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RESEARCH NEWS

VEGFR-1: A Safe Target for Prophylaxis of Retinopathy of Prematurity?

A review of: Shih SC, Ju M, Liu N, Smith LE 2003 Selective stimulation of VEGFR-1 prevents oxygen-induced retinal vascular degeneration in retinopathy of prematurity. J Clin Invest 112:50–57

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ISCHEMIC PROLIFERATIVE RETINOPATHIES, such as retinopathy of prematurity (ROP) and diabetic retinopathy, are major causes of blindness. These disorders are characterized by obliteration of pre-existing blood vessels and in the case of ROP, by an associated arrest in the normal development of retinal vasculature leading to retinal ischemia. In response to ischemia, the retina upregulates the secretion of angiogenic factors, including vascular endothelial growth factor (VEGF), and a proliferative phase follows. Proliferation of new brittle intravitreal blood vessels can result in hemorrhage, the formation of tractional fibrovascular membranes, retinal detachment and irreversible blindness. Hence, the vaso-obliterative phase seems to play a critical role in preretinal neovascularization. Moreover, recent convincing experimental data indicate that the ischemic phase also leads to disorders in visual acuity arising from retinal dysfunction detected by electroretinogram (1).

Possible therapeutic approaches to these disorders include inhibition of preretinal neovascularization, promotion of revascularization of the ischemic retina (2), and prevention of retinal vaso-obliteration. that ideally would avoid retinal ischemia. The latter therapeutic possibility remains mostly unexplored, although some factors have been found to contribute to the vaso-obliterative phase, notably peroxidation products including isoprostanes and their major mediator thromboxane (3). VEGF can also prevent retinal microvascular degeneration, but this carries the risk of leading to the development of pathological neovascularization (4).

VEGF acts as a major angiogenic stimulus for normal and pathological retinal neovascularization, and is also an important survival factor for immature vessels. Physiologically, the retinal vasculature develops in utero, secondary to VEGF release triggered by the rising oxygen demand of the differentiating retinal neurons. In ROP, the exposure of preterm infants to relatively high levels of oxygen in their atypical extrauterine environment, increases oxygen levels in the blood and diminishes the physiological VEGF production. As a result, retinal angiogenesis is inhibited and immature vessels degenerate. As the retina matures progressively from a structural (increased thickening) and metabolic stand point, the mal-adapted inner retina becomes ischemic as the choroid (source of oxygen provided from the outer retina) becomes incapable of supplying sufficient oxygen to the inner retina; this results in high levels of VEGF and subsequently pathological neovascularization.

Exogenous VEGF administration effectively prevents vessel degeneration in animals (4) and has therefore been suggested as prophylaxis in human disease. However, because VEGF also triggers the development of pathological neovascularization, it may pose significant risk. The study of Shih et al. (5) suggests a possible solution by targeting specific VEGF receptors. VEGF exerts its effect in the eye via two protein kinase receptors, VEGF-receptor 1 (VEGFR-1, Flt-1) and VEGF-receptor 2 (VEGFR-2, KDR, Flk-1). While there is abundant evidence that VEGFR-2 mediates the effect of VEGF in endothelial cell proliferation and permeability, the role of VEGFR-1 is somewhat more complicated. Deletion of the entire VEGFR-1 gene leads to abnormal vascular development and early embryological lethality, while the deletion of only the VEGFR-1 tyrosine kinase domain has no impact on development or angiogenesis (6). Surprisingly, VEGFR-1 activation was sufficient to completely inhibit the oxygen-induced degeneration of the retinal vessels, while having no effect on pathological neovascularization. On the contrary, VEGFR-2 stimulation had no protective effect on vessel degeneration but was responsible for the development of the neovascularization. This "division of chores" might come in handy in the development of a safe prophylactic treatment for ROP, as VEGFR-1 stimulation in oxygen exposed infants could prevent retinal vascular degeneration without increasing the risk of pathological neovascularization; this will necessitate a topical readily diffusible and preferably relatively small molecule ligand of VEGFR-1.

However, actions of VEGFR-1 may not be as specific as presented by Shih *et al*. Since VEGFR-1 activation by PlGF-1 induces tissue factor (TF) expression, and the TF ligand Factor VIIa elicits angiogenesis (6), one cannot exclude VEGFR-1-induced neovas-

cularization mediated via the TF/Factor VIIa pathway. Accordingly, although in the majority of endothelial cell preparations VEGFR-1 has not been shown to exert angiogenesis, recent convincing experiments using animals with disrupted PlGF-1 genes and PlGF-1 neutralizing antibodies have revealed a role for PlGF-1/VEGFR-1 in ocular neovascularization including in preretinal neovascularization in the oxygen-induced animal model (7). Perhaps, the appropriate timing and duration of administration of PlGF-1 and ensued activation of VEGFR-1 may explain discrepant findings between studies.

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