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Novel Tumor Suppressor Role of miR-876 in Cholangiocarcinoma

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Cholangiocarcinoma is a rare, highly invasive malignancy and its incidence is increasing globally. MicroRNAs (miRNAs) mediate a broad range of cellular processes by coordinately repressing target genes involved in cell proliferation, migration, invasion and apoptosis. Deregulated expression of miRNAs may affect these biological processes and eventually lead to cancer. The functional and biological roles of miRNAs in cholangiocarcinoma (CCA) are not fully elucidated. Here, we report that copy number and expression levels of miR-876 are significantly suppressed in the TCGA cohort of cholangiocarcinoma tissue samples. Expression of miR-876 was substantially downregulated in cholangiocarcinoma cell lines and primary patient samples. Using in-silico algorithm databases and sequence alignments, BCL-XL was identified as a potential target of miR-876. There was an inverse relationship between BCL-XL and miR-876 expression levels in CCA cell lines. miR-876 overexpression significantly suppressed the luciferase activity of a reporter plasmid containing the 3'UTR of BCL-XL. miR-876 mediated suppression of BCL-XL led to substantial decreases in cell survival, cell cycle progression, and induced apoptosis and caspase 3/7 activity. The effects of miR-876 overexpression on cholangiocarcinoma cell growth and apoptosis were reversed by BCL-XL overexpression. Stable overexpression of miR-876 produced potent tumor suppressor activity and reduced tumor cell growth *in vivo*. Overexpression of miR-876 in a patient derived xenograft (PDX) cell line led to a significant decrease in spheroid formation, BCL-XL expression and induced apoptosis and caspase 3/7 activity. This study demonstrates a novel tumor suppressor role for miR-876 in cholangiocarcinoma, identifies BCL-XL as a target of action, and suggests a potential therapeutic role for miR-876 in cholangiocarcinoma.