論 文 要 旨

Molecular pathogenesis of breast cancer: impact of miR-99a-5p and miR-99a-3p regulation on oncogenic genes

（乳癌の分子的病因：発癌遺伝子に対する miR-99a-5p およびmiR-99a-3p 調節の影響）

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Abstract

Our recent research has revealed that passenger strands of certain microRNAs (miRNAs) function as tumor-suppressive miRNAs in cancer cells, e.g., miR-101-5p, miR-143-5p, miR-144-5p, miR-145-3p, and miR-150-3p. Thus, they are important in cancer pathogenesis. Analysis of the miRNA expression signature of breast cancer (BrCa) showed that the expression levels of two miRNAs derived from pre-miR-99a (miR-99a-5p and miR-99a-3p) were suppressed in cancerous tissues. The aim of this study was to identify oncogenic genes controlled by pre-miR-99a that are closely involved in the molecular pathogenesis of BrCa. A total of 113 genes were identified as targets of pre-miR-99a regulation (19 genes modulated by miR-99a-5p, and 95 genes regulated by miR-99a-3p) in BrCa cells. Notably, FAM64A was targeted by both of the miRNAs. Among these targets, high expression of 16 genes (C5orf22, YOD1, SLBP, F11R, C12orf49, SRPK1, ZNF250, ZNF695, CDK1, DNMT3B, TRIM25, MCM4, CDKN3, PRPS, FAM64A, and DESI2) significantly predicted reduced survival of BrCa patients based upon The Cancer Genome Atlas (TCGA) database. In this study, we focused on FAM64A and investigated the relationship between FAM64A expression and molecular pathogenesis of BrCa subtypes. The upregulation of FAM64A was confirmed in BrCa clinical specimens. Importantly, the expression of FAM64A significantly differed between patients with Luminal-A and Luminal-B subtypes. Our data strongly suggest that the aberrant expression of FAM64A is involved in the malignant transformation of BrCa. Our miRNA-based approaches (identification of tumor-suppressive miRNAs and their controlled targets) will provide novel information regarding the molecular pathogenesis of BrCa.