Novel Regulators of Retinal Vascular Disease

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Abstract

Aberrant neovascularization contributes to diseases such as cancer, blindness and atherosclerosis, and is the consequence of inappropriate angiogenic signalling. Although many regulators of pathogenic angiogenesis have been identified, our understanding of this process is incomplete. We explored the transcriptome of retinal microvessels isolated from mouse models of retinal disease that exhibit vascular pathology, and uncover an upregulated gene, leucine-rich alpha-2-glycoprotein 1 (*Lrg1*), of previously unknown function. We show that in the presence of transforming growth factor-β1 (TGF-β1), LRG1 is mitogenic to endothelial cells and promotes angiogenesis. Mice lacking *Lrg1* develop a mild retinal vascular phenotype but exhibit a significant reduction in pathological ocular angiogenesis. LRG1 binds directly to the TGF-β accessory receptor endoglin, which, in the presence of TGF-β1, results in promotion of the pro-angiogenic Smad1/5/8 signalling pathway. LRG1 antibody blockade inhibits this switch and attenuates angiogenesis. These studies reveal a new regulator of angiogenesis that mediates its effect by modulating TGF-β signalling.