Seminars in Cell & Developmental Biology 22 (2011) 1019–1027

Contents lists available at SciVerse ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Neuronal action on the developing blood vessel pattern

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ARTICLE INFO

Article history:
Available online 29 September 2011

Keywords:
Neuro-vascular development
Vascular patterning
Vessel ingression
Blood brain barrier
Arterial differentiation

ABSTRACT

The nervous system relies on a highly specialized network of blood vessels for development and neuronal survival. Recent evidence suggests that both the central and peripheral nervous systems (CNS and PNS) employ multiple mechanisms to shape the vascular tree to meet its specific metabolic demands, such as promoting nerve-artery alignment in the PNS or the development the blood brain barrier in the CNS. In this article we discuss how the nervous system directly influences blood vessel patterning resulting in neuro-vascular congruence that is maintained throughout development and in the adult.

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1. Introduction

Blood vessels deliver oxygen and nutrients throughout the body, supporting organ development as well as metabolism and homeostasis. During embryogenesis, a primary capillary plexus undergoes extensive vascular remodeling and develops into a hierarchical vascular branching network. However, little is known about the anatomical template or environmental cues that control the highly stereotypic pattern of blood vessel branching in an organ-specific manner. The nervous system also forms a highly branched network reaching every organ in the body, and it relies on a dense network of blood vessels to supply oxygen and nutrients to meet its substantial metabolic demands, as well as neurotrophic factors for survival.

It has been recognized for hundreds of years that the vascular network closely associates with the neuronal network throughout development and in the adult. Among the many elaborate and intricate blood vessel patterning events taking place in the embryo, we focus on two vascular development models coordinated by the central and peripheral nervous systems (CNS and PNS). In this review, we discuss the cellular mechanisms and signaling pathways the CNS and PNS employ to directly interact with blood vessels, resulting in the formation of a specialized vascular network capable of supporting the nervous system. In the neural tube vascular patterning model, we discuss how CNS neural tube-derived signals

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1084-9521/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.semcdb.2011.09.010

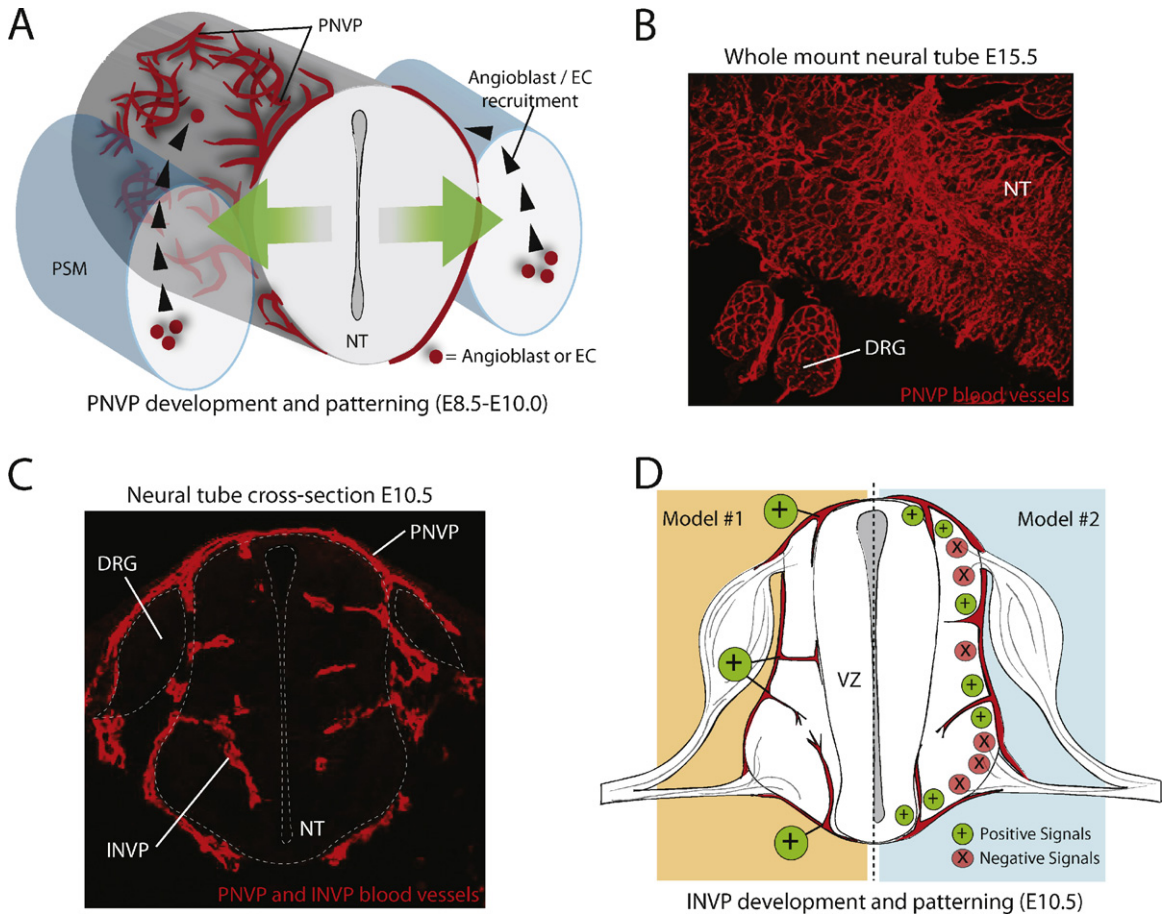

Fig. 1. PNVP and INVP recruitment and patterning in the neural tube. (A) Model of PNVP recruitment. At E8.5, angioblasts and ECs from the PSM respond to positive vessel patterning signals secreted from neural cells (green arrows) by differentiating, proliferating, and migrating to the surface of the neural tube. They surround the neural tube, forming a blood vessel plexus. (B) Immunofluorescence on a whole-mount, E15.5 NT (dorsal view), detecting blood vessels of the PNVP. PNVP vessels form a remodeled network on the surface of the NT and DRG. (C) Immunofluorescence on a cross-section of an E10.5 mouse embryo detecting both PNVP and INVP blood vessels. Blood vessels from the PNVP invade the neural tube at this stage, forming the INVP. (D) Two models for stereotypical vessel invasion during INVP formation. Model #1 depicts positive blood vessel patterning cues (such as matrix-binding VEGF-A) being localized to precise points of blood vessel invasion, whereas Model #2 depicts a balance of positive and negative blood vessel patterning cues to regulate the ingression pattern. Abbreviations: Peri-neural vessel plexus (PNVP), intra-neural vessel plexus (INVP), pre-somitic mesoderm (PSM), dorsal root ganglia (DRG), neural tube (NT), endothelial cell (EC), ventricular zone (VZ).

regulate sprouting capillaries to form a stereotypic vessel ingression pattern (Fig. 1) and acquire CNS vasculature-specific blood brain barrier (BBB) characteristics within the neural tube (Fig. 2). In the limb skin vascular patterning model, we discuss how PNS nerve-derived signals direct arterial differentiation and patterns of angiogenic remodeling to establish the congruence of nerve and arterial vessel branching patterns (Fig. 3). These two models demonstrate the action of neuronal signals on the formation of an architecturally complex vascular network.

2. Blood vessel patterning in the developing spinal cord of the CNS

Vascularization of the embryonic spinal cord is crucial for CNS development and homeostasis. In early embryogenesis, there are no endothelial cells (ECs) or endothelial cell precursors (angioblasts) in the neuroectoderm, nor can cells within this tissue give rise to ECs [1–4]. Almost as soon as the anlagen CNS forms a tube, it begins communicating with the surrounding mesodermal tissue—where angioblasts and endothelial cells reside. In this narrow developmental window (E8.5-E10.0 in mouse or Day 2–4 in avian embryos), the neural tube recruits angioblasts and ECs to coalesce into a ring of vessels, known as the peri-neural vessel plexus (PNVP) (Fig. 1A and B). This is the first blood vessel patterning process coordinated by the neural tube of the CNS. As neural development proceeds within the neural tube, blood vessels invade the neuroectoderm via sprouting angiogenesis—forming an intra-neural vessel plexus (INVP) (Fig. 1C). This is the second major blood vessel patterning event coordinated by the CNS. Both the PNVP and INVP acquire specific properties unique to CNS vasculature that form the blood brain barrier (BBB) [5–8] (Fig. 2).

2.1. Formation of the peri-neural vessel plexus (PNVP)

The neural tube was identified as the source tissue for positive blood vessel patterning signals capable of inducing EC migration and directing PNVP formation. Ectopically grafted, mouse-derived neural tubes in avian hosts recruited a PNVP, whereas grafted acrylic beads, or notochords (an embryonic midline patterning structure) did not [9]. Furthermore, analysis of Tbx6 mutant mouse embryos, with defects in paraxial mesoderm specification resulting in the formation of multiple neural tubes lateral to the endogenous neural tube, revealed that these ectopic neural tubes also have the ability to recruit PNVPs [9,10]. These experiments clearly demonstrate that the neural tube is the source of a diffusible blood vessel patterning signal coordinating PNVP formation. Furthermore, the ability of the neural tube to pattern a PNVP is not