論 文 要 旨

Molecular Pathogenesis of Colorectal Cancer: Impact of Oncogenic Targets Regulated by Tumor Suppressive *miR-139-3p*

大腸癌の分子病態：

癌抑制型マイクロ RNA（miR-139-3p）により制御される

癌促進型遺伝子の影響

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Abstract: We recently determined the RNA sequencing-based microRNA (miRNA) expression signature of colorectal cancer (CRC). Analysis of the signature showed that the expression of both strands of pre-miR-139 (miR-139-5p, the guide strand, and miR-139-3p, the passenger strand) was significantly reduced in CRC tissues. Transient transfection assays revealed that expression of miR-139-3p blocked cancer cell malignant transformation (e.g., cell proliferation, migration, and invasion). Notably, expression of miR-139-3p markedly blocked RAC-alpha serine/threonine-protein kinase (AKT) phosphorylation in CRC cells. A combination of in silico database and gene expression analyses of miR-139-3p-transfected cells revealed 29 putative targets regulated by miR-139-3p in CRC cells. RNA immunoprecipitation analysis using an Argonaute2 (AGO2) antibody revealed that KRT80 was efficiently incorporated into the RNA-induced silencing complex. Aberrant expression of Keratin 80 (KRT80) was detected in CRC clinical specimens by immunostaining. A knockdown assay using small interfering RNA (siRNA) targeting KRT80 showed that reducing KRT80 expression suppressed the malignant transformation (cancer cell migration and invasion) of CRC cells. Importantly, inhibiting KRT80 expression reduced AKT phosphorylation in CRC cells. Moreover, hexokinase-2 (HK2) expression was reduced in cells transfected with the KRT80 siRNAs or miR-139-3p. The involvement of miRNA passenger strands (e.g., miR-139-3p) in CRC cells is a new concept in miRNA studies. Our tumor-suppressive miRNA-based approach helps elucidate the molecular pathogenesis of CRC.