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Sprouting Angiogenesis: An Integrated Experimental and Multiscale Modeling Study

Angiogenesis requires a highly coordinated cellular response to both cellular and molecular signals. This response is triggered by cell surface receptors responsible for the activation of an intracellular cascade that efficiently initiates migration and proliferation programs. While the molecular players that coordinate these effects have been identified, recent findings have expanded our understanding of cell-cell and cell-matrix interactions, affects endothelial cell responses to growth factors. Experiments have revealed that the cellular composition of a growing vascular sprout is molecularly and functionally heterogeneous. The endothelial cells at the invasive front exhibit unique properties and can be distinguished from their neighbors by the expression of a specific subset of molecules. Differentiating into tip, stalk, and phalanx cell types, the endothelial cells organize into sprouts, which branch and fuse to form networks that support blood-flow. Retinal angiogenesis in embryonic mouse provides an excellent experimental system to study all these aspects of angiogenesis.

Based on experimental data from retinal angiogenesis, we have developed a cell-based, multiscale mathematical model of sprout formation. The model incorporates three level descriptions: 1) VEGF activated Dll4-Notch signaling, which regulates endothelial differentiation; 2) tip, stalk and phalanx cell types for endothelial cells along the sprout; and 3) tissue level extracellular-matrix representation and dynamics of VEGF and other growth factors. The model reproduces many phenomena observed in sprouting angiogenesis, including sprout morphology dynamics and tip competition. Our simulations explain and predict some perturbation experiments on Notch/Delta and VEGF pathways.