VEGF in the nervous system: an important target for research in neurodevelopmental and regenerative medicine

Vascular endothelial growth factor (VEGF) in neurodevelopment and regeneration: VEGF is a well-known factor that promotes vasculatization and angiogenesis. Besides its role in the pathogenesis of several diseases, such as colorectal carcinoma, lung cancer or diabetic retinopathy. Within the last decade, VEGF has been successfully integrated into the treatment of such diseases, for example as a therapy for colorectal cancer with the VEGF-receptor (VEGFR)-Inhibitor axitinib. VEGF-expressing cells were microinjected with plasmids encoding for RFP-ac 

\[ \text{Guaiquil et al., 2014).} \]

Figure 1). VEGF-effects in actin-signaling: A structure of upmost importance for axonal growth and neurodevelopment is the growth cone, which is a highly motile structure at the tip of growing axons that lead growing axons to their final destination to form synapses. It was shown that growth cones of chicken dorsal root ganglion (DRG) neurons rapidly respond to VEGF stimulation and that VEGF acts as an attractant for growth cones, leading to directed growth. Furthermore, it was shown that VEGF-stimulation resulted in growth cones with larger circumference and areas compared to control growth cones (Figure 1). The measured sizes were comparable to results of NGF-stimulated growth cones. The combination of VEGF and NGF even potentiated these effects, leading to very large growth cones (Olbrich et al., 2013). As the growing velocity of growth cones is related to the size of the growth cone, bigger growth cones grow faster, smaller growth cones grow slower (Argiro et al., 1984). Hence it was shown that VEGF attracts growth cones and enhances the speed of growth. These effects are mediated via different VEGF receptors. For example, NRP1 is the corresponding receptor that is indispensable for the development of the optic chiasm, where it directs growth and axon crossing (Erskine et al., 2012). Just recently, VEGFR3 has been discussed to be important during brain development, as this receptor is highly expressed during early developmental stages in rat neurons of the forebrain, however the receptor’s expression then decreases throughout development (Wang et al., 2015). Because of the high diversity of expressed receptors in different neuronal tissues, cooperating receptors and even alternations in the expression levels of these different receptors at different stages of development is important to understand the cellular mechanisms of VEGF stimulation downstream of the receptors.

Neurological diseases and VEGF: VEGF is suspected to play a role in different neurological diseases such as Alzheimer’s disease, amyotrophic lateral sclerosis or multiple sclerosis. It also participates in the development of brain tumors such as glioblastoma, by supporting tumor growth. Initial studies have shown that the inhibition of VEGF has positive effects against glioblastoma cells, but successful integration into the clinical treatment procedures of those tumors has not yet been possible with such positive effects as suspected. In clinical studies with Bevacizumab treatment, to block VEGF in glioblastoma tissue, patients with glioblastoma did not show any increase in the overall survival, compared to patients who received a placebo. The progression-free interval of glioblastoma was increased after VEGF treatment (Chintor et al., 2014). In recent studies, VEGF was also shown to participate highly in stroke. In ischemic hippocampal neurons, VEGF was able to attenuate the increase of outwardly delayed potassium currents, which support neuronal survival. Besides stroke, those currents also play a role in Alzheimer’s disease and seizures (Wu et al., 2015). This underlines the role of VEGF in neuroprotection under unfavorable conditions, such as hypoxia. Therefore, VEGF might be an option for the treatment of neurodegenerative diseases.
Conclusions: VEGF is highly involved in axonal growth, neurodevelopment and in the pathogenesis of different neurological disorders. It enhances neuroprotection under unfavorable conditions and supports the growth of cerebral tumor tissue. The effects of VEGF in axon guidance are primarily mediated via reorganization of the actin cytoskeleton, but the exact downstream signaling of VEGF signaling is not clear yet. All of those aspects lead us to suspect that VEGF will play a big role in upcoming neurological investigations and clinical treatments. It is conceivable that stimulation of axonal growth via VEGF will be used to support rehabilitation or regenerative processes after spinal cord injuries or axonal damage. Furthermore, the therapies of cerebral tumors by inhibition of VEGF or the support of neuroprotective mechanisms after ischemic insults by up-regulation of VEGF are therapeutic options that might be of interest to future investigations.

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