Role of the long non-coding RNA MALAT-1 in Pancreatic Cancer

Yating Cheng[1], Parisa Imanirad[1], Indira Jutooru[2], Aline Rodrigues Hoffmann[3], Ben Morpurgo[4], Andrei E. Golovko[4], Stephen Safe[1]

1. Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX, USA.
2. Covance, Inc., Madison, WI, USA
3. Department of Veterinary Pathobiology, Texas A&M University, College Station, TX, USA
4. Texas Institute for genomic medicine, Texas A&M University, College Station, TX, USA

Long non-coding RNAs (Lnc RNAs) contain > 200 nucleotides and based on limited studies there is evidence that they regulate multiple functions and contribute to cellular homeostasis and diseases including cancer. The lncRNA Metastasis-Associated-in-Lung-Adenocarcinoma-Transcript-1 (MALAT-1) is overexpressed in pancreatic and other cancer cell lines and tumors and is a negative prognostic factor for multiple cancers. MALAT-1 function was investigated by RNAi in Panc-1 and Miapaca2 pancreatic cancer cell lines and knockdown of MALAT-1 (siMALAT-1) decreased the cell viability, migration/invasion, induced G2/M cell cycle arrest and apoptosis, which suggest that MALAT-1 plays a role in pancreatic cancer cell survival. Panc1 cells were transfected with siCtrl (control siRNA), siMALAT-1 and also oligonucleotide targeting MLL-1 and EZH2 which are important components of histone modification complexes. Functional and pathway analysis for differential expressed genes after knocking down of MALAT-1, MLL-1 or EZH2 were analyzed by Ingenuity software and showed that MALAT-1 is involved in multiple pathways including those associated with cell death, proliferation and migration/invasion, and the interferon signaling was most significant pathway from the canonical pathway analysis. Venn diagram analysis showed that 107 common genes were co-upregulated by siMALAT-1 or siEZH2 treatment, and 75 genes were co-downregulated by siMALAT-1 or siMLL1 treatment. Some representative coregulated genes related to cell migration and invasion were further investigated by real time PCR, confirming that expression of both SMAD3 and EZR were decreased after knockdown of MALAT-1 or MLL1, and sprouty2 (SPRY2) and NDRG1 expression were increased after knockdown of MALAT-1 or EZH2. We have also generated heterozygous floxed p53/Kras^{GD12} mice (p53L/+: LSL-Kras^{GD12}L/+:p48Cre+/-) which spontaneously develop pancreatic tumors, and these have been crossed with MALAT$^{-/-}$ mice. A comparison of the lifespan of these mice expressing wild-type or deleted MALAT-1 (homo plus heterozygote mice) showed that with the loss of one or both MALAT-1 alleles, there was an increase in lifespan demonstrating an in vivo pro-oncogenic role of MALAT-1 in a mouse model of pancreatic cancer.