2004 - 2006	Ph.D. - University of Granada, Spain
2004 - 2011	PostDoc - Vlanders Interuniversity Institute for Biotechnology (VIB), Leuven, Belgium (Prof. Peter Carmeliet)
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Carmen Ruiz de Almodóvar

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 during development of the central nervous system.

Background

Despite their distinct functions, the nervous and vascular systems share many more similarities and common principles than previously anticipated. It is striking how similar axons and blood vessels grow. At the end of a growing axon, the *growth cone* is responsible for extending filopodia, sensing the environment and guiding the axon to its final target (Figure 1). Similarly, at the tip of a sprouting blood vessel, a specialized endothelial cell, the *endothelial tip cell*, extends numerous *filopodia* and senses the guidance signals (Figure 1). Both networks also share regulatory molecular mechanisms and guidance cues during the process of pathfinding and growth. These recent observations bring up the new concept of an existing Neurovascular link controlling vascular and neuro-developmental processes. 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 angiogenic factors beyond its normal tissue environment (the vascular system). In addition, nowadays we know that communication between both networks is essential for their precise development and function; yet, the molecular mechanisms of this Neuro-Vascular crosstalk remain still poorly understood.

Research Highlights

The key angiogenic factor, vascular endothelial growth factor (VEGF-A, termed from hereon VEGF), as well as other members of its family such as VEGF-C and VEGF-D, and their receptors, apart of controlling vascular development, are also expressed in neuronal cells and participate in processes such as neurogenesis, neuronal migration, axon guidance, dendritogenesis and dendrite maintenance. Our previous research showed that VEGF and its receptor VEGFR-2 (also termed Flk1) act as a guidance cue and guidance receptor respectively in neuronal migration during cerebellar development. Moreover, we identified that NMDARs act as co-receptors for VEGFR-2 in migrating cerebellar granule cells (GC). VEGF regulates GC migration by binding to VEGFR-2 and modulating NR2B properties to enhance NMDARs-mediated calcium influx. Additionally, we identified that VEGF can act as a commissural axon guidance cue during spinal cord development. Despite these initial findings, still little is known about the biology of VEGF or of any other angiogenic factors in neurons, the

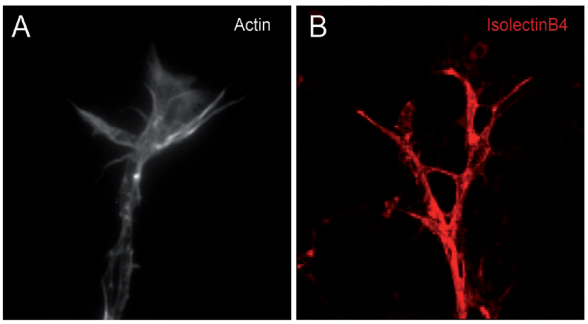

Fig. 1: Axon growth cone and endothelial tip cell
A) *Image of a growing growth cone from an isolated hippocampal neuron.* ***B)*** *Image of an endothelial tip cell from a growing blood vessel in the mouse retina.*

signaling pathways that they activate and their functional role in neurodevelopment. Thus, our group is currently focused in further elucidating these processes using as a model systems the developing mouse spinal cord, cerebellum and hippocampus.

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 the CNS angiogenesis.

Here, as model systems we are focused in the developing mouse CNS (brain, spinal cord and retina) (Figure 2). Similar to as above, our experimental approaches also comprise *ex vivo* and *in vivo* methodologies using RNAi technologies and mouse genetics, *in vitro* cell biology and biochemistry and state of the art microscopy.

Selected Publications 2011 - 2013

Luck, R & Ruiz de Almodovar, C. Axon guidance factors in developmental and pathological angiogenesis, Book chapter, *Springer*, in press.

Carmeliet, P, Ruiz de Almodovar, C. VEGF ligands and receptors: implications in neurodevelopment and neurodegeneration. *Cell Mol Life Sci.* 2013, May;70(10):1763-78.

Snuderl M*, Batista A*, Kirkpatrick ND*, Ruiz de Almodovar C*, et al. Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. *Cell*, 2013 Feb 28;152(5):1065-76.

Meissirel, C*, Ruiz de Almodovar, C* et al. VEGF modulates NMDA receptor activity via a Src-family-kinase-dependent cross-talk. *Proc Natl Acad Sci U S A.* 2011 Aug 16;108(33):13782-7.

Ruiz de Almodovar, C*, Fabre, P* et al. VEGF mediates commissural axon chemoattraction through its receptor Flk1. *Neuron* 2011, June 9 (70):966-78.

(* Equal contribution)

Awards and Honors

2009	FEBS Young Investigator Award
2011	Marie Curie Career Integration Grant
2013	ERC Starting Grant

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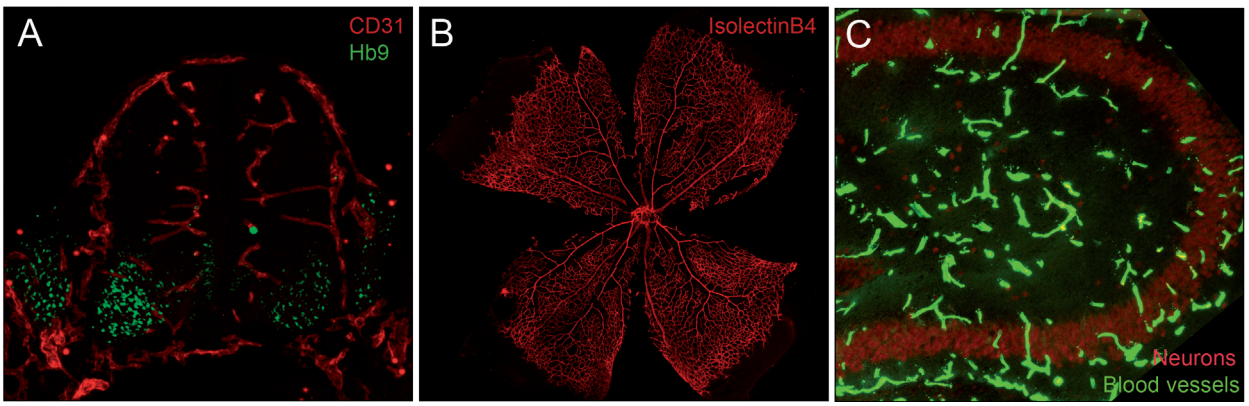

Fig. 2: Model systems to study neuro-vascular communication during CNS development. A) *Image of a spinal cord cross-section from a E11.5 mouse embryo where blood vessels are labeled with the endothelial cell marker CD31 (red) and motor neurons with the HB9 marker (green).* ***B)*** *Whole mount image 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).*