Wnting Out Ocular Neovascularization

Using Nanoparticle Delivery of Very-Low Density Lipoprotein Receptor Extracellular Domain as Wnt Pathway Inhibitor in the Retina

Julia V. Busik, Maria B. Grant

Although angiogenesis is a very important part of normal blood vessel physiology and repair, it can go awry, leading to pathological neovascularization. This is an especially difficult problem when involving the eye where aberrant blood vessel growth can lead to irreversible vision loss. Thus, it is not surprising that neovascularization is of major concern in several ocular pathologies, including retinopathy of prematurity, proliferative diabetic retinopathy, age-related macular degeneration, and corneal injury. Recent success with using anti-vascular endothelial growth factor (VEGF) antibody treatment for neovascularization and macular edema further confirms that blocking VEGF overproduction is promising therapeutic direction. However, several concerns remain, including that VEGF is an important trophic factor in the retina and specifically an endothelial cell survival factor. Although anti-VEGF therapy works well as a short-term approach, it may not be a viable long-term solution. Moreover, >40% of patients are reported to be nonresponders to anti-VEGF therapy. Thus, new approaches to control ocular neovascularization are clearly needed. The article by Wang et al in the April 2015 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* proposes an interesting approach to control ocular neovascularization through the modulation of the canonical Wnt pathway. Wnt ligands bind to frizzled and low-density lipoprotein receptor–related protein 5/6 complex, leading to attenuation of phosphorylation and stabilization of cytoplasmic β-catenin (Figure). β-Catenin is then translocated into the nucleus, where it associates with and activates T cell factor. T cell factor activation leads to transcription of Wnt target genes, including VEGF (Figure).

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The authors previously reported Wnt signaling activation in the retina of humans with diabetic retinopathy and corroborated these findings in animal models of diabetic retinopathy. It was also reported that Wnt signaling mediates neovascularization in oxygen-induce retinopathy, such as retinopathy of prematurity. Very-low density lipoprotein receptor (VLDLR<sup>−/−</sup>) mice spontaneously develop retinal and subretinal neovascularization, and VLDLR deficiency results in Wnt signaling activation in the retina. VLDLR is known to shed its N-terminal ectodomain (VLN) into the extracellular space as a soluble protein. The authors previously demonstrated the inhibitory effect of VLN on Wnt signaling in vitro.

In this study, nanoparticles with a plasmid-mediated expression of the soluble VLN were generated, and the inhibitory effect of VLN on retinal neovascularization and Wnt signaling were determined in 3 models, the VLDLR<sup>−/−</sup> mice, the oxygen-induce retinopathy model, and alkali burn–induced neovascularization. The results of this study provide several important findings. First, successful delivery of VLN plasmid cargo and its expression in the retina was achieved using intravitreal injections of poly (lactic-co-glycolic acid) polymer nanoparticles. Second, VLN overexpression led to inhibition of lipoprotein receptor–related protein 6 expression followed by destabilization of β-catenin, inactivation of T cell factor, and inhibition of transcription of Wnt target genes, including VEGF (Figure). This, in turn, resulted in reduced neovascularization in the 3 test models.

Wnt pathway is involved in almost every cellular function; thus, it is not surprising that there remain many unanswered questions about its involvement in pathological retinal neovascularization. For instance, although it could be beneficial for reducing neovascularization, long-term inhibition of Wnt pathway could lead to microglia activation and neurodegeneration, ultimately exacerbating retinal pathology. However, the results of this article provide an important first indication that Wnt pathway inhibitors may one day be part of the therapeutic armamentarium for treatment of ocular neovascularization.

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