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Vascular endothelial growth factor blockade: A potential new therapy in the management of cerebral arteriovenous malformations

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Cerebral Arterio Venous Malformations (AVM) occurs universally in 1.1 per 100000 people. They are the cause of serious neurological morbidity or even death when they bleed. AVM's are not necessarily static congenital abnormalities. They can undergo internal changes due to angiogenesis resulting in vascular remodeling. They can even re-grow after successful therapy. Vascular endothelial growth factors (VEGF) play an important role in angiogenesis. Drugs are available that block the action of VEGF on VEGFR receptors on the endothelial cell surface. This blockade causes an anti-angiogenetic effect. Anti-angiogenic drugs are widely used as adjuvant therapy in the management of cancers because they suppress the formation of new blood vessels required by the tumor for growth. For similar reasons they are used in the treatment of age related macular degeneration. The present treatment options for AVM's are surgery, embolization and irradiation either on their own or in combination. Irradiation with Stereotactic Radiosurgery (SRS) offers the advantage of being non invasive, but relies on the late radiation effects to achieve its therapeutic goal of complete obliteration. This latent time (1-3 years) during which the risk for a bleed remains is an inherent drawback of SRS. The histopathology of surgical specimens of post SRS AVM's demonstrates a role of endothelial cells in repairing the radiation damage. Suppressing their activity post SRS by a VEGF Blockade has the potential to enhance the radiation damage and hence speed up the obliteration process and reduce the latent time. It is postulated that such a "VEGF Blockade" could be useful as an adjuvant therapy to SRS. In addition there is the potential for a neo adjuvant use, whereby a VEGF blockade could cause regression in the size of the AVM, making definite therapy easier. The rationale for the VEGF-blockade concept will be presented and discussed.

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Molecular mechanism and prevention of VEGF-induced micro-vascular leakage in the retina of diabetic mice

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Diabetic retinopathy is predominantly caused by vascular endothelial growth factor (VEGF)-induced micro-vascular leakage; however, the underlying mechanism is unclear. Here, we demonstrated that hyperglycemia induced micro-vascular leakage by activating TGase2 and this vascular leakage was inhibited by C-peptide in diabetic retina. VEGF elevated TGase2 activity through sequential elevation of intracellular $Ca2^{+}$ and reactive oxygen species (ROS) levels in endothelial cells. The TGase inhibitors cystamine and monodancylcadaverin or TGase2 siRNA prevented VEGF-induced stress fiber formation and vascular endothelial (VE)-cadherin disruption, which play a critical role in modulating endothelial permeability. C-peptide inhibited the VEGF-induced ROS generation, stress fiber formation and disassembly of vascular endothelial cadherin in endothelial cells. Intra-vitreal injection of C-peptide, two TGase inhibitors, or TGase2 siRNA successfully inhibited hyperglycemia-induced TGase activation and micro-vascular leakage in the retinas of diabetic mice. Thus, our findings suggest that C-peptide prevents VEGF-induced micro-vascular permeability by inhibiting ROS-mediated activation of TG2 in diabetic mice.

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