# Molecular Pathogenesis and Regulation of the miR-29-3p-Family: Involvement of ITGA6 and ITGB1 in Intra-Hepatic Cholangiocarcinoma



# 論 文 要 旨

## Molecular pathogenesis and regulation of the miR-29-3p-family: Involvement of ITGA6 and ITGB1 in intrahepatic cholangiocarcinoma

（ *miR-29-3p-family* の分子病態と制御：
―肝内胆管癌における ITGA6 と ITGB1 の関与―）

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**【Abstract】**

Abstract: The aggressive nature of intrahepatic cholangiocarcinoma (ICC) renders it a particularly lethal solid tumor. Searching for therapeutic targets for ICC is an essential challenge in the development of an effective treatment strategy. Our previous studies showed that the miR-29-3p-family members (miR-29a-3p, miR-29b-3p and miR-29c-3p) are key tumor-suppressive microRNAs that control many oncogenic genes/pathways in several cancers. In this study, we searched for therapeutic targets for ICC using the miR-29-3p-family as a starting point. Our functional studies of cell proliferation, migration and invasion confirmed that the miR-29-3p-family act as tumor-suppressors in ICC cells. Moreover, in silico analysis revealed that “focal adhesion”, “ECM-receptor”, “endocytosis”, “PI3K-Akt signaling” and “Hippo signaling” were involved in oncogenic pathways in ICC cells. Our analysis focused on the genes for integrin-6 (ITGA6) and integrin-1 (ITGB1), which are involved in multiple pathways. Overexpression of ITGA6 and ITGB1 enhanced malignant transformation of ICC cells. Both ITGA6 and ITGB1 were directly regulated by the miR-29-3p-family in ICC cells. Interestingly, expression of ITGA6/ITGB1 was positively controlled by the transcription factor SP1, and SP1 was negatively controlled by the miR-29-3p-family. Downregulation of the miR-29-3p-family enhanced SP1-mediated ITGA6/ITGB1 expression in ICC cells. MicroRNA-based exploration is an attractive strategy for identifying therapeutic targets for ICC.