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Abstract

Angiogenesis: From Discovery to Therapy

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Angiogenesis, the development of new blood vessels, is a fundamental physiological process. In addition, angiogenesis plays a key role in the pathogenesis of several disorders, including cancer and eye disorders such as diabetic retinopathy and age-related macular degeneration (AMD). However, identifying the regulators of angiogenesis proved challenging. Numerous factors that stimulated angiogenesis in various bioassays were identified, but their pathophysiological role remained unclear. In 1989, we reported the isolation and cloning of vascular endothelial growth factor (VEGF, VEGF-A) as an endothelial cell-specific mitogen and angiogenic factor. The tyrosine kinases Flt-1 (VEGFR-1) and KDR (VEGFR-2) were subsequently identified as VEGF receptors. Loss of a single vegfa allele results in defective vascularization and embryonic lethality in mice, emphasizing the essential role of VEGF in the development of blood vessels. Subsequently, we reported that anti-VEGF monoclonal antibodies block growth and neovascularization in tumor models. These findings paved the way for the clinical development of a humanized anti-VEGF antibody and other VEGF inhibitors for cancer therapy. To date, several VEGF inhibitors represent standard of care for colorectal cancer and other difficult to treat malignancies. VEGF is also implicated in intraocular neovascularization associated with retinal disorders as well as neovascular AMD. Our group developed a humanized anti–VEGF-A antibody fragment (ranibizumab) for the treatment of wet AMD. Ranibizumab not only maintained but also improved visual acuity and has been approved worldwide for the treatment of wet AMD and other neovascular disorders. Other VEGF inhibitors, including bevacizumab and aflibercept, have also resulted in significant clinical benefits. Today anti-VEGF drugs represent the most effective therapy for intraocular neovascularization. Current research addresses the need to reduce the frequency of intravitreal injections as well the identification of additional pro-angiogenic pathways that could result in improving could result in improving therapeutic outcomes.