論 文 要 旨

Tumor-suppressive *microRNA-206* as a dual inhibitor of *MET* and *EGFR* oncogenic signaling in lung squamous cell carcinoma.

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Abstract

Expression of the oncogene hepatocyte growth factor receptor (MET) and phosphorylation of the MET protein have been associated with both primary and acquired resistance to tyrosine kinase inhibitors (TKIs) used in therapy targeting the epidermal growth factor receptor (EGFR) in patients with non-small cell lung cancers (NSCLCs). Therefore, simultaneous inhibition of both of these receptor tyrosine kinases (RTKs) should improve disease treatment. Recently, our study of microRNA (miRNA) expression signatures of lung squamous cell carcinoma (lung-SCC) revealed that *microRNA-206* (*miR-20*6) was significantly reduced in lung-SCC tissues, suggesting that *miR-206* functions as a tumor suppressor in the disease. Furthermore, putative *miR-206* binding sites were annotated in the 3'-UTRs of *MET* and *EGFR* RTKs in miRNA databases. The aim of the study was to investigate the functional significance of *miR-206* in lung-SCC and to confirm the inhibition of both *MET* and *EGFR* oncogenic signaling by expression of *miR-206* in cancer cells. We found that restoration of mature *miR-206* inhibited cancer cell proliferation, migration, and invasion in EBC-1 cells through downregulation of both mRNA and protein levels of MET and EGFR. Interestingly, phosphorylation of ERK1/2 and AKT signaling were inhibited by restoration of *miR-206* in cancer cells. Overexpression of MET and EGFR were observed in clinical specimens of lung-SCC. Tumor-suppressive *miR-206* inhibited dual signaling networks activated by MET and EGFR, and these findings will provide new insights into the novel molecular mechanisms of lung-SCC oncogenesis and new therapeutic approaches for the treatment of this disease.