***Investigating the Role of KCNQ1 and CFTR as Colorectal Cancer Tumor Suppressors***

Colorectal cancer (CRC) is the second-highest cause of cancer deaths in the United States. A comprehensive understanding of disease development and progression is critical for the advancement of effective diagnostic and treatment methods for CRC patients. Forward genetic screens have identified numerous candidate genes that may be driving tumor development and progression (Starr et al. 2009). Two identified candidate genes are potassium voltage-gated channel subfamily Q member 1 (KCNQ1) and cystic fibrosis transmembrane conductance regulator (CFTR). Previous studies show knockout of KCNQ1 or CFTR alone causes increased intestinal tumorigenesis in the Apc-Min mouse model, and low expression of KCNQ1 or CFTR in CRC tumors is associated with poor outcomes in human CRC (Than, et al.). To further investigate the role of these genes as CRC tumor suppressors, we harvested intestinal organoids from KCNQ1 and CFTR knockout and wild-type mice and isolated RNA from these organoids. Illumina Next-Generation RNA Sequencing and quantitative reverse-transcriptase PCR was performed using organoid RNA to evaluate and compare gene expression. In addition, preliminary phenotypic characterization of organoids derived from KCNQ1 and CFTR WT and KO mice was performed. Bioinformatic analysis by Gene Set Enrichment Analysis using human cancer datasets further characterized gene expression changes in KCNQ1 and CFTR low-expression phenotypes. Our data show KCNQ1 is localized to the stem cell compartment of the small intestines, and loss of KCNQ1 and CFTR effect gene expression in isolated organoids as well as primary tissue. Loss of these tumor suppressive genes alter specific biological pathways, including cholesterol biosynthesis and the unfolded protein response, that may lead to cancer development and progression.