Special Focus: Angiogenesis in the Central Nervous System

Cell lineages and early patterns of embryonic CNS vascularization

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First steps of blood vessel formation and patterning in the central nervous system (CNS) of higher vertebrates are presented. Corresponding to the regional diversity of the embryonic CNS (unsegmented spinal cord vs segmented brain anlage) and its surroundings (segmented trunk vs unsegmented head mesoderm, neural crest-derived mesenchyme), cells of different origins contribute to the endothelial and mural cell populations. The autonomous migratory potential of endothelial cells is guided by attractive and repulsive clues. Nevertheless, a common pattern in both spinal cord and forebrain vascularization appears, with primary ventral vascular sprouts supplying the periventricular vascular plexus of the neural tube, whereas dorsolateral sprouts appear later.

Building the House Around the Plumbing?

Vascular beds of different organs exhibit highly specific patterns that would allow diagnosis of any organ just from a vascular cast or an X-ray angiogram, i.e., without information about the parenchyma. The traditional view upon this intimate relationship between different tissues and their vascular supply has been that, during development, primordial organs (anlagen) dictate the vessel patterns to comply with their growth and function. However, this hierarchical and very general concept of “building the plumbing in the house” needs modification. First, the primordial blood vessels, together with other molecules, specifies motor neurons in the basal chyma. The traditional view upon this intimate relationship between blood vessels originating from parenchymal cells, other signals have shown that a feedback of blood flow-induced mechanical forces into vascular cells is sufficient for the generation of nicely lobulated vascular patterns, without the need for a parenchyma.

Taken together, there is considerable evidence that the structure of some organs may depend critically on the vasculature, i.e., “building the house around the plumbing.” Perhaps, both concepts can best be reconciled by stating that organ anlage and blood vessels mutually influence each other during morphogenesis, and that this mutual influence may vary considerably with respect to region and cell lineage. But does this idea also hold for CNS vascularization? To address this question, I will try to unfold some aspects of regional and cellular diversity of the CNS in higher vertebrates.

Cellular and Regional Diversity of CNS Anlagen

In contrast to most organs which are confined to relatively small regions, the CNS extends itself along the entire anterior-posterior (a-p) axis of the body. The CNS originates through the process of neurulation, i.e., formation of a neural tube (NT) in the midline of the body by two different mechanisms, primary vs secondary neurulation. The NT is a purely epithelial structure which anteriorly (primary) is formed by separation from the ectodermal epithelial layer, and posteriorly (secondary) by condensation, epithelialization and cavitation of mesenchymal cells. Neurulation starts in the cranio cervical transition zone and proceeds in a-p direction, thereby forming a bilaterally symmetric tube (the later spinal cord) with a clear dorso-ventral (d-v) morphologic and chemical pattern: the ventral, unpaired floor plate is induced by Sonic hedgehog (Shh) from the underlying notochord to produce Shh itself, whereas the dorsal, unpaired roof plate is induced by bone morphogenetic proteins (BMP) from the overlying ectoderm to produce BMP4 itself. In this dorsal region, so-called neural crest (NC) cells emigrate from the NT to form large parts of the peripheral nervous system. As differentiation of neuronal and glial cell types proceeds, three layers become visible along the medio-lateral axis: (1) the innermost, ependymal or ventricular layer, where neuroblasts proliferate; (2) the intermediate or mantle layer, where the postmitotic neurons accumulate; and (3) the outer or marginal layer where the axons accumulate. The mantle layer is to become the gray matter, the marginal layer the white matter of the spinal cord. The neurons which accumulate between floor and roof plate arrange themselves as paired basal plates and alar plates. They thus are exposed to (at least) two opposing d-v gradients of signaling molecules, which induce different types of transcription factors and thus specify different types of neurons. For example, the combined ventral expression of Nkx6.1 and Pax6, together with other molecules, specifies motor neurons in the basal plates.

Anteriorly, the NT undergoes more complex developmental changes to become the hindbrain, midbrain and forebrain. While
some inductive mechanisms are similar in the spinal cord and the forebrain, like ventral Shh and dorsal BMP expression, others are dissimilar, like dorsal Pax6 expression in the forebrain vs ventral expression in the spinal cord. The details are clearly beyond the scope of this article, but four important differences between developing spinal cord and the brain anlagen should be pointed out: (1) the brain primordium is segmented (best studied in the so-called rhombomeres of the hindbrain), while the spinal NT is not; (2) the NC of the brain (cephalic NC) produces most tissues of the face and skull (notably, vascular smooth muscle cells, vSMC), in addition to those cell types the spinal NC can give rise to, and is important for forebrain development; (3) especially in the cerebellum and the mammalian telencephalon, their enormous size is associated with additional proliferating zones and neuronal migration, and a more complex layering of neuroblasts and neurons; (4) the retina and optic nerve, and the olfactory bulb represent highly specialized extensions of the forebrain.

**Cellular and Regional Diversity of Mesenchyme around CNS**

Like the CNS, the blood vascular system extends over the entire length of the body, and likewise it exhibits regional differences with respect to origins of its endothelial (EC) and mural cells (pericytes, PC and vSMC). In all regions, EC are exclusively derived from mesoderm, be it segmented (trunk) or unsegmented (head). Of note, the dorsal aortas arise as paired structures from confluent blood islands and subsequently fuse into a single aorta along the a-p axis. Synchronous with neurulation, segmental epithelial blocks, the somites, condense in the paraxial mesoderm, i.e., on either side of the NT and notochord. In each somite, gene expression patterns establish an a-p and d-v axis, whereby a ventral sclerotome which expresses Pax1 is induced via Shh signaling from the notochord, and is separated from a dorsal dermamyotome (expressing Pax3, induced via Wnt signaling from the NT roof plate). The latter will give rise to striated muscles and dermis, whereas the former will give rise to the vertebral column. In addition to these fates, cells of all somite compartments (and not blood islands), will give rise to EC in the body wall and extremities—and in the NT. In addition, PC and vSMC can also be derived from somite cells.

However, PC and vSMC originate from mesoderm only in most of the trunk and extremities, but exclusively from cephalic NC (so-called mesectoderm) for the vessels belonging to branchial arches (head, neck). In the head region anterior to the otic placode, no somites are formed, and this unsegmented head mesoderm can only produce striated muscle and EC.

**Cellular and Regional Diversity of CNS Blood Vessel Formation**

We have seen now that considerable differences exist along the a-p and d-v axis of the CNS and its surroundings, with respect to potential cell fates in the NT and in the mesoderm, and with respect to morphological organization. One should therefore keep in mind that vascularization of different regions of the CNS involves different types of EC and vSMC, and different settings of segmentation or CNS layering. However, a unifying aspect is the purely epithelial nature of the NT which grows to considerable thickness before the first EC make their entrance into it, approaching the “oxygen diffusion limit” of 100 μm. Before we address possible other unifying concepts, a detailed description of the initial vascular patterns of the avian spinal cord will be given and briefly compared with that in other CNS regions.

The NT does not become vascularized before the fourth day of incubation (E4) in chicken or quail embryos (corresponding to E9.5 in mice, or 4th week in humans). However, the NT is surrounded by a perineural vascular plexus (PNVP) during E3 in avians, well after the somites have differentiated into sclerotomes and dermamyotomes. Development of the PNVP proceeds from the cervical to more caudal regions, and from the ventral to the dorsal circumference of the NT. Interspecific grafting of paraxial mesoderm showed that somite-derived EC contribute to the PNVP (and other vascular structures) exclusively on one side of the embryo. It was concluded that the notochord, not the NT, provides a “barrier” to migrating EC. But also the NT itself was proposed as an axial structure which on the one hand attracts EC to form the PNVP, while it on the other hand prevents their crossing the body midline. In the PNVP, the ventral primitive arterial tracts connect to the aorta and are located on either side of the notochord—floor plate complex, whereas the lateral parts are connected to the cardinal veins. Interestingly, the first EC enter the NT exactly at the lateral margins of the floor plate and then form longitudinal arcades (Fig. 1A). The spacing of these sprouts (separated in a-p direction by about 20 to 50 μm) is not related to the

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**Figure 1. Early vascularization of the cervical NT in E4 quail embryos.**

(A–C) Confocal microscopy of QH1 immunofluorescent endothelial cells (and macrophages, arrowheads) reveals “tip cells” with extremely long filopodia inside NT; (D) India ink injection reveals initial perfusion pattern. (A) In a longitudinal section, the non-segmental spacing of ventral sprouts at approx. 40 μm intervals, and their arcade formation inside the NT is visible. The PNVP (arrow) lies between the somite (s) and the NT. (B) In a transverse section, the preferential orientation of numerous “tip cell” filopodia towards the ventricular layer is visible; note the lateral sprout from the PNVP (arrow). (C) In an oblique section, first contacts are visible which are formed between “tip cells” (curved arrow) of ventral arcades and lateral sprouts from the PNVP (arrow). (D) The first perfused capillary loop inside the NT is established ventrally, around the motor columns (mc). Note the lack of dorsal vessels inside the NT, despite a well-developed dorsal PNVP. From Kurz H. J Neuro-Oncol 2000; 50:17–35, with permission from Kluwer Academic.
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segmental mesoderm pattern. At the tips of these sprouts, extremely long and numerous filopodia are visible, which appear to be preferentially oriented in the direction of the radial glia, i.e., extending into the ventricular zone (Fig. 1B). After the ventral sprouts from the primitive arterial tracts have formed, lateral sprouts invade the NT from the venous part of the PNVP (Fig. 1B) and form connections with the ventral sprouts (Fig. 1C). Thus, the first functional circulation inside the NT is formed around the future motor column (Fig. 1D). No sprouting occurs from the dorsalmost part of the PNVP, rather, “tip cells” from the ventral intraneural sprouts extend dorsally, closely following the ventricular zone and connecting to lateral sprouts (Fig. 2). Notably, the “tip cells” do not proliferate, whereas regular EC do, albeit at a lower rate than outside the NT.29

With respect to the main body axes, the early vascular pattern of the NT can be summarized as follows (Fig. 3): the location of sprout invasion appears random (non-segmental, variably spaced) along the a-p axis, but is exactly defined (no sprouts dorsally or into the motor column) in the mediolateral direction and along the circumference of the NT. With respect to internal structures, vessel segments and their “tip cells” appear to be attracted towards, but mostly stay outside the highly proliferative ventricular layer. With respect to external structures, sprouts originate first from arterial, then from venous parts of the PNVP. The PNVP may establish bilateral connections over the roof plate, but both sides remain unconnected between floor plate and notochord for quite some time.

Can this pattern be explained by a single unifying concept? There is overwhelming evidence for a strong instructive influence of the vascular endothelial growth factor (VEGF) signaling system on EC growth and patterning.32-38 The expression of VEGF inside the NT is highest in the ventricular zone in E4 chicken and E9.5 mice (but appeared to be shifted towards the marginal zone in E9.5 mice). I was concluded that the NT attracts EC to form the PNVP via VEGF signaling. An additional source of VEGF in the motor neurons was reported in E10.5 mice, and a different sequence of first lateral, then ventral sprouting into the NT.40 It was concluded that VEGF and Shh jointly stimulate angiogenesis in the NT. In experiments using global hypoxia in avian embryos, expression of hypoxia inducible factors (HIF1) and of VEGF appeared to correlate well with locally different tissue hypoxia, which was also interpreted as an instructive influence of the NT on the vascular pattern. Perhaps the most striking arguments for a key role of VEGF in NT vascularization come from conditional gene knockout studies, where VEGF expression was more or less eliminated from the NT.42,43 These mice had vastly reduced numbers of intraneural EC already at E10.5 if VEGF was completely deleted, or at E13.5 if a hypomorphic VEGF was used. All these data, together with the established role of VEGF isoforms and gradients for “tip cell” formation and sprout orientation, are currently interpreted as evidence for a clear-cut, positive instructive role of the NT on its vasculature. Concomitant defective CNS development then eventually follows from insufficient vasculature, not directly from insufficient VEGF signaling or missing EC signals (like BDNF) to neurons.

However, several aspects of the pattern may not easily be explained by VEGF alone: Why does the NT remain avascular, and become so hypoxic in the beginning? And even after vascularization, why is the vessel density inside the NT so much lower than in the mesenchyme around it (see Fig. 2)? Why don’t the vascular sprouts invade...
directly the motor column or the ventricular layer of proliferating neuroblasts? Why is there no sprouting from the dorsal PNVP, and why is there longitudinal arcade formation by the ventral sprouts (see Fig. 1A)? In my opinion, these peculiarities can best be explained by two additional mechanisms: cell-autonomous migratory potential of EC, and inhibitory signals within and around the NT. The enormous migratory capacity of (mouse and avian) somite-derived EC has been demonstrated repeatedly.14,19,20,44 Most important, these migrating cells do not appear to follow any VEGF gradients and build vascular plexuses where there is little or no hypoxia. From the viewpoint of the migrating or sprouting EC, the NT represents a structure which is difficult to enter: there is a basal lamina around the neural epithelium, and there is no classical extracellular matrix, rich in fibronectin and other migration promoting molecules, inside the NT.45 It is not known, however, if there are local clues in the NT basal lamina that allow the entrance of EC sprouts at those exactly defined ventral and lateral sites (see above), and prohibit dorsal entrance; or whether there are inhibitory factors that cause the EC to avoid, e.g., the motor column (see Fig. 1D). Possibly, molecules which are known to be involved in axonal pathfinding may contribute to the intraneural guidance of EC.46 Notably, Dll4-Notch signaling has been shown to participate in “tip cell” regulation.47,48

Moreover, it is not known whether the expression of different transcription factors in the somite (ventral Pax1, dorsal Pax3) or inside the NT (ventral Pax6, dorsal Pax3) are related to cell-autonomus EC behavior, such that dorsal somite-derived EC do not have the potential to penetrate the NT basal lamina dorsally, whereas ventral somite-derived EC have. A comparable mechanism could be effective in the mouse brain where it has been suggested that transcription factors are linked to the cell-autonomous behavior of EC—49,50—but no relationship between Pax gene expression in head mesoderm and intraneural EC is known. In summary, I would like to repeat (and slightly modify) my statement from 1996:23 EC usually go on their own and they are not only told where to go, but are also told where not to go.

While the question “who instructs whom” seems to be largely answered by “NT instructs EC” inside the CNS anlagen, the situation may be different around the early CNS, where we have a PNVP that may instruct formation of the definite meninges. The so-called meninx primitiva surrounds the PNVP and only later differentiates into an ectomeninx (to become the dura mater) and an endomeninx (to become the arachnoid and pia mater).

**Brain Vascular Patterns and Mural Cells**

Similar to the situation of the spinal cord, the PNVP around the brain anlagen is formed in a ventral to dorsal direction. And as we could show for the avian hindbrain, the first sprouts into it were formed in the ventral (medial) region, and not dorsally, although the PNVP already covered the entire surface of the hindbrain.25 A similar, ventral to dorsal developmental pattern has been described for the forebrain in mice—and in rabbits, using traditional ink injection.51 However, the origin of EC in and around the brain is not from somites but from blood islands in the unsegmented head mesoderm15 (which has a different gene expression pattern, and a much more restricted developmental potential, as mentioned above). It therefore appears possible that head EC also differ from trunk EC with respect to their expression of transcription factors or cell-autonomous behavior. In this context, it should be noted that vascularization of the (human) retina has been described in two phases:52 initially, immigrating EC precursors formed cords of EC and patent vessels, quite different from other CNS regions; later, sprouting from these early vessels occurred in a characteristic, planar arrangement, but no relation to neuronal patterns was reported. On the other hand, in the special vascular setting of the (adult) olfactory bulb,53 neurons were shown to use blood vessels during their radial migration54 and an instructive role for EC has been proposed.55 However, whether “vasophilic” migration of neurons happens during embryonic development, and in other regions, remains to be shown.

The NT of the head, in a reciprocal fashion, shows gene expression patterns and developmental potential which are different from those of the trunk. While details of gene expression are beyond the scope of this article, the developmental potential of the brain anlagen and head NC will be briefly discussed. Cephalic NC contributes the majority of head mesenchyme, and thus connective tissue cells to the meninges of the brain, and mural cells (PC and vSMC) to the vascular walls of both PNVP and intraneural vessels.9,11 Both an early immigration of PC shortly after or together with EC,56 and immigration of PC in advance of EC into the brain57 or retina58 were described. We showed that, as an alternative to immigration of NC-derived cells, direct differentiation of neuroblasts to PC was possible22 (Fig. 4), a finding, which implies an instructive role of EC on the neural tissue.59 Moreover, recent observations indicate that brain PC have stem cell characteristics and may be able to differentiate into neurons.60,61 Clearly, the brain PC remains an enigmatic cell, which is also involved in blood-brain-barrier maturation,62 stabilization of microvessel,63-66 and perfusion control.67 It remains an open question, how PC participate in the angiogenic and neurogenic niches which persist throughout life (in mammals) in the
subgranular zone of the hippocampus and in the subventricular zone in the walls of the lateral ventricles, which are seasonally active in songbirds. In view of the increasingly important concept of “neurovascular unit” for clinical research, such investigations into developmental aspects appear highly rewarding.

Conclusions

In the context of vascular patterns and cells, the term “CNS” should be used carefully, because differences exist between trunk/spinal cord, and head/brain regions, with respect to developmental potential and spatial arrangement of precursor tissues. Observations that were made in either spinal cord or brain, retina or olfactory bulb, may not so easily be extended to CNS in general. Likewise, different species may use different patterns and cell lineages.

However, some mechanisms and patterns appear to be common to both spinal cord and brain: Endothelial cells always stem from the mesoderm, they have cell-autonomous migratory potential, but follow attractive and repulsive clues. The early NT in all regions remains vascular until it reaches a considerable thickness. Then, within hours, a well-developed perfused intraneuronal network emerges. With respect to the early spinal cord and brain, a ventral to dorsal pattern of immigration and internal sprouting is observed. The most prominent feature of intraneural vascular sprouts is the morphology of “tip cells” with extremely long and numerous filopodia which are used for orientation. VEGF signaling (together with other mechanisms) is a key regulator of EC guidance. In addition, signals which emanate from EC may also provide instructive clues for the NT.

Future work will have to show how the growing number of molecules that can influence both blood vessels and neurons is utilized in reality, if differential adhesiveness of the neural tissue influences EC pathfinding, and how the different vascular niches for neurogenesis are established in the embryo and modified in postnatal life.

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