論 文 要 旨

Molecular pathogenesis of triple-negative breast cancer based on microRNA expression signatures :antitumor miR-204-5p targets AP1S3

（マイクロ RNA 発現プロファイルに基づく

トリプルネガティブ乳癌の分子病態:

腫瘍抑制型 miR-204-5p とその標的遺伝子 AP1S3）

戸田　洋子

Abstract

Triple-negative breast cancer (TNBC) is an aggressive type of cancer associated with a poor prognosis. Identification of novel therapeutic targets in TNBC is urgently needed. Here, we investigated the microRNA (miRNA) expression signature of TNBC using clinical specimens. In total, 104 miRNAs (56 upregulated and 48 downregulated) were significantly dysregulated in TNBC tissues; miR-204-5p showed the most dramatic downregulation. We then examined the antitumor roles of miR-204-5p in breast cancer (BC) cells. Notably, cancer cell migration and invasion were significantly reduced by ectopic expression of miR-204-5p in BC cells. Genome-wide gene expression analysis and in silico database search revealed that 32 genes were putative miR-204-5p targets. High expression of AP1S3, RACGAP1, ELOVL6, and LRRC59 was significantly associated with poor prognosis in patients with BC, and adaptorrelated protein complex 1 sigma 3 subunit (AP1S3) was directly regulated by miR-204-5p, as demonstrated by luciferase reporter assays. AP1S3 overexpression was detected in TNBC clinical specimens and enhanced cancer cell aggressiveness. We further analyzed downstream RNA networks regulated by AP1S3 in BC cells. Overall, this miRNA signature is expected to be an effective tool for identification of miRNA-mediated molecular mechanisms of TNBC pathogenesis.