論 文 要 旨

Molecular Pathogenesis of Gene Regulation by the *miR-150* Duplex: *miR-150-3p* Regulates *TNS4* in Lung Adenocarcinoma

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Abstract.

Based on our miRNA expression signatures, we focused on *miR-150-5p* (the guide strand) and *miR-150-3p* (the passenger strand) to investigate their functional significance in lung adenocarcinoma (LUAD). Downregulation of *miR-150* duplex was confirmed in LUAD clinical specimens. In vitro assays revealed that ectopic expression of *miR-150-5p* and *miR-150-3p* inhibited cancer cell malignancy. We performed genome-wide gene expression analyses and *in silico* database searches to identify their oncogenic targets in LUAD cells. A total of 41 and 26 genes were identified as *miR-150-5p* and *miR-150-3p* targets, respectively, and they were closely involved in LUAD pathogenesis. Among the targets, we investigated the oncogenic roles of tensin 4 (*TNS4*) because high expression of *TNS4* was strongly related to poorer prognosis of LUAD patients (disease-free survival: $p = 0.0213$ and overall survival: $p = 0.0003$). Expression of *TNS4* was directly regulated by *miR-150-3p* in LUAD cells. Aberrant expression of TNS4 was detected in LUAD clinical specimens and its aberrant expression increased the aggressiveness of LUAD cells. Furthermore, we identified genes downstream from *TNS4* that were associated with critical regulators of genomic stability. Our approach (discovery of anti-tumor miRNAs and their target RNAs for LUAD) will contribute to the elucidation of molecular networks involved in the malignant transformation of LUAD.