



## Updates on angiogenesis in diabetic retinopathy

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In 1948, Michaelson proposed the hypothesis that a 'factor X' produced in the ischemic retina stimulates neovascularization. Although many candidates have been investigated since then, recent studies suggested that vascular endothelial growth factor (VEGF) is the most important peptide associated with retinal and choroidal neovascularization. VEGF is a 45-kDa homodimer glycoprotein with both vasopermeability and angiogenic activity. There are four different forms according to the number of amino acids; VEGF121, VEGF165, VEGF189, and VEGF206. Two receptors for VEGF were identified; VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). It was reported that VEGFR-2 mediates the proliferation of vascular endothelial cells and the increased permeability.

VEGF levels in the vitreous of the patients with proliferative diabetic retinopathy have been shown substantially increased in comparison with non-diabetic individuals. In addition, VEGF concentrations in the vitreous had been reduced in patients having received panretinal photocoagulation. VEGF is also found in the microvascular endothelial cells of fibrovascular membranes from diabetic patients. Recent findings indicate that the elevation of VEGF level in the retina of diabetic rats occurs before extensive non-perfusion, suggesting that VEGF may play a role in early stages of diabetic retinopathy. Our recent studies suggested that VEGF causes retinal leukostasis through the enhanced expression of the adhesion molecule ICAM-1 of the retinal vascular endothelial cells. Leukocyte adhesion to the vascular endothelium consequently causes the breakdown of the blood-retinal barriers. Activation of protein kinase C is involved in the postreceptor event after VEGF is bound to its cell membrane receptors. PKC inhibitor has been shown effective to prevent retinal neovascularization and to reduce retinal leukostasis. Various approaches to inhibit the action of VEGF are now under the investigation for treatment of neovascular complications and macular edema.