It is well recognized that endothelial cells (ECs) form the lining of the vascular system and provide a conduit for 1) nutrient and oxygen delivery, and 2) removal of metabolic waste. More recently, investigators have recognized that ECs play an active role in modulating the function of surrounding cells. Our laboratory has investigated the role of angiocrine signaling in colorectal cancer (CRC). We found that ECs secrete a soluble factor that mediates the cancer stem cell properties of CRC cells. This was confirmed with established cell lines as well as freshly isolated ECs and CRC cells. To identify the factors secreted by ECs that mediate cancer stem cell-ness, we first identified the cancer stem cell pathways activated in target colon cancer cells. We created vectors with promoters of cancer stem cell mediators, infected them into CRC cells, and determined which cancer stem cell pathways were activated. We found that the Notch pathway was activated, a pathway typically requiring cell-cell contact (juxtacrine) signaling. We identified a novel soluble form of the Notch ligand, Jagged-1 that lacked the C-terminal domain. Proteomic studies identified the cleavage site of Jagged-1 composed of an amino acid sequence cleaved by the protease ADAM-17. We are constructing antibodies to the cleaved site of Jagged-1, with the intent to prevent the induction of the cancer stem cell phenotype in CRC cells by blocking angiocrine signaling. In addition, our studies identified ADAM-17 as a target of angiocrine signaling. ADAM-17 has also been investigated as a target in cancer by other groups.

References