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REVIEW

Different networks, common growth factors: shared growth factors and receptors of the vascular and the nervous system

Sabine Raab · Karl H. Plate

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Abstract Growth factors and their respective receptors are key regulators during development and for homeostasis of the nervous system. In addition, changes in growth factor function, availability or downstream signaling is involved in many neuropathological disorders like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, stroke and brain tumours. Research of the recent years revealed that some growth factors, initially discovered as neural growth factors are also affecting blood vessels [e.g. nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF)]. Likewise, vascular growth factors, such as vascular endothelial growth factor (VEGF), which was previously described as an endothelial cell specific mitogen, also affect neural cells. The discovery of shared growth factors affecting the vascular and the nervous system is of relevance for potential therapies of vascular and neurological diseases. This review aims to give an overview about the growing field of common growth factors and receptors within the two different networks.

Keywords Angiogenesis · Growth factor · Neurogenesis · Neuroprotection · Neurorepair · VEGF

Introduction

At the first glance, the vascular and nervous system appear to be functionally and structurally different. However, both systems share multiple similarities in their development, construction and function: during development nerves and vessels often project long distances to reach their target areas within the body whereby they are guided by gradients of growth factors. For path finding, a specialized endothelial cell (EC) at the tip of invading vessels and the growth cone of neurons extend their filopodia to find their way through the body [30, 40]. Furthermore, blood vessels and axons often follow parallel routes in the peripheral tissue and the interaction between both appears to be bi-directional [30, 169].

The vascular and nervous system both convey important information. While in the vasculature information is carried by solutes transported through the blood, transmission of information and stimuli in nerve cells is carried out mainly by electric transmission.

After the development of the vascular and the nervous system has been completed, the generation of new vessels or neurons is limited to a few physiological processes and restricted areas [21, 148]. Interestingly, neurogenesis, the generation of new neurons, occurs within vascular niches where ECs proliferate [135]. In addition, many neuropathological diseases are associated with cerebrovascular pathology. Malperfusion, aberrant blood vessel growth or breakdown of the blood brain barrier are the determining factors of diseases like stroke, brain tumours, multiple sclerosis, late-onset dementia, age-related macular degeneration or diabetic retinopathy, reflecting the dependence of the nervous system on the vasculature [106].

Development and homeostasis of the vascular and nervous system were believed to be controlled by different, specialized growth factors and their receptors. Yet various recent studies have discovered that the vascular and the nervous system share an overlapping repertoire of growth factors affecting the development and the homeostasis of both systems (Table 1). This suggests the evolution of

S. Raab · K. H. Plate (✉)
Institute of Neurology (Edinger Institute),
Johann Wolfgang Goethe-University,
Frankfurt/Main, Germany
e-mail: karl-heinz.plate@kgu.de

universally applicable molecular mechanisms to control path finding, spatial patterning, proliferation and protection. In recent years, the number of shared growth factors discovered to be important for both systems increases continuously. These include members of the vascular endothelial growth factor (VEGF), ephrin and neurotrophin growth factor families (Table 1).

One prominent example for a shared growth factor is VEGF-A, an important stimulator of blood vessel growth during development and in the adult. VEGF-A is of high medical relevance, since it also stimulates aberrant blood vessel growth in cancer and inhibition of VEGF-A or its signaling capacity is a promising approach of anti-angiogenic cancer therapy [48]. However, it has also been discovered that the function of VEGF-A is not solely restricted to ECs. Besides others, VEGF-A appears to directly affect neural cells, an important realization on the background of anti- or pro-angiogenic therapies.

This review aims to provide an overview about the growing field of shared growth factors and receptors affecting development and homeostasis of both, the vascular and the nervous system.

The VEGF-family

The VEGF family includes six different homologous factors, VEGF-A–E and placenta growth factor (PlGF). Members of the VEGF family are involved in the development of the vasculature and display multiple functions on ECs. While VEGF-A, VEGF-B, VEGF-D, VEGF-E and PlGF mainly affect the growth of blood vessels, VEGF-C is important for the development and homeostasis of lymphatic vessels. In addition, latest studies point to direct effects of VEGF-A, VEGF-B and VEGF-C on neural cells.

VEGF-A

VEGF-A in the vascular system

VEGF-A was initially discovered as a vascular permeability factor [158] and was considered for a long time to be an endothelial-specific mitogen. In early publications VEGF-A is referred to as VEGF. VEGF-A induces the generation of new vessels in the developing and adult organism under physiological and pathological conditions. Vessels are generated by two different processes, vasculogenesis and angiogenesis [148]. Vasculogenesis describes the de novo formation of blood vessels from differentiating endothelial precursor cells (angioblasts) [150]. During development the extra- and intraembryonic primary vascular plexus, the dorsal aorta and the primitive heart are formed by vasculogenesis. Angiogenesis, the generation of new blood vessels from pre-existing vessels, then results in the further expansion of the primary vascular plexus [148]. Vasculogenesis was considered to be limited to the developing organism. However, endothelial progenitor cells exist in the adult bone marrow. They are mobilized into the circulation on demand and then recruited to sites of tissue trauma or ischemia [197]. Whether they are able to differentiate into ECs and integrate into new vessels is still a matter of debate.

The defects caused by the general inactivation of VEGF-A in mice (VEGF-A knockout mice) demonstrate the particular importance of VEGF-A for blood vessel growth. Already the loss of one VEGF-A allele leads to embryonic lethality at mid-gestation due to defective vasculo- and angiogenesis throughout the entire embryo [28, 49]. Therefore, VEGF-A is irreplaceable for embryonic blood vessel development. Also during later embryonic and postnatal development VEGF-A stimulates vessel growth [42, 53]. The specific inactivation of VEGF-A in the developing brain results in impaired brain angiogenesis causing growth retardation of the brain and the skull accompanied by massive neural apoptosis [61, 144].

VEGF-A stimulates EC proliferation and is a survival factor for newly formed blood vessels [47]. In addition, newly formed blood vessels are guided to their target by VEGF-A gradients. A specialized, non-proliferating tip cell at the front of navigating vessels extends filopodia, recognizes the VEGF-A gradient by its VEGF receptors and guides the vessel stalk towards their target area [56, 153]. The gradients are caused by the high VEGF-A expression in the target area and different binding capacities of VEGF-A isoforms to the extracellular matrix. VEGF-A isoforms (in human $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$ and $VEGF_{206}$) result from alternative splicing and $VEGF_{165}$ is the predominant one [47]. These isoforms have diverse binding capacity to heparan sulphate proteoglycan (which is located on cell surfaces and in basement membranes) and therefore different diffusion abilities within the tissue.

VEGF-A transmits its signal via binding to the receptor tyrosine kinases (RTKs) VEGF receptor-1 (VEGFR-1 ; fms-related tyrosine kinase 1 (Flt-1) and VEGF receptor-2 (VEGFR-2; fetal liver kinase 1 (Flk-1) (Fig. 1). Both are strongly expressed on proliferating ECs. Although VEGFR-1 has a higher affinity to VEGF-A than VEGFR-2, VEGFR-1 autophosphorylation upon VEGF-A binding is weak in comparison to VEGFR-2. In contrast to the early embryonic lethality of the VEGFR-1 knockout mice, mice lacking only the intracellular signaling part of VEGFR-1 develop almost normal and reach adulthood. Therefore, VEGFR-1 appears to function mainly as a “decoy receptor” during development by regulating VEGF availability. Besides membrane-bound VEGFR-1, a soluble form exists (sFlt-1) which has also the capacity to perform decoy functions.

Table 1 Growth factors affecting development and homeostasis of the vascular and the nervous system

Effects on the vascular system		Growth factor	Effects on the nervous system	
Vascular permeability Vasculogenesis Angiogenesis EC survival Blood vessel wiring	[4, 6, 47, 55, 56, 148, 150, 158]	VEGF-A	Neurogenesis Neuroprotection Retinogenesis Axonal outgrowth Soma path finding	[26, 30, 45, 62, 71, 155, 166, 167]
Heart development Angiogenesis	[2, 16, 130, 162]	VEGF-B	Neuroprotection in vitro Neurogenesis	[171, 172]
Angiogenesis Lymphangiogenesis Vascular permeability EC migration	[75, 80, 98]	VEGF-C	Trophic factor for embryonic neural progenitor cells Oligodendrocyte precursor cell proliferation	[96]
Vascular remodeling Cardiovascular development Angiogenesis Tumour angiogenesis (EphB4/ephrinB2) markers of the arterial/venous interface Vessel guidance Sprouting/remodeling of lymphatic vessels	[4, 54, 107, 134, 180]	Ephrins	Axonal guidance and bundling Neural crest migration Patterning of the embryonic brain Neural crest cells migration Neurogenesis Neural progenitor cell apoptosis Neuroblast migration	[9, 32, 34, 67, 147]
Vessel branching and guidance Angiogenesis EC proliferation EC migration	[104, 137, 159]	Netrins	Axonal path finding Neuronal migration Neural plasticity Neuroblast migration	[13, 46, 85, 118, 123, 159]
Vascular expression of robo-4 Angionesis (robo-4) EC migration (robo-1) Tumour angiogenesis (slit-2/robo-1)	[117, 138, 170, 179]	Slits	Axonal path finding Neuroblast migration	[123]
Vasculogenesis Angiogenesis (indirect) by regulating expression of angiogenic cytokines	[120, 141, 178]	Sonic hedgehog	Cell differentiation in the neural tube Early neural tube patterning Precursor proliferation in the developing dorsal brain Neural precursor/progenitor proliferation Early neural programmed cell death	[93, 127, 133, 154, 195]
EC proliferation, survival and migration Angiogenesis	[25, 38, 41, 89, 95]	NGF	Survival and differentiation of neurons in the PNS and CNS	[31, 68, 95, 100]
EC survival Angiogenic factor	[39, 83, 89]	BDNF	Survival and growth promoting function on some neurons Synaptic function and plasticity Memory function in the hippocampus Neurogenesis Axonal branching	[5, 20, 68, 97, 200]
Induction of angioblasts Angiogenic factor	[10, 142]	FGF-2	Neurogenesis (development and adult) Axonal branching Neuroprotection	[146]

Table 1 continued

Effects on the vascular system		Growth factor	Effects on the nervous system	
Induction of angioblasts Angiogenic factor	[10, 142]	FGF-2	Neurogenesis (development and adult) Axonal branching Neuroprotection	[146]
Angiogenic factor	[51, 149]	PDGF-A	Mitogen for oligodendrocyte progenitors Proliferation of oligodendrocyte progenitors Effects retinal astrocytes Migration of oligodendrocytes and neural stem cells in vitro Mitogen and survival factor for embryonic neural precursor cells Initiation of neuronal differentiation in ventricular zone progenitor cells Increase of the number of neurons in cultivated neural precursor cell populations	[18, 43, 66, 186]
Proliferation and recruitment of VSMC/PC Angiogenic factor	[18, 149]	PDGF-B	Induction of neurogenesis after 6-hydroxydopmain lesion	[115]
Angiogenesis Remodeling, maturation and maintenance of the vascular plexus Lymphangiogenesis	[145, 189]	Ang-1	Neuroprotection CNS development Neurite outgrowth from dorsal root ganglia	[88, 136, 175, 183]

Ang-1 angiopoietin-1, *EC* endothelial cell, *BDNF* brain-derived neurotrophic factor, *CNS* central nervous system, *FGF* fibroblast growth factor, *NGF* nerve growth factor, *PC* pericyte, *PDGF* platelet-derived growth factor, *PNS* peripheral nervous system, *VEGF* vascular endothelial growth factor, *VSMC* vascular smooth muscle cell

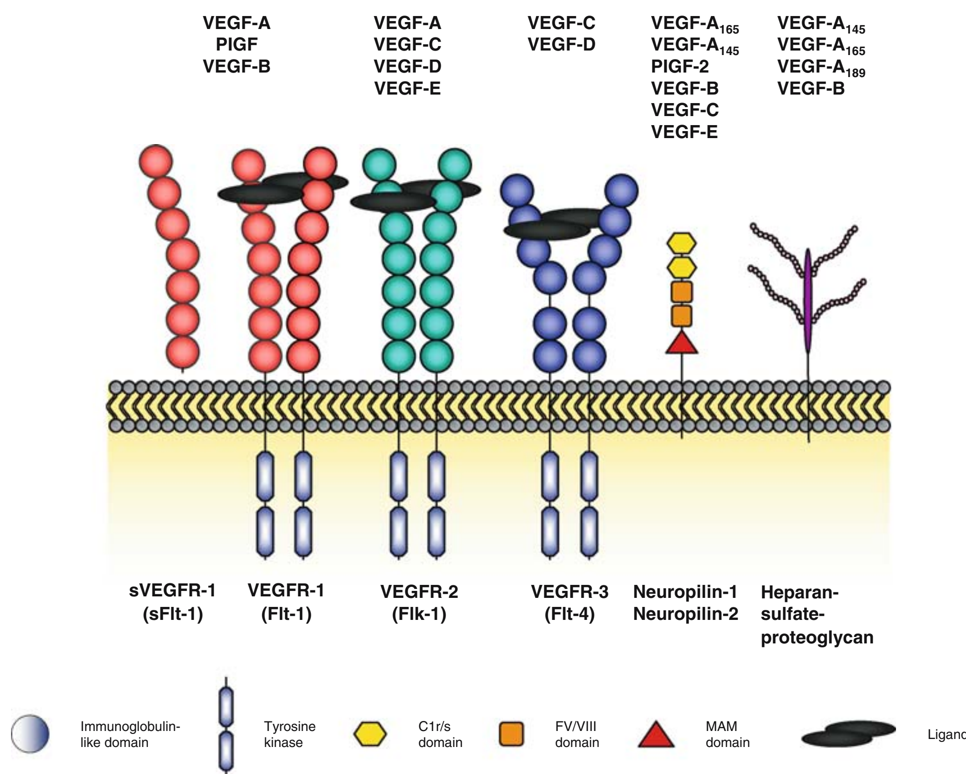

Fig. 1 VEGF growth factor and receptor family. VEGF family members bind to different VEGF receptors. The main receptors for VEGF growth factor family members are the three receptors tyrosine kinases (VEGFR-1–3). In the mouse VEGFR-1 is also referred to as Flt-1, VEGFR-2 as Flk-1 and VEGFR-3 as Flt-4. VEGFRs are typical RTKs comprised of extracellular immunoglobulin-like domains, a single transmembrane segment and a split intracellular tyrosine kinase domain. Ligand binding induces receptor homodimerization. sVEGFR-1 (sFlt-1) is a secreted splice variant of VEGFR-1. Heparan sulphate proteoglycans bind and present VEGFs while neuropilins act as VEGFs co-receptors, both of which can influence the VEGFR-mediated responses

Furthermore, $VEGF_{165}$ binds to neuropilin-1 (Nrp-1), which acts as a co-receptor for VEGFR-2 (Fig. 1). Nrp-1 is also a receptor for semaphorin (Sema)-3A, a neurorepellent involved in axonal guidance. Neuropilin-2 is a receptor for the VEGF isoforms $VEGF_{165}$ and $VEGF_{145}$ as well as for Sema-3C and Sema-3F (Fig. 1). VEGFR-1, VEGFR-2 and Nrp-1 knockout mice die during embryonic development. They are characterized by massive defects in blood vessel development [47].

VEGF-A and its receptors are of utmost significance for many diseases accompanied by vascular pathology and inflammation like cancer, stroke, intraocular neovascular syndromes, inflammatory disorders (e.g. wound healing, psoriasis and rheumatoid arthritis) and brain oedema. The impact of VEGF-A and its receptors for pathological angiogenesis, malignancies and inflammation is summarised in several reviews [27, 47, 48, 106, 168].

VEGF-A in the nervous system

Initial research indicated that, VEGF-A acts specifically on ECs via the RTKs VEGFR-1 and VEGFR-2 [148]. Recent evidence suggests that, VEGF-A also directly affects neurons. The following section will focus on the effect of VEGF-A in the developing and adult nervous system, in particular with regard to angiogenesis, neurogenesis, cell survival and neuronal migration.

VEGF-A in the developing nervous system

Almost a decade ago, Yang and Cepko postulated a direct role of VEGF-A for the developing nervous system [190]. They demonstrated VEGFR-2 expression in neural progenitor cells and some differentiated cells of the developing, at this time point still avascular mouse retina. VEGF-A is expressed adjacent to the VEGFR-2 expressing cells implicating a direct role of VEGF-A and VEGFR-2 for retinal neurogenesis and development. This direct effect of VEGF-A on retinal cells was confirmed in an in vitro study using isolated retinal cells from newborn rats, in which VEGF-A increased the number of photoreceptor and amacrine cells [196]. In addition, Hashimoto et al. demonstrated that VEGF-A, by activating VEGFR-2 regulates retinal progenitor cell proliferation and neuronal differentiation in the developing chick retina [62].

During early brain development VEGF-A is expressed on neuroectodermal cells located in the ventricular zone and VEGFR-1 and -2 on invading ECs [22, 23]. According to this expression pattern VEGF-A stimulates brain angiogenesis and guides the invading blood vessels [61, 144]. Diverse results exist concerning neural expression of VEGF receptors in the developing and postnatal brain. In situ hybridization demonstrated neural expression of VEGFR-1 and VEGFR-2 mRNA in the developing retina; however, in the embryonic brain VEGFR-1 and -2 mRNA

appeared to be predominantly present in blood vessels [22, 23, 151, 190]. Neuronal VEGFR-1 and -2 expression in the developing brain was demonstrated by immunohistochemistry [126, 191]. Yang et al. demonstrated VEGFR-1 and -2 expression on neurons and ECs in the postnatal rat brain. Whereas VEGFR-1 expression was distributed most densely in the hippocampus, parts of the cortex and in the striatum, neuronal VEGFR-2 expression was described as being evenly distributed in the postnatal brain [191]. Interestingly, it appears that VEGFR-1 and VEGFR-2 expression switches during postnatal development: while the number of VEGFR-1 expressing neurons in the cingulate cortex and the hippocampus is high during the first 2 weeks of postnatal development it declines later and is almost absent in the adult brain. The number of VEGFR-2 expressing neurons does not significantly change in the cortex within the first 2 weeks after birth. However, during later development the number of VEGFR-2 positive neurons increases dramatically in the cortex and the hippocampus and peaks in the adult [191]. The role of VEGF-receptor expression on neural cells for normal embryonic and postnatal brain development remains to be clarified. No pathological changes were described so far in the brains of mice bearing a knockout for VEGFR-2 in neural cells of the developing brain or in VEGFR-1 signaling deficient mice [61, 65]. This suggests that neural signaling of VEGF receptors during development exerts no essential function for proliferation, differentiation or survival. However, direct neural effects of VEGF-A may be important for defined fine tuning of developmental processes within the nervous system as it has been shown for the facial nerve, where $VEGF_{164}$ controls soma migration of the facial nerve motor neurons [157].

VEGF-A in adult neurogenesis

The dogma that new neurons do not develop in the adult organism has been rebutted in recent times [59, 77]. A process called neurogenesis generates new neurons also in the adult vertebrate brain. Although adult neurogenesis is limited mainly to specific regions of the CNS, the potential to develop new neurons may provide a new chance for future therapies of neurodegenerative diseases. The knowledge of cellular and molecular mechanisms regulating adult neurogenesis is a prerequisite for future regenerative therapeutic approaches. In the adult mammalian brain, neurogenesis constitutively occurs in the subventricular zone (SVZ) of the lateral ventricle/olfactory bulb and the dentate gyrus of the hippocampus [114]. In the olfactory system neural stem cells are located in the anterior part of the SVZ of the lateral ventricles [37, 57, 102, 105]. These cells give rise to transiently amplifying progenitor cells, which differentiate into neuroblasts. Neuroblasts migrate along the rostral migratory stream (RMS) into the olfactory bulb, where they differentiate to granule cells and periglomerular interneurons [7, 17, 78]. Although tens of thousands of neurons are generated daily in the olfactory bulb, many of them die before they complete their differentiation [8, 19, 187]. In the hippocampus neural progenitor cells are located in the subgranular zone (SGZ) of the dentate gyrus where they produce new hippocampal granule cell neurons.

Adult neurogenesis is regulated by a variety of growth factors, neurotransmitters and hormones. The importance of VEGF-A and its receptors has been investigated in several in vitro studies. Neural stem cells, isolated from the SVZ of the lateral ventricle of adult rats or mice, when cultivated as neurospheres, express VEGFR-2 and VEGF-A, which are secreted into the medium [112, 113, 155]. VEGF-A stimulates proliferation and inhibits apoptosis of neural stem cells in vitro in a dose-dependant manner. Both effects appeared to be mediated via VEGFR-2, since they can be blocked by specific VEGFR-2 antibodies [155]. Meng et al. suggested a biphasic effect of exogenous VEGF on adult neural progenitor cells in vitro. While a low dose of VEGF (50 ng/ml) enhances VEGFR-1 and VEGFR-2 expression but does not alter proliferation and differentiation, higher doses of VEGF-A (500 ng/ml) down-regulate receptor expression, reduce proliferation but enhance neuronal differentiation [113]. Besides the proliferative and survival effects of the VEGF ligand–receptor system, VEGF-A acts as a chemoattractant for FGF-2 stimulated neural progenitor cells generated from the SVZ of newborn rats [198]. VEGF-A induces neural progenitor cell migration in vitro via VEGFR-2 [198]. In addition, VEGF-A also affects the migration of neural progenitor cells in SVZ explants [198].

In vivo intracerebroventricular (ICV) infusion of recombinant VEGF-A increases the number of neurospheres generated from the ventricular zone of the lateral ventricle in vitro [155] and stimulates neurogenesis in the SVZ/olfactory bulb and the dentate gyrus [71, 155]. A reduced number of apoptotic cells and unaltered proliferation after ICV VEGF-A infusion suggested a survival effect of VEGF-A on neural progenitor cells [155]. Jin et al. demonstrated that, VEGF-A stimulates neurogenesis in vivo, albeit they report a proliferative effect of VEGF-A on neurogenesis without affecting cell survival [71]. Therefore, there either may be different mechanisms how VEGF-A induces neurogenesis or it may be dependant on VEGF-A concentrations. High VEGF-A doses affect several cell types and increase the number of BrdU-positive neurons, astrocytes and ECs [71]. There appears to be a link between neurogenesis and proliferating ECs, which may provide instructive cues for neurogenesis. A study by Palmer et al. provided the first evidence that adult neurogenesis occurs within an angiogenic niche where ECs proliferate [135].

Also testosterone-induced neurogenesis in the higher vocal centre of the adult songbird appears to be linked to increased angiogenesis and is thought to be caused through endothelial brain-derived growth factor (BDNF) [103]. ECs release soluble factors that stimulate self-renewal of neural stem cells, inhibit their differentiation and enhance their neural production [160]. Hence, VEGF-A may influence adult neurogenesis directly by stimulating neuronal progenitor cells and indirectly by enhancing EC proliferation, survival and stimulation of growth factor release.

In the adult rodent brain VEGF-A is constitutively expressed throughout the entire brain by neurons and astrocytes and strongly expressed by epithelial cells of the choroid plexus (Fig. 2) [22, 155]. Expression of VEGF-A by the choroid plexus epithelial cells has been shown to induce the fenestration of ECs in vitro. Inhibition of VEGF-A leads to a decreased vascular density in the choroids plexus and reduced endothelial fenestrations in vivo [44, 76]. In addition, VEGF-A is secreted by the choroid plexus into the cerebral spinal fluid [155]. Interestingly, ependymal cells, which are specialized cells separating the ventricular system from the brain parenchyma, express VEGFR-2 but not VEGFR-1 or Nrp-1 (Fig. 2) [155]. Therefore it is likely that VEGF-A (in the cerebral spinal fluid) affects ependymal cells by binding to VEGFR-2. However, the biological relevance is not clear. VEGF-A may have a general, homeostatic paracrine function for the ependymal cell layer. According to recent studies, in which ICV infusion of VEGF-A stimulates adult neurogenesis, it seems also possible that endogenous VEGF-A is important for adult neurogenesis [71, 155]. However, the impact of endogenous VEGF-A levels for adult neurogenesis in the SVZ remains unknown.

Different mechanisms are conceivable how VEGF-A may affect adult neurogenesis in the SVZ (Fig. 3): 1. Ependymal cells may possess neural stem cell properties [74]. Therefore, VEGF-A may stimulate asymmetric division of ependymal cells and thereby affect the generation of SVZ progenitor cells. 2. VEGF-A signaling in ependymal cells may be involved in the release of growth factors stimulating subventricular neural stem cells, neural progenitor cells

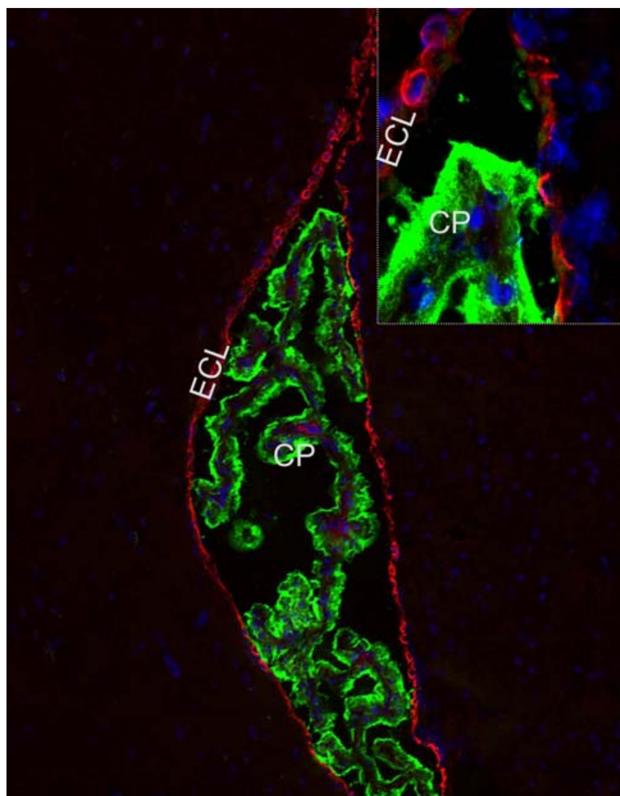

Fig. 2 VEGFR-2 and VEGF-A localization in the lateral ventricles. Strong VEGF-A expression (*green*) is detected in the cells of the choroid plexus in close proximity to the VEGFR-2 expressing ependymal cells of the lateral ventricle (*red*). Cell nuclei are stained in *blue*. *CP* choroid plexus, *ECL* ependymal cell layer (adapted from Schänzer et al. [155]; Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor; Brain Pathology; Blackwell Publishing)

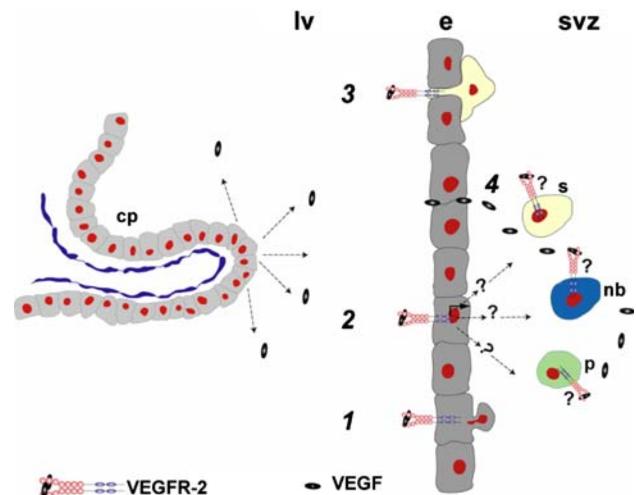

Fig. 3 Possible mechanism of VEGF-A induce adult neurogenesis in the SVZ. Putative mechanisms for VEGF-A action in rodents: VEGF-A is released from the choroid plexus (*cp*) into the cerebrospinal fluid. (1) VEGF-A directly acts on ependymal cells (*e*, *grey*) which may possess neural stem cell properties. Thus, VEGF-A stimulates asymmetric division, and might affect the generation of subventricular progenitor cells. (2) VEGF-A stimulates the release of unknown neurogenic mediators from the ependymal cells stimulating subventricular neural stem cells (*s*, *yellow*), progenitor cells (*p*, *green*) or neuroblast (*nb*, *blue*). (3) Alternatively VEGF-A stimulates GFAP expressing cells in the SVZ, which are considered to be neural stem cells (*yellow*). These cells are located in the SVZ and occasionally send processes in between the ependymal cell layer. (4) Finally, VEGF-A may diffuse into the SVZ and stimulate subventricular neural stem cells. It remains unclear if neural stem cells, progenitor cells or neuroblasts express VEGFR-2; *cp* choroid plexus, *e* ependymal cell layer, *lv* lateral ventricle, *p* progenitor cells (*green*), *nb* neuroblasts (*blue*), *s* neural stem cells (*yellow*), *SVZ* subventricular zone

and/or neuroblasts. 3. VEGF-A may stimulate glial fibrillary acidic protein (GFAP)-positive cells of the radial glial line, which are considered to be neural stem cells. These cells are localized in the SVZ and occasionally extend a process between ependymal cells to contact the lateral ventricle [36]. 4. VEGF-A may diffuse into the subventricular layer and stimulate subventricular neural stem cells, neural progenitor cells and/or neuroblasts. However, it remains unclear if non-ependymal cells of the SVZ express VEGFR-2.

Besides the induction of neurogenesis in the SVZ, VEGF-A also induces hippocampal neurogenesis and links hippocampal activity with neurogenesis, learning and memory [26, 155]. Hippocampal expression of VEGF-A is increased in rats after learning tasks and in rats housed in enriched environment [26]. Overexpression of VEGF-A in hippocampal neurons results in enhanced neurogenesis accompanied by increased angiogenesis and improved cognition. The stimulating effect of VEGF-A appears to be independent from hippocampal angiogenesis since PlGF also induced hippocampal angiogenesis in a comparable manner, but did not induce neurogenesis. Neurogenesis induced by an enriched environment was completely inhibited by VEGF-A knockdown. Neural expression of a dominant-negative VEGFR-2 resulted in a 50% decrease of proliferating cells in the hippocampus and thereby impaired learning [26]. In addition to learning, voluntary exercise (running in a wheel) stimulates hippocampal but not olfactory bulb neurogenesis in rodents [24, 177]. Furthermore, VEGF-A concentration in the peripheral blood is important for exercise-induced adult hippocampal neurogenesis [45]. However, blockade of peripheral VEGF-A does not affect neurogenesis in non-runners, which suggests that basal neurogenesis was maintained by signals independent of peripheral VEGF-A [45]. But the mechanism by which peripheral blood VEGF-A influences neurogenesis has not been completely elucidated yet.

Neurotrophic and neuroprotective effects of VEGF-A

The neuroprotective properties of VEGF-A appear to be due to a combination of direct neuroprotective effects and the stimulation of angiogenesis. The latter results in an advanced blood perfusion causing an enhanced supply of oxygen and nutrients, which indirectly has neuroprotective impact. The assessment of direct neurotrophic effects of angiogenic factors, like VEGF-A, is always difficult, because administration or depletion of these factors often concomitantly alters vascular structure and function.

The direct neuroprotective force of VEGF-A has been demonstrated in several in vitro studies including different neuronal cell types and diverse neurotoxic stimuli. VEGF-A has neurotrophic effects on cultured neural cells of the peripheral and the central nervous system by stimulating axonal outgrowth and by protecting neural cells from serum deprived-, glutamate-induced or hypoxia-induced cell death [70, 111, 126, 161, 164, 166, 174, 185]. It appears that the neuroprotective effects are mainly transmitted via VEGFR-2 [70, 72, 73, 111, 126, 166, 185]. Neuroprotection by VEGF-A through the regulation of potassium currents in acutely isolated hippocampal neurons from 14-day-old rat brains appeared to be related to the presence of VEGFR-1, but not VEGFR-2 [143, 188].

A neuroprotective effect of VEGF-A has also been demonstrated in various brain disease models, e.g. stroke, Parkinson's disease or amyotrophic lateral sclerosis (ALS). In stroke interception of blood flow causes hypoxia and hypoglycaemia. Hypoxia is a well-known stimulus of VEGF-A expression. VEGF-A and its receptors are up-regulated in the ischemic region [14, 63, 99, 139]. After stroke, VEGF-A induces angiogenesis, which results in a partial revascularization of the peri-infarct area. Revascularization improves the supply of oxygen and nutrients and has therefore beneficial impact on the infarcted area. VEGF-A also induces vascular permeability and thereby oedema formation, which has detrimental effects on the brain infarct. Therefore, alteration of the endogenous VEGF-A levels in the ischemic brain has beneficial and detrimental effects on the brain, depending on the time point of intervention and the animal model used. Early intravenous post-ischemic administration [1 h after middle cerebral artery occlusion (MCAO)] of VEGF-A to ischemic rats increases vascular leakage and the ischemic lesion. However, late (48 h after MCAO) administration of VEGF-A to ischemic rats enhances angiogenesis in the ischemic penumbra, which is conductive to the brain, since it improves neurological recovery [199]. Trapping VEGF-A by intraperitoneal injection of a soluble VEGFR-1 chimeric protein significantly reduces the brain oedema and conserves cortical tissue in a model of transient ischemia in mouse brain [176]. ICV infusion of VEGF-A on days 1–3 after transient MCAO in rats reduces infarct size, improves neurological outcome, stimulates neurogenesis and increases angiogenesis in the penumbra [173]. Also neuron-specific overexpression of human VEGF-A in mice causes post-ischemic neuroprotection, but induces at the same time haemodynamic steal phenomena with diminished blood flow in the infarcted area and increased blood flow outside the MCA territory [182]. Due to the pleiotropic effects of VEGF-A and its receptors during stroke, a beneficial stroke therapy using either VEGF-A for neuroprotection or improvement of angiogenesis or trapping VEGF-A to decrease vascular permeability appears to be accompanied by a high risk of side effects.

Recent studies have demonstrated that VEGF-A also has neuroprotective effects on motorneurons. $VEGF_{165}$ protects cultured motor neurons under conditions of low-oxygen

tension, oxidative stress and serum deprivation by binding to VEGFR-2 and Nrp-1 [132]. VEGF$^{\delta/\delta}$ mice, which carry a deletion of the hypoxia-responsive element (HRE) in the *vegf* promoter and therefore express decreased VEGF-A levels develop adult-onset motor neuron degeneration reminiscent of ALS [132]. ALS is a progressive neurodegenerative disease characterized by the degeneration and loss of motor neurons in the spinal cord, the brainstem and the cerebral cortex. ALS patients suffer from muscle atrophy and paralysis and die usually within 5 years after onset of the symptoms [152]. In a mouse model for hereditary ALS (SOD^{G93A} mice) the deletion of the *vegf* HRE causes reduced survival, whereas intramuscular transfer of the *vegf* gene or neuronal overexpression of VEGFR-2 prolongs the survival [11, 94]. ICV infusion of VEGF-A in a SOD-1^{G93A} rat model of ALS delays the onset of paralysis, improves motor performance, prolongs survival and preserves neuromuscular junctions [168]. In VEGF$^{\delta/\delta}$ mice structural vascular defects or leakiness were not detected; however the neural tissue perfusion was reduced and motor neurons in the spinal cord were hypoxic. Therefore, vascular dysfunction and reduced direct neuroprotection appears to contribute to the ALS phenotype observed in VEGF$^{\delta/\delta}$ mice.

Besides experimental stroke or ALS, VEGF-A displays also neuroprotective effects on 6-OHDA-treated dopaminergic neurons, an animal model for Parkinson disease [161, 192]. In this model the neuroprotective effect of VEGF-A likely functions directly by effecting neurons and indirectly by promoting angiogenesis. The effect of VEGF-A appeared to be dose dependent, since low doses protect the dopaminergic neurons whereas high doses induce brain oedema [194]. Transplantation of VEGF-A expressing cells into the striatum of 6-OHDA lesioned rats results in a reduction in the number of amphetamine-induced rotations, a preservation of neurons in the substantia nigra and in glial proliferation in the striatum [193].

Wang et al. investigated the role of VEGF-A and its receptors in denervation-induced neuronal reorganization of the brain. Following entorhinal deafferration VEGF-A and VEGFR-2 are up-regulated in the denervated areas. VEGF-A is up-regulated in astrocytes and VEGFR-2 in reactive astrocytes and neurites suggesting that VEGF-A and VEGFR-2 may be involved in reorganization of the differentiated hippocampus [181]. In addition, VEGF-A plays a role in ischemic and diabetic neuropathy and spinal cord injury (for further detailed information see [29]).

Effects of VEGF-A on non-neuronal cells of the nervous system

VEGF-A also influences non-neuronal cells in the peripheral and central nervous system. Besides the already mentioned effect on ECs, VEGF-A affects astrocytes, schwann cells and microglia. Astrocytes express VEGFR-1 and exogenous application of VEGF-A to mesencephalic explants in vitro or intracerebrally in vivo increases the number of astrocytes and ECs [91, 161]. This biological effect was confirmed in a model for wound repair, where intracerebral infusion of VEGF-A-neutralizing antibodies decreased angiogenesis, astrocyte proliferation and increased endothelial and astrocyte degeneration resulting in enlarged wound cavities [90]. In addition, inhibition of VEGFR-1 but not VEGFR-2 using antisense oligonucleotides reduced GFAP-immunoreactivity in cultured fetal and postnatal cerebral explants [109]. These data demonstrate a mitogenic effect of VEGF-A on astrocytes. However, it remains to be elucidated if VEGF-A stimulates astrocyte proliferation directly or indirectly.

Different effects of VEGF-A on Schwann cells have been described. In explant cultures of dorsal root and superior cervical ganglia VEGF-A reduced the number of apoptotic Schwann cells and stimulated their proliferation [164]. VEGF-A pretreated nerve grafts stimulate the outgrowth of Schwann cells, but graft invading Schwann cells exhibit a significant change in morphology [165]. Schwann cells express VEGFR-1, VEGFR-2 and Nrp-1 and inhibition of VEGFR-2 completely inhibits VEGF-A-induced migration of Schwann cells [156]. Furthermore, VEGF-A$_{121}$, which cannot bind to Nrp-1 is as potent as VEGF$_{165}$ in inducing Schwann cell chemotaxis, indicating that VEGF-A-induced Schwann cell migration is dependent on VEGFR-2. Finally, VEGF-A also can induce proliferation and migration of cultivated microglia cells, which express VEGFR-1 but not VEGFR-2 [50].

Neuropilins in nerve and blood vessel development

Nrp-1 receptor was discovered to be important for both, blood vessel development and development of the nervous system. Nrp-1 is amongst others a receptor for Sema-3A, which acts as an axonal-repellent factor. Nrp-1 is a transmembrane receptor with only a small cytoplasmatic domain, which is not essential for the transduction of the repulsive effect of Sema-3A [52, 121]. For downstream signal transduction Nrp-1 and Nrp-2 form complexes with receptors of the plexin family [122]. Mice in which Nrp-1 was ubiquitously expressed and mice in which Nrp-1 was inactivated by gene-targeting experiments, display defects in the nervous, but unexpectedly also in the vascular system, demonstrating the overlapping activity of Nrp-1 for the development of both [82, 84]. In 1998 Nrp-1 was described by Soker et al. as a receptor for VEGF$_{165}$ [163]. Nrp-1 can form complexes with either VEGFR-1 or -2 and appears to act as an enhancer of VEGFR-2 activity [163, 184]. VEGF-A and Sema-3A share an overlapping binding site and compete for binding to Nrp-1. Alteration of either,

the Sema-3A or the $VEGF_{165}$-binding site of Nrp-1 revealed that VEGF-A/Nrp-1 activation in ECs is required for angiogenesis whereas Sema-3A/Nrp-1 signaling is not essential for vascular development, but required for axonal path finding of several population of neurons in the CNS and PNS. Heart development is dependent on both ligands, $VEGF_{165}$ and Sema-3A [60].

Using a neuroectodermal progenitor cell line Bagnard et al. have shown that Sema-3A via Nrp-1 binding and VEGFR-1 activation acts as a repellent guidance cue and induces apoptosis [12]. $VEGF_{165}$ antagonizes the Sema-3A-induced effects and promotes cell migration, survival and proliferation. In the facial motor neuron Nrp-1 contributes to axonal guidance and soma migration. While Sema-3A/Nrp-1 activation controls axonal guidance, it is not required for path finding of the soma, which is mediated via VEGF-A/Nrp-1 [157].

VEGF-B

VEGF-B is also a secreted growth factor displaying strong homology to VEGF-A [58, 130, 131]. VEGF-B is expressed in two isoforms, which can bind to VEGFR-1 and Nrp-1 [108, 129] (Fig. 1). Like VEGF-A, VEGF-B stimulates EC proliferation in vitro and angiogenesis in vivo [130, 162]. However, VEGF-B is less potent than VEGF-A in inducing angiogenesis. In accordance with this, $VEGF\text{-}B^{-/-}$ mice are viable and fertile, but display abnormalities in cardiac development and function [2, 16, 130, 162]. Therefore, VEGF-B is, in contrast to VEGF-A, not of irreplaceable importance for vasculogenesis and angiogenesis during development.

During development and also in the adult, VEGF-B is expressed in parts of the rodent CNS and VEGF-B expression is up-regulated by brain injury [92, 119]. In $VEGF\text{-}B^{-/-}$ mice infarct size is increased and the mice have severer neurological deficits after stroke [171]. VEGF-B reduces hypoxic cell death of cultured cerebral cortical neurons in vitro; therefore, the protective effect of VEGF-B in stroke may be at least in part mediated by a direct effect of VEGF-B [171].

VEGF-B stimulates BrdU incorporation in cerebral cortical cultures derived from mouse embryos (E15) [172]. Furthermore, ICV administration of VEGF-B increases the number of BrdU-positive cells, which also express the immature neuronal marker doublecortin. Adult neurogenesis in the SVZ and the SGZ is reduced in $VEGF\text{-}B^{-/-}$ mice, an effect which is abrogated after ICV VEGF-B administration [172].

VEGF-C

VEGF-C, a further member of the VEGF growth factor family, shares ~30% homology with VEGF-A and is structurally closely related to VEGF-D [75]. VEGF-C binds to VEGFR-2, VEGFR-3 and Nrp-2 (Fig. 1) [75, 80]. Like VEGF-A, VEGF-C is mitogenic for ECs, increases vascular permeability and stimulates the migration of ECs, although higher VEGF-C concentrations are needed than for VEGF-A [75, 98]. VEGF-C is an important regulator of lymphangiogenesis. VEGF-C is required for the delamination of lymphatic progenitor cells from embryonic veins [79]. Therefore, VEGF-C-deficient mice lack lymphatic vessels and die before birth. The lymphangiogenic potential is meditated by the VEGFR-3 since the sprouting defect of the knockout mice can be rescued by VEGF-C and VEGF-D but not VEGF-A, which only binds to VEGFR-1 and -2 (Fig. 1) [79].

Knockdown studies in Xenopus tadpoles indicate that, VEGF-C is a trophic factor for neuroepithelial cells. The knockdown of VEGF-C results in tadpoles with abnormal brain development with reduced size of the forebrain and hypoplasia of the ventricular and SVZ. The phenotype is accompanied by a severe reduction in neuroepithelial cell proliferation without affecting neural cell apoptosis [96].

In contrast to the Xenopus tadpole, where VEGFR-3 expression is more widespread, VEGFR-3 expression in the developing mouse brain starts at later developmental stages and is more restricted (most prominently in the olfactory bulb, the optic nerve region and the optic nerve itself) [96]. VEGF-C is expressed in adjacent areas, suggesting a paracrine receptor–ligand interaction. In the suprachiasmatic region VEGFR-3 and VEGF-C are expressed in ventricular and subventricular cells. In the optic nerve VEGFR-3 is expressed in oligodendrocyte precursor cells (OPCs). The VEGF-C expression in radial glia and astroglia precursor cells of the optic nerve, correlates temporally with OPC colonization of the optic nerve [96]. In contrast to VEGF-A, VEGF-C induces a dose-dependent mitotic increase in proliferation of VEGFR-3 positive OPCs prepared from the optic nerve and Olig2+ cells prepared from the ventral telencephalon. The effect appears to be mediated by VEGFR-3 signaling. VEGF-C deficiency in mice results in a depletion of OPCs in the optic nerve and the SVZ of the suprachiasmatic area caused by impaired OPC proliferation. In vitro VEGF-C also stimulates the proliferation of nestin-expressing progenitor cells prepared from the embryonic olfactory bulb [96].

Ephrins and Eph receptors

Eph receptors and ephrin ligands exert a wide variety of functions during development as well as in plasticity processes of the adult organism by effecting both, the vascular and the nervous systems. Like VEGFR-1 and VEGFR-2 the Eph receptors belong to the RTK family. Eph receptors are

the largest RTK family. Based on sequence similarity and their ligands, Eph receptors are subdivided into A-type (EphA1–EphA8) and B-type Eph receptors (EphB1–EphB4 and EphB6) [134]. The Eph-receptor ligands are the ephrins, which in contrast to members of the VEGF family are membrane bound. Therefore, unlike VEGF growth factors, which mediate long-range communication, Eph receptors and ephrin ligands are expressed on adjacent cells, necessitating direct cell–cell contact for ephrin-mediated signaling [134].

A-type Eph receptors typically bind A-type ephrins (ephrinA1–ephrinA5), which are tethered to the membrane by a glycosylphosphatidylinositol (GPI) anchor. B-type Eph receptors bind B-type ephrins (ephrinB1–ephrinB3), which are membrane bound with a transmembrane and a small cytoplasmatic domain [86]. EphA4 receptor poses an exception, since also ephrinB2 and ephrinB3 bind to this receptor. The Eph-receptor/ephrin system is characterized by the ability to perform bi-directional signaling. Ephrin ligands induce downstream signaling via Eph receptors ("forward signaling") but also transmit a signal themselves to the ephrin expressing cell ("reverse signaling") [134].

Ephrins and Eph receptors in the nervous system

In the nervous system, Eph receptors and ephrins direct axons by contact-mediated repulsion, affect dendritic spine morphogenesis, regulate fasciculation and defasciculation of axons and direct neural crest cell migration [86]. In addition, recent studies have shown that Ephrins and Eph receptors are also relevant for neurogenesis. EphA2, A3 and A4 and one of their cognate ligands, ephrinA2 are expressed by neuroepithelial cells of the developing telencephalon and by embryonic neural precursor cells in vitro [9]. Activation of EphA receptors in embryonic neural precursors facilitates the commitment to the neuronal fate in vitro. In addition, inhibition of ephrinA induced forward signaling by the extracellular domain of EphA2 decreases the number of cells positive for Tuj1 in embryonic forebrain slice cultures [9]. Eph receptors and ephrins also regulate neural progenitor cell apoptosis. Gene disruption of EphA7 causes a reduction in the normally occurring apoptosis of forebrain neural progenitors during development resulting in an increase in cortical size [34]. In line with this finding, ectopic expression of ephrinA5 in EphA7 expressing early cortical progenitor cells causes a transient wave of neural progenitor cell apoptosis, resulting in a loss of progenitors and a reduction in cortical size [34].

Cells located in the SVZ of adult mice express EphB1, B2, B3 and EphA4 and their ligand ephrins B2 and B3 [32]. EphrinB2 and B3 are expressed by subventricular astrocytes in the lateral wall of the lateral ventricle (which have stem cell properties) and in astrocytes that ensheath chains of migrating neuroblasts [32]. Conover et al. infused clustered ectodomain of either EphB2, ephrinB1 and ephrinB2 into the lateral ventricle [32]. The ectodomain of EphB2 can activate ephrinB ligands but blocks EphB2 signaling by binding to the endogenous ephrinB ligands and thereby preventing their binding to the endogenous Eph receptors. Conversely, the ephrin ectodomains can activate the receptor but at the same time block endogenous ephrinB signaling by sequestering the endogenous receptor. Intraventricular infusion of ectodomain of either EphB2 or ephrinB2 results in a severe disruption of chains of migratory cells, thus ephrins on ensheathing astrocytes may help to restrict the migration of neuroblasts [32]. Apart from the effect on cell migration, Conover et al. also showed an effect of the Eph/ephrin-system on cell proliferation. EphB2-ectodomain infusion increases proliferation and thereby the number of subventricular astrocytes; however, the number of neuroblasts is decreased [32]. In line with this, stimulation of SVZ cells in vitro with clustered EphB2 decreases SVZ cell migration and increases proliferation [117]. In addition, it promotes neural fate of neural precursors independent of cell survival in vitro [81].

Interestingly, neuroblast migration in the SVZ and the RMS is not altered in the ephrinB3 null mice, demonstrating that ephrinB3 does not function to maintain SVZ and RMS boundaries by preventing migration into the surrounding tissues [147]. Instead, the proliferation and apoptosis of SVZ cell was increased in ephrinB3 null mice and thus ephrinB3 regulates cell proliferation and survival within the SVZ of adult mice [147].

Recently, it has been shown in EphA7 and ephrinA2-deficient mice, that EphA7 and ephrinA2 act as negative regulators of progenitor cell proliferation and that the effect is mediated by ephrinA2 reverse signaling [67]. In contrast to this, ICV infusion of clustered and unclustered ephrinA2 and EphA7, increases proliferation in cells of the SVZ [67]. In the adult brain EphA7 is expressed in ependymal cells and a subset of subventricular astrocytes and ephrinA2 ligand is expressed in neural progenitor cells and neuroblasts, but not in ependymal cells or astrocytes indicating a paracrine effect on neurogenesis [67].

Ephrins and Eph receptors in the vascular system

Beside the multiple functions of Eph receptors and ephrin ligands in the nervous system Eph receptors and ephrins are also relevant for the growth and maturation of the vascular system during embryonic and postnatal development and in the adult under physiological and pathological conditions [134]. Some aspects of the role of Eph receptors and ephrins for vascular development and interactions between VEGF and ephrin-signaling are summarized in this section. EphB4 and ephrinB2 have been shown to be essential for

vascular development during embryogenesis [3]. Knockout mice lacking either ephrinB2 or EphB4 display similar defects in cardiovascular development and die around mid-gestation [4, 54, 180]. In both knockout mice vascular remodeling is impaired, resulting in an immature, primitive vascular plexus. It still remains unclear, if EphB4 forward or ephrinB2 reverse signaling or both are important for cardiovascular development [33].

EphrinB2 and its receptor, EphB4, are expressed at the arterial–venous interface. EphrinB2 is specifically expressed in arterial endothelium, whereas EphB4 is expressed in venous endothelium, suggesting that repulsive signals mediated by the EphB4/ephrinB2 interaction might restrict intermingling of arterial and venous ECs at the arterio–venous boundary [3]. Furthermore, ephrinB1 and ephrinB2, expressed by somitic cells, restrict the migration of Eph-positive ECs during intersomitic vessels growth [4, 64].

During limb development the coordinated interaction of nerves, blood vessels and their common growth factors are important for vessel differentiation. Here, peripheral nerves are important for arterial differentiation and branching. Studies by Mukouyama et al. demonstrated that, VEGF-A expressed by sensory neurons, motoneurons and Schwann cells induces artery specific Nrp-1 expression and that Nrp-1 is required for arterial differentiation. In addition, VEGF-A strongly enhances the expression of the arterial marker ephrinB2 [116, 117].

Some ephrins and Eph receptors are up-regulated at sites of active neovascularization (e.g. tumours) and soluble Eph receptors have been used in animal models to block tumour vascularization [134]. The expression of several Eph receptors and ephrins has been reported in various tumour types [35, 101, 125]. Ephs and ephrins have been reported to be involved in tumour angiogenesis. Furthermore they directly influence tumour cells and their metastatic potential [110, 124, 134]. Interestingly, there is a cross talk between ephrin and VEGF-A-mediated signaling. EphrinA1 is a downstream target gene of VEGF-A and inhibition of EphA receptor activity impairs specifically VEGF-A-dependant EC migration, sprouting and survival in vitro and angiogenesis in vivo [134]. EphrinA1 and ephrinB2 reduce the VEGF-A-induced activation of Erk and MAPK, suggesting as well a cross-talk between Eph receptors and VEGF receptors. In line with this, EphA signaling after ephrinA1 binding inhibits VEGF-A-induced VEGFR-2 phosphorylation and its downstream-signaling cascade including PKC, Erk and Akt and injection of ephrinA1 suppresses retinal neovascularization in vivo [128].

Netrins and slits

Netrins are a family of laminin-related, secreted proteins that affect a wide range of migrating neurons and outgrowing axons during development [13]. Four members of the netrin gene family have been cloned so far in mammals: netrin-1, netrin-3 and netrin-4/β and G-netrins [13]. With the exception of G-netrin, netrins bind to the deleted in colorectal cancer (DCC) receptor family and to receptors of the uncoordinated-5 (UNC5) family. The latter include UNC5A, B, C and D. Netrins are chemoattractive for some neurons and chemorepulsive for others, depending on the receptor used. The DCC family consists of the DCC and neogenin receptor. DCC is expressed on axons and axonal chemoattraction of netrin-1 is mediated by binding to DCC. Deletion of either DCC or netrin-1 in mice causes comparable axonal path-finding defects [46, 159]. In contrast netrin-1 binding to UNC5 receptors results in axonal repulsion [85].

Netrins are highly conserved throughout evolution and expressed in the mid-line of animals with bilateral symmetry. Netrin-1 defines the mid-line where it attracts axons, while repelling other axons, which are migrating away from the mid-line. Furthermore, netrin-1 takes part in the development of additional projections of the nervous system [13]. Besides its function in axonal guidance, netrin-1 appears to be involved in neuronal migration, e.g. for the migration of late-born striatal-neurons, dopaminergic neurons in the mid-brain, cerebellar granule cells and neural precursors in the RMS during development [13, 118]. Netrin-1 is also a chemorepellant for oligodendrocyte precursors in the embryonic spinal cord and the developing optic nerve.

Netrin-3 is predominantly expressed in the developing peripheral nervous system. Although it has been shown to promote axonal outgrowth of spinal commissural axons, little is known about the in vivo function of netrin-3. Netrin-4/β is expressed in kidney, heart, ovary, retina, olfactory bulb and a limited set of fibre tracts in the brain. Netrin-4/β is a basement membrane component in the kidney, ovary and vasculature and the latter may implicate a role for angiogenesis [87]. Netrins-G are a netrin subfamily. They differ from the other netrins in several aspects: they are membrane-bound by a GPI anchor, they do not bind to any of the netrin receptors and their expression is limited to vertebrates. Netrins-G are preferentially expressed in the CNS. In adult brain netrins-G are expressed in the hippocampal interneurons, where they may be involved in neural plasticity [13].

Besides the roles in the nervous system netrins and their receptors are important for angiogenesis and vascular morphogenesis. Interestingly, UNC5B expression is largely restricted to the vascular system during development, whereas UNC5A and DCC expressions appear to be avascular [104]. UNC5B is restricted to arterial ECs, a subset of capillary ECs and endothelial tip cells of arterial and venous sprouts. Disruption of UNC5B in mice results in

embryonic lethality at E12.5 with abnormal arterial vasculature including increased vessel branching of the carotic artery, intersomitic vessels and vessels in the nervous system [104]. UNC5B deficiency in mice selectively affects vessel branching, since EC proliferation, apoptosis, arterio–venous marker expression or vessel wall assembly is not altered [85]. In line with this, UNC5B or netrin-1a knockdown in zebrafish exhibit aberrant extension of endothelial tip cell filopodia, excessive vessel branching and abnormal navigation of intersomitic vessels, which migrate laterally instead of dorsally. Abnormal lateral migration occurs at the level of the horizontal myoseptum, where netrin-1 is expressed. Therefore, netrin-1 and UNC5B provide a repulsive signal at this level to direct the vessels further dorsally. Netrin-1a causes in UNC5B expressing ECs filopodia retraction. Taken together, these results suggest that UNC5B functions as a repulsive netrin receptor on ECs controlling morphogenesis of the vascular system. In contrast to these findings Park et al. showed that netrin-1 induces EC proliferation and migration and promotes adhesion of endothelial and smooth muscle cells [137]. Furthermore, netrin-1 induces angiogenesis in vivo, although the receptor responsible for these effects in ECs is not identified yet [1]. However, the in vivo relevance of netrin-1 as an angiogenic factor during development is unclear, since no vascular defect was described in netrin-1 deficient mice [159].

Comparable to netrin, slits' effects on axons are bi-functional. Slits are secreted molecules that can act as chemorepellant for axons and stimulate the branching and elongation of other axons. Slit-1, 2 and 3, are known in mammals. Slits mediate their signal by binding to roundabout (robo) receptors of which robo-1, 2, 3 and 4, are known in mammals. Netrins and slits are expressed in the nervous system midline and regulate in cooperative manner axon guidance across the mid-line. Slits and robo control also other guidance events like, e.g. guiding the ipsilateral and contralateral axons through the optic chiasm by providing a repulsive corridor.

Slits appears to have multiple roles in the control of cell migration in the RMS [123]. Robo-2 and robo-3 are expressed in the SVZ and the RMS and slit-1 and slit-2 are expressed in the adult septum [123]. The septum and the choroids plexus have chemorepulsive activity to SVZ cells and it has been shown that slit-1 and -2 are responsible for the repulsive activity in vitro. Slits are discussed to be involved in guiding the migration of SVZ cells. Interestingly, in adult mice lacking slit-1 neuroblast migration is altered, since small chains of SVZ-derived cells migrate caudally into the corpus callosum [123]. In addition, Nguyen-Ba-Charvet et al. described expression of slit-1 in SVZ neural progenitor cells and in neuroblasts. Although progenitor cell proliferation is normal in slit-1 deficient mice, in vitro studies using SVZ explants or isolated neurospheres demonstrate that migration of SVZ cells is altered in the absence of slit-1 [123].

Like the ephrins and netrins, slits and their receptors are also involved in vascular development. Of importance for vascular development is robo-4 (also known as magic roundabout), showing a highly EC specific expression pattern during development [138]. Also in the adult robo-4 expression is vessel-associated, being expressed by ECs and vascular-smooth muscle cells [138]. Vascular robo expression has been shown in heart, lung, brain and different tumours [69, 138]. Controversy exists about the ligand of robo-4 and about the role of robo-4 and slit-2 in EC migration. Park et al. demonstrated that robo-4 binds slit-2 and that similar to the role of robo in the nervous system slit-2 inhibits cell migration of robo-4 expressing ECs [138]. In contrast, Suchting et al. showed that soluble robo-4 receptor inhibits EC migration, suggesting a stimulating rather than an inhibitory effect for endothelial migration [170]. Furthermore, they demonstrated that, recombinant slits-1, -2, -3 bind robo-1 but not robo-4 [170]. The soluble extracellular domain of robo-4 (robo-4 Fc) inhibits angiogenesis in vivo, tube formation in the aortic ring assay and EC proliferation [170]. Gene knockdown and overexpression of zebrafish robo-4 reveal that, robo-4 is important for coordinated symmetric and directed sprouting of intersomitic vessels, indicating that robo-4 is involved in vessel guidance [15]. Interestingly, slit-2 deficient mice die perinataly; however, a vascular phenotype has not yet been described [140]. Tumour vessels also express robo-1. Slit-2 is expressed in malignant melanoma xenografts and in several cancer cell lines [179]. Here slit-2 promotes EC migration and tube formation in a robo-1 dependant manner. Moreover, overexpression of slit-2 in tumour xenografts results in increased vessel density and accelerated growth, whereas neutralization of robo-1 reduces microvessel density and tumour mass of human malignant melanoma cells in vivo. This demonstrates a potential role of slit-2/robo-1 in tumour angiogenesis and highlights the implications for the pathogenesis of cancer [179].

Conclusions and outlook

The nervous system and the vascular system share several morphological and functional characteristics. Both axons and vessels form tube-like structures that need to cover long distances in order to find their appropriate target tissues. As a consequence, anatomically, nerves and vessels often run side-by-side. Both neurons and ECs need to connect with their neighbor cells and to interact with and signal to support cells such as astrocytes and pericytes. Further, ECs need to directly interact with neuroectodermal cells in

order to acquire blood-brain barrier characteristics. Despite these many similarities, it was thought that the molecular regulation of the processes mentioned above is highly specific for both, the vascular and the nervous systems. Recent findings have discovered however an unexpected overlap of molecules that regulate the development, differentiation, and function of the nervous system and vascular system. It has been shown that molecules that regulate axonal guidance and repulsion can also directly act on vascular cells suggesting a common regulation of vascular and axonal path-finding processes. The existence of adult neural stem cells has been convincingly demonstrated in the past years and it has been shown that molecules that regulate hematopoietic precursor cell as well as EC function are also important for the maintenance of adult neural stem cell function, neurogenesis and neuroprotection. Adult neural stem cells reside in specific areas of the brain such as the SVZ and the hippocampus. It has been demonstrated that adult neural stem cells reside close to vessels and possibly need to directly interact with vascular cells ("vascular niche of adult neural stem cells"). Bone marrow derived cells enter the circulation and home into the nervous system where they exert specific functions, including but not limited to immunosurveillance. Recent evidence suggests that bone marrow derived cells may even fuse with resident neuroectodermal cells, suggesting that bone marrow derived cells can participate in brain plasticity and regeneration. This new and rapidly emerging field may open new avenues for the better understanding of both vascular and neural development as well as disease and reaction to injuries.

The unexpected overlap of growth factors that affect both the vascular and the nervous system will also have a profound effect on cellular and molecular therapies, originally designed specifically for the treatment of cardiovascular or neurological diseases. VEGF-A for example, the major tumour angiogenesis factor, is highly up-regulated in brain tumours such as glioblastomas and hemangioblastomas. Clinical trials to inhibit VEGF-A functions in these tumours are well underway. The observations that VEGF-A blocking may inhibit neurogenesis, neuronal survival and axonal path finding suggest that such interventions may in the long run cause problems in the nervous system of patients. Vice versa, VEGF-A therapy is highly promising for certain neurodegenerative diseases, most importantly ALS. Continuous VEGF-A delivery to the nervous system is unlikely to induce tumours, but it is possible that the (undesired) stimulation of angiogenesis would be able to trigger the growth of occult, yet undetected tumours in a patient. The same problems must be taken into account for other putative cellular or molecular therapies that affect any of the growth factors or their respective receptors listed in Table 1. This, however, may not exclude the possibility to design specific clinical therapies. VEGF-A for example, exerts its functions on the nervous system probably at lower concentrations than it does on the vascular system. Thus, therapies that target the nervous system but not yet the vascular system might be possible. Further, potential side effects need to be judged with regard to the treatment of chronic or acute disease. Thus, in a therapy designed to inhibit angiogenesis in a rapidly growing tumour with an unfavorable prognosis such as a glioblastoma, potential long-term effects on the nervous system might be considered insignificant with regard to prognosis of the patient.

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