

Vascular Endothelial Growth Factor-C (VEGFC) Could Be a Future Target for Pathological Retinal Angiogenesis

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In past decade, a tremendous increase in interest over the mechanism of pathological retinal angiogenesis and Retinopathy of Prematurity (ROP) has been experienced. Targeting the molecular mechanism angiogenesis could be a therapeutic tool for ROP and diabetic retinopathy thus inspiring many clinician and researcher to join this field. However, the point need to focus that despite the great biological importance and therapeutic promises, the molecular basis of pathological retinal angiogenesis is still incompletely understood. The process of pathological angiogenesis differs from normal physiological angiogenesis in both at molecular and phenotypic levels. Physiological angiogenesis refers to the formation of precursor tip cells which after differentiation forms primitive blood vessels via stalk cells into a primitive vascular plexus. These plexuses then undergo a complex remodeling process, including degradation of extracellular matrix to make paves for endothelial cell (EC) migration, sprouting and lumen formation and formation of a functional vasculature. Pathological angiogenesis follows the similar processes of physiological angiogenesis, but dysregulation in any of normal physiologic events can contribute to non-patterning and non-productive vessel formation which does not reach resolution upon the establishment of a new vascular perfusion to drive the establishment of new blood vessels. From decades, a lot of work has been done to demonstrate the physiological and pathological role of vascular endothelial growth factor (VEGF) in pathological angiogenesis. It is now clear that new blood vessel formation, growth and maturation is a highly complex and coordinated processes which require the sequential activation of a series of EC membrane receptors by its ligands like VEGFA, VEGFB, VEGFC VEGFD and VEGFE. However, from various reports it is well established that VEGFA signaling is a crucial and rate-limiting step in physiological as well as pathological retinal angiogenesis. VEGFA induces angiogenesis via its ability to stimulate growth, migration, capillary-like structure formation of EC cells and their permeability. Among the three receptors of VEGF legend family, namely, Flt1, Kdr, and Flt4 (known as VEGFR1, VERFR2 and VEGFR3, respectively), that are characterized thus far, VEGFA binds to both Flt1 and Kdr. On other hand VEGFB binds only with Flt1 and VEGFC and VEGFD both Kdr as well as Flt4. In the case of VEGFE it binds with Kdr and mediate angiogenic events. VEGFA binds with both Flt1 and Kdr, most of its angiogenic activity and cellular effects is mediated through Kdr receptor. Although, VEGFA binds with receptor Flt1 with more affinity, it might not activate receptor and mediate its cellular effects due to low receptor kinase activity. Recently, a group of researcher shows that despite of the role of VEGFA in pathological neovascularization another isoform VEGFC is also associated with retinal neovascularization but with opposite function. VEGFC may be have high affinity for Kdr then VEGFA. So, it can be postulated that VEGFC can be a therapeutic tool and can be a rate-limiting molecule for the VEGFA mediated pathological angiogenesis. Thus, due of functional redundancies among these various VEGF functional molecules, and complexities in their receptor selectivity's, the use of anti-angiogenesis based therapies targeting VEGFA or its receptor Kdr for ischemic diseases such as retinal neovascularization, diabetic retinopathy and ROP can be more promising.

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