Endoglin regulates biology and signal transduction in vascular smooth muscle cells

Angiogenesis is the physiological process by which new blood vessels arise from pre-existing vessels. Angiogenesis has prominent roles in both physiological processes (i.e. embryonic development and wound healing) and pathological conditions, including cancer and Hereditary Hemorrhagic Telangiectasia (HHT).

Blood vessels are made by a specialized cell called the endothelial cell. When endothelial cells form new blood vessels, the cells at the front, called endothelial tip cells, follow signals to guide which way the blood vessel grows. Endothelial tip cell formation is regulated by the vascular endothelial growth factor (VEGF) pathway. During angiogenesis, endothelial tip cells express high levels of receptors for VEGF. However, the mechanism of how tip endothelial cells maintain expression of these VEGF receptors is unknown. Endoglin is a cell surface receptor for the transforming growth factor family-β (TGF-β).

Dr. Tian reports that endoglin promotes VEGF-induced tip cell formation. Mechanistically, endoglin interacts with VEGF receptors in a VEGF-dependent manner, which sustains VEGF receptors on the cell surface and prevents their degradation. Endoglin mutants which cannot interact with VEGF receptors do not sustain VEGF receptors on the cell surface or promote VEGF-induced tip cell formation. Further, an endoglin-targeting monoclonal antibody, TRC105, cooperated with a VEGF-A targeting monoclonal antibody, bevacizumab, to inhibit VEGF signaling and tip cell formation and to inhibit tumor growth, metastasis and tumor-associated angiogenesis in a murine cancer model. These studies demonstrate a novel mechanism by which endoglin initiates and regulates VEGF driven angiogenesis while providing a rationale for combining anti-VEGF and anti-endoglin therapy in human cancer patients.