Cell. Mol. Life Sci. (2013) 70:1673–1674
DOI 10.1007/s00018-013-1276-6

Cellular and Molecular Life Sciences

MULTI-AUTHOR REVIEW

The power of VEGF (vascular endothelial growth factor) family molecules

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Received: 15 January 2013 / Revised: 28 January 2013 / Accepted: 28 January 2013 / Published online: 12 March 2013

Abstract Vascular endothelial growth factors (VEGFs) and their high-affinity tyrosine kinase VEGF receptors (VEGFRs) are key regulators of both angiogenesis and neurogenesis. The current issue of CMLS discusses recent literature and work implementing these signals in nervous system development, maintenance and disease pathology.

Keywords Vascular endothelial growth factors (VEGFs) · Vascular endothelial growth factors receptors (VEGFRs) · Angiogenesis · Neurogenesis · Neurovascular interactions · Brain diseases and disorders

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Introduction

The power of VEGF (vascular endothelial growth factor) family molecules extends beyond the vascular system where they function as regulators of angiogenesis and vascular permeability. VEGF ligands and their receptors (VEGFRs) have aroused growing interest among neurobiologists and can now be considered as unmistakable actors of developmental processes in the nervous system. Twenty years ago, Werner Risau's group reported the seminal discovery that embryonic brain cells expressed high levels of VEGF-A along the ventricle walls [1], Eli Keshet's group showed that VEGF-A expression is regulated by hypoxia in glioblastoma [2], and Connie Cepko's group showed soon afterwards that VEGFR-2 (Flk-1) was expressed on the surface of neural progenitors in mouse retina and may play a critical role in retinal neurogenesis [3]. Since then, increasing efforts have been made to understand to what extent and by which molecular mechanisms VEGF family molecules participate in the establishment, the maintenance, and the repair of cerebral vascular circuits and neural cell populations.

The aim of this special issue of *Cellular and Molecular Life Sciences*, entitled 'Neurobiology of vascular growth factors and receptors', was to assemble the reflections of scientists who have contributed to establish VEGF family molecules as key regulators of nervous system development. Taken together, the reviews cover a very large scope of studies that have been performed on VEGF family molecules in the nervous system. Ruhrberg and Bautch summarize current views on the development of the cerebral vasculature [4]. Chauvet et al. [5], as well as Carmeliet and Ruiz de Almodovar [6], review guidance mechanisms of cerebral vessels and axons, highlighting the common signals used by neural and endothelial cells to colonize their environment, and also unvealing interplays between these signals,

such as neural guidance molecules which regulate VEGF function during vascular development. The contribution of VEGF family molecules to the production of new neural cells has been analyzed by Wittko-Schneider et al. [7] and Thomas et al. [8] who focused on the biology of neural stem cells and neurogenic niches, with additional insights into Notch-VEGFRs interactions [8], while Licht and Keshet [9] explored the role of VEGF-A in the plasticity of nervous circuits and in cognitive functions. In the adult, VEGF-A has been examined in mice and humans by Greenberg and Jin, for its role and potential interest in the response to stroke [10], as well as by Newton et al. [11] for its implication in the control of mood and cognition, while Carmeliet and Ruiz de Almodovar extend their study to other VEGF family members in the context of various pathologies of the peripheral and central nervous system [6].

All authors point out that VEGF family molecules exert a strong and pleiotropic power over the nervous system and have the potential to treat several neurological diseases in humans. They propose new avenues of research to solve questions raised by the current state of discoveries. For example, it is not always known if VEGF factors act directly on neurons or affect neuronal development and function indirectly by stimulating angiogenesis and release of neurotrophic factors from newly formed blood vessels. In many cases, the specific receptors mediating the effect of VEGF factors on neurons remain to be identified. Futhermore, overlapping as well as specific actions of different VEGF family members, such as VEGF-B, VEGF-C and VEGF-D in the nervous system, remain to be better understood.

With respect to human neurodegenerative diseases, a majority of studies have so far concentrated on VEGF-A, which appears to be neuroprotective by promoting neuronal survival as well as maintenance of the cerebral vasculature. This beneficial action is, however, counteracted by simultaneous deleterious effects of VEGF-A such as vascular leakage and blood–brain barrier breakdown, which currently impair the design of therapies to counter neurodegenerative diseases. To circumvent this problem, the scope of investigations should also be turned toward other VEGF family members, which have reduced angiogenic effects when compared to VEGF-A. It is predictable that the resulting findings will be highly valuable for our knowledge on VEGF family actions in the process of nervous system pathologies and, in the future, for manipulating VEGF family molecules to treat neurological and neurovascular diseases in humans.

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