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Inhibition of S-adenosylmethionine-dependent methyltransferase attenuates TGF-β1-induced EMT and metastasis in pancreatic cancer: Putative roles of miR-663a and miR-4787-5p

Identification of epigenetic reversal agents for use in combination chemotherapies to treat human pancreatic ductal adenocarcinomas (PDAC) remains an unmet clinical need. Pharmacological inhibitors of enhancer of zeste homolog 2 (EZH2) are emerging as potential histone methylation reversal agents for the treatment of various solid tumors and leukemia; however, surprisingly small set of mRNA targets identified with EZH2 knockdown suggests novel mechanisms that contribute to their anti-tumorigenic effects. Here we report 3-deazaneplanocin-A (DZNep), an inhibitor of S-adenosyl-L-homocysteine hydrolase and EZH2 histone lysine-N-methyltransferase, to significantly reprogram noncoding miRNA expression and dampen TGF-β1-induced epithelial-to-mesenchymal (EMT) signals in pancreatic cancer. In particular, we identify miR-663a and miR-4787-5p as PDAC-downregulated miRNAs that are reactivated by DZNep to directly target TGF-β1 for RNA interference. Lentiviral overexpression of miR-663a and miR-4787-5p reduced TGF-β1 synthesis and secretion in PDAC cells and partially phenocopied DZNep's EMT-resisting effects, whereas locked nucleic acid (LNA) antagomiRs counteracted them. In vivo, DZNep, miR-663a, and miR-4787-5p reduced tumor burden and metastases in an orthotopic mouse pancreatic tumor model. Taken together, these findings suggest the epigenetic reprogramming of miRNAs by synthetic histone methylation reversal agents as a viable approach to attenuate TGF-β1-induced EMT features in human PDAC and uncover putative miRNA targets involved in the process.

Biography

Rajgopal Govindarajan has completed his PhD from University of Nebraska Medical Center and Post-doctoral studies from University of Washington School of Pharmacy. He is currently an Associate Professor at the College of Pharmacy, Ohio State University.

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