing the mechanisms by which neuroepithelium-derived VEGF controls blood vessel growth and guidance within the CNS.

Apart of controlling vascular development, VEGF as well as other members of its family, and their receptors, are also expressed in neuronal cells and participate in processes such as neurogenesis, neuronal migration, axon guidance, dendritogenesis and dendrite maintenance. In the last years, we have focused in further elucidating how VEGF might control axon and dendritic branching of developing neurons of the hippocampus. Finally, Angiopoietins and their Tie receptors, another classical vascular ligand-receptor pair, are also expressed in distinct neuronal populations during CNS development. However, whether their expression is only required for proper CNS vascularization or whether they also exert an additional function on developing neural cells remains unknown. Using mouse genetics we are characterizing the specific function that they might have on the nervous system.

Selected Publications 2014 - 2016

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