The Role and Therapeutic Potential of miRNAs in Colorectal Liver Metastasis

Ruchi Bansal[1], Smiti Snigdha Sahu[1, 2*], Sarah C. Nabinger[1*], Jiang Guanglong[3]*, Alison Bates, Sangbin Lee[1], Tanaka Hiromi[1], Yunlong Liu[1, 3, 4], and Janaiah Kota[1, 5, 6]

[1]Department of Medical and Molecular Genetics, Indiana University School of Medicine; [2]Department of Pathology, Indiana University School of Medicine; [3]Center for Computational Biology and Bioinformatics, Indiana University-Purdue University Indianapolis; [4]Center for Medical Genomics, Indiana University School of Medicine; [5]The Melvin and Bren Simon Cancer Center, Indiana University School of Medicine; [6]Center for Pancreatic Cancer Research, Indiana University- Purdue University Indianapolis.

*These authors contributed equally to this work

Colorectal cancer (CRC) is the third most common malignancy worldwide. Liver metastasis occurs in 60% of CRC patients and responds poorly to the available treatments making it the major cause of their mortality. MicroRNAs (miRNAs) are highly conserved, endogenously encoded small, non-coding RNA molecules that regulate global gene expression. The role of microRNAs in cancer pathogenesis, including CRC, has been well documented. However, in-depth miRNA expression analysis on a large cohort of CRC tumors is needed to identify the clinically relevant miRNAs and explore their potential to target liver metastases. To this purpose, we analyzed miRNA expression data of 406 CRC tumors from the publicly available colorectal cancer genome sequencing project and identified 58 miRNAs that were significantly downregulated. 10 miRNAs were selected for further analyses that were either known to target genes in cellular pathways or located within the commonly lost chromosomal loci associated with CRC liver metastases. Of these 10 miRNAs, miR-132, miR-378f, miR-605 and miR-1976 showed significant downregulation with >2 fold change ($p>0.05$) in primary and CRC liver metastasis tissues and in CRC cell lines. To investigate their anti-tumorigenic and metastatic properties, we transfected 3 different CRC cell lines (SW620, HCT-116 and CT-26) with miR-mimics and subjected them to cell proliferation, apoptosis and cell transformation assays. Ectopic expression of miR-378f, -605 and -1976 suppressed CRC cell proliferation, anchorage independent growth, migration and invasion and induced apoptosis. Interestingly, CRC patients with high miR-378f and miR-1976 had better survival compared to low expressing patients ($p<0.044$). Our *in vitro* data suggest the anti-tumorigenic/metastatic properties of miR-378f, -605 and -1976 in CRC. Further understanding of their functions and *in vivo* therapeutic evaluations may help in developing novel therapeutic strategies for this malignancy.

Mentor: Janaiah Kota, Department of Medical and Molecular Genetics, Indiana University School of Medicine.