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Abstract of the Alumni Association Medical Research Fund Prize Memorial Lecture

MicroRNA Expression Profiles in Lung Cancer Cooperated with Drug Sensitivity to EGFR Tyrosine Kinase Inhibitor

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Abstract

Lung cancer is the leading cause of cancer death and the most common cause of smoking-related mortality both in the United States and worldwide. However, approximately 25% of cases of lung cancer are not attributable to smoking. Molecular and clinical characteristics of lung cancers in never-smokers are extremely different from those in smokers. For example, G to T transversions of the p53 gene and K-ras mutations occur more frequently in lung adenocarcinomas from smokers than in lung carcinomas from never-smokers. In contrast, mutations of the epidermal growth factor receptor (EGFR) gene are frequently observed in adenocarcinomas from never-smokers. Striking differences in response rates to EGFR tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib and erlotinib, have been observed between lung cancers in never-smokers and those in smokers. Further understanding of the biological differences between lung cancers in never-smokers and those in smokers is necessary for the treatment strategies of lung cancer in never-smokers.

MicroRNAs (miRNAs) are small noncoding RNA molecules comprising 18 to 25 nucleotides which are frequently located at previously reported regions for genetic alterations in cancers, suggesting that miRNAs are a new class of genes involved in human tumorigenesis. Expression levels of miRNAs are altered in most human cancers, including lung cancers. Recently, miRNAs have also been demonstrated to be prognostic biomarkers, including for the response to therapy, in leukemia, lung cancer, and colon cancer. These findings suggest that miRNA could serve as a novel diagnostic marker and a therapeutic target in human cancers, including lung cancer. We have previously analyzed the miRNA profiles of 104 lung cancers and found that high miR-155 expression and low let7a expression, as independent risk factors, have a negative prognostic impact in patients with lung adenocarcinoma. The altered miRNA profiles were reflected primarily by the profiles of lung cancers in smokers.

In this study of 28 lung cancers in never-smokers, we found high expression levels of unique miRNAs in

tumor tissues with a further statistically significant increase in cases with EGFR mutations by miRNA microarray analyses. In addition, the level of miR-21 was high in the lung adenocarcinoma cell line H3255, which contains an EGFR mutation and is hypersensitive to AG1478, an EGFR-TKI. After treatment with AG1478, expression levels of miR-21 were significantly decreased in H3255 cells with and without epidermal growth factor stimulation. Furthermore, inhibition of the miR-21 by antisense oligonucleotide-enhanced AG1478 induced apoptotic activities in lung cancer cells, which showed intermediate sensitivity to AG1478. These results suggest that aberrant expression of miR-21 contributes to the development of lung cancers in never-smokers through the activation of the EGFR signaling pathway. Our findings support the possibility of developing a treatment combining an EGFR-TKI with the inhibition of miR-21 in lung cancers from never-smokers.