Wnting Out Ocular Neovascularization

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

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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 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).

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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