Project 1: Pancreatic Carcinogenesis: Understand the mechanisms of progression to drug resistance

My Laboratory conducts research on pancreatic cancer (Pancreatic ductal adenocarcinoma, PDAC) using *in vitro* and *in vivo* experimental approaches to understand the mechanism of the genesis of pancreatic cancer and resistance to conventional therapy and for its prevention. This work is funded by VA Merit Award grant.

A patient with PDAC has the worst survival rate due to its late detection, early metastasis and resistant to conventional chemotherapy. We have shown that CCN1/Cyr61, a secreted protein, plays a critical role in pancreatic carcinogenesis with the progression of the disease and resistant to chemotherapy. CCN1/Cyr61 is consistently overexpressed in early precursor lesions and continues with advancing disease. CCN1/Cyr61 also plays a critical role through the regulation of miRNA in EMT induction, reprogramming of stemness and migration activity. (Mol Cancer. 2011 Jan 13;10:8). However, it remains unknown that how CCN1/Cyr61 functions at the cellular and molecular level to promote PDAC growth. Recently, it is evident from our unpublished data that CCN1 is an upstream regulator of sonic hedgehog (SHh), a secreted signaling molecule. Aberrant expression of SHh in pancreatic-ductal epithelial cells, which is absent in the developing and mature pancreas, plays critical role in PDAC development from early lesions to invasive growth of the disease. We also found that CCN1 modulates Notch-1 followed by SHh through the direct binding with integrin receptors (avb3) signaling pathway [J Biol Chem. 2012, 287 (46): 38569-79]. Collectively, these studies hypothesized that CCN1 could be an ideal attractive therapeutic avenue for PDAC treatment.
My second project is on tumor angiogenesis. New blood vessel formation/angiogenesis and remodeling is a complex event and is dependent on the mobilization of endothelial cells (ECs) and mural cells (MCs) including vascular smooth muscle cells (SMCs) and pericytes (PCs). Recently, our studies have found that breast tumor cells are capable of modulating the migration of vascular smooth muscle cells in vitro and this event is mediated through VEGF/PDGF-neuropilin-1 (NRP-1) signaling pathways (Mol Carcinog. 2006 Nov;45(11):871-80; Biochemistry. 2008 Mar 18;47(11):3345-51). This study, for the first time to our knowledge, shed light on the molecular interactions of tumor cells with vascular SMCs, and offer new opportunities to improve the understanding of the regulation of pathologic angiogenesis by cell-cell interactions through successive studies. Interaction of breast tumor cells (tumor cells derived growth factors) with mural precursor cells for the differentiation and recruitment of mural precursor cells to vascular smooth muscle cells/pericytes are vital events for tumor angiogenesis (Mol Cancer. 2010 Aug 5;9:209).
Research Projects:

Current Project:
1. The role of matricellular protein Cyr61/CCN1 in pancreatic cancer development, progression and drug resistance.
2. Role of DKK1 in pancreatic cancer progression.

Research Interest:
1. Tumor angiogenesis and cancer
2. EMT, stemness and cancer
3. Hormonal and chemical carcinogenesis
4. Genomic alterations, cell proliferation and cancer
5. Matricellular protein and pancreatic cancer progression

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**Publications: (Selected Publications)**


