論 文 要 旨

Molecular pathogenesis of pancreatic ductal adenocarcinoma: impact of *miR-30c-5p* and *miR-30c-2-3p* regulation on oncogenic genes

（膵癌の分子病因：発癌性遺伝子に対する *miR-30c-5p* と *miR-30c-2-3p* の影響）

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive types of cancer, and its prognosis is abysmal; only 25% of patients survive one year, and 5% live for five years. MicroRNA (miRNA) signature analysis of PDAC revealed that both strands of pre-*miR-30c* (*miR-30c-5p*, guide strand; *miR-30c-2-3p*, passenger strand) were significantly downregulated, suggesting they function as tumor-suppressors in PDAC cells. Ectopic expression assays demonstrated that these miRNAs attenuated the aggressiveness of PDAC cells, e.g., cell proliferation, migration, and invasiveness. Through a combination of in silico analyses and gene expression data, we identified 216 genes as putative oncogenic targets of *miR-30c-5p* and *miR-30c-2-3p* regulation in PDAC cells. Among these, the expression of 18 genes significantly predicted the 5-year survival rates of PDAC patients ($p < 0.01$). Importantly, the expression levels of 10 genes (*YWHAZ, F3, TMOD3, NFE2L3, ENDOD1, ITGA3, RRAS, PRSS23, TOP2A*, and *LRRFIP1*) were found to be independent prognostic factors for patient survival ($p < 0.01$). We focused on *TOP2A* (DNA Topoisomerase II Alpha) and investigated its potential as a therapeutic target for PDAC. The overexpression of *TOP2A* and its transcriptional activators (*SP1* and *HMGB2*) was detected in PDAC clinical specimens. Moreover, the knockdown of *TOP2A* enhanced the sensitivity of PDAC cells to anticancer drugs. Our analyses of the PDAC miRNA signature and tumor-suppressive miRNAs provide important insights into the molecular pathogenesis of PDAC.