VEGF-regulated vascular permeability: Molecular mechanisms and contribution to disease

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The vasculature serves to supply tissues with oxygen and nutrients and may thereby promote pathological growth. It moreover provides access for inflammatory cells to the tissue; these cells may provide growth factors and suppress immunity against the pathology. In this scenario, the vasculature may itself become hyperstimulated, leading to abnormal and leaky blood vessels. The leakiness results in a build-up of interstitial pressure and impaired delivery of drugs to the pathology. Increased vascular permeability is specifically regulated by vascular endothelial growth factor-A (VEGFA) and by inflammatory cytokines such as bradykinin and histamine. VEGFA regulates permeability by activating the receptor tyrosine kinase VEGF receptor-2 (VEGFR2). VEGFR2 acts through the adaptor protein TSAd to induce activation of the cytoplasmic tyrosine kinase c-Src, thereby transiently opening endothelial cell-cell junctions. A key protein phosphorylated by c-Src in endothelial cell junctions is Vascular endothelial cadherin (VE-cadherin). Even though VEGFA/VEGFR2 appear to regulate vascular permeability differently from inflammatory cytokines, the molecular details are not clear. Such knowledge is valuable since it may allow pharmaceutical targeting to suppress unwanted, excess permeability. We have created a series of mouse models mutated or silenced, in the VEGFA/VEGFR2 signal transduction pathway to decipher the specific prerequisite for opening of junctions in response to VEGFA compared to inflammatory cytokines. The eventual goal is to determine the contribution of excess permeability to lifestyle diseases such as cancer and cardiovascular disease.

Role of the microenvironment in the regulation of tumor angiogenesis

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Angiogenesis, the development of new blood vessels, is a fundamental pathophysiological process. Vascular endothelial growth factor (VEGF)-A has been shown to be a key regulator of blood vessel growth during embryonic development and in a broad variety of physiological processes. Several VEGF inhibitors have been shown to block tumor growth in numerous preclinical models, consistent with an important role of VEGF-A in tumor angiogenesis. We developed a humanized anti-VEGF-A monoclonal antibody (bevacizumab) to test the hypothesis that blocking VEGF-A-induced angiogenesis may result in a clinical benefit in patients. Bevacizumab has been approved by the FDA and worldwide for the treatment of several malignancies. Furthermore, blocking VEGF-A prevents vision loss and had a major impact on the progression of neovascular age-related macular degeneration and other intraocular neovascular disorders.

We have been recently studying the mechanisms of resistance to anti-VEGF therapies in various tumor models. These studies indicate that multiple pro-angiogenic mechanisms may be implicated. We identified factors produced by myeloid cells and by fibroblasts were identified as key mediators of angiogenesis. In recent studies we identified IL-17, a key product of Th17 Helper T cell, as a key factor mediating angiogenic escape and resistance to VEGF inhibitors. Efforts are ongoing to determine the translational and clinical significance of such findings.