

Abstracts of the 2010th Encouragement Award's Memorial Lectures of the 78th Annual Meeting of the Medical Association of Nippon Medical School

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Search for Diagnostic and Therapeutic Biomarkers in Lung Cancer

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Introduction

Lung cancer is the leading cause of cancer death in Japan. Prognoses remain poor despite recent improvements in chemotherapies and molecularly targeted therapies. Identification of sensitive biomarkers predictive of diagnosis, outcome, and drug sensitivity could have significant effects on treatment strategies. Therefore, we attempted to identify molecular biomarkers for lung cancer using transcriptome, proteome, and microRNA (miRNA) analyses.

Diagnostic Biomarker of Lung Cancer Using Proteomic Analysis

Recent clinical trials have demonstrated that drugs for patients with non-small cell lung cancer (NSCLC) should be selected on the basis of histological classification. Therefore, we performed proteomic studies of lung cancer cells to clarify the mechanisms that determine histological phenotype¹. Thirty lung cancer cell lines with 3 different histological backgrounds (squamous cell carcinoma, small cell lung carcinoma, and adenocarcinoma) were subjected to 2-dimensional difference gel electrophoresis. Spot ranking analysis using a support-vector-machine algorithm and unsupervised classification methods identified 32 protein spots essential for classification. The proteins corresponding to the spots were identified with mass spectrometry. Among them, fatty acid-binding protein 5 was considered the most informative spot for the discrimination of adenocarcinoma from squamous cell carcinoma. Thus, fatty acid-binding protein 5 may be useful for distinguishing adenocarcinoma and squamous cell carcinoma.

Prognostic Biomarkers for Lung Cancer Using Cytokine Gene Expression Profiles

Several randomized trials have found that adjuvant chemotherapy significantly lengthens the survival of patients with early stage NSCLC after resection. Biomarkers are needed to identify patients who may benefit

from adjuvant therapy.

Therefore, we analyzed 15-cytokine gene profiles of noncancerous tissue and corresponding tumor tissue from 80 lung adenocarcinomas². A unique 15-cytokine gene signature of noncancerous lung tissue allowed 80 lung adenocarcinoma cases to be classified into 2 major groups that reflected lymph node status, whereas the gene signature of the corresponding lung tumor tissue predicted outcomes independent of lymph node status in a clustering analysis. A combined classification algorithm from analyses of both noncancerous and tumor specimens with the Cytokine Lung Adenocarcinoma Survival Signature of 11 genes (CLASS-11), a refined 11-gene signature, accurately predicted the high-risk of death from adenocarcinoma, including stage I disease. Thus, CLASS-11, consisting of proinflammatory and anti-inflammatory cytokines, identifies cases of stage I adenocarcinoma of the lung with a poor prognosis and provides a potential predictive and mechanistic strategy for adjuvant cancer therapy.

Therapeutic Target of Lung Cancer Using miRNA Expression Profiling

MiRNAs are small noncoding RNA molecules comprising about 20 nucleotides which were are frequently located at previously reported regions of genetic alterations in cancers. Therefore, miRNAs might be a new class of genes involved in human tumorigenesis. Recently, miRNAs have also been demonstrated to be prognostic biomarkers and therapeutic targets in leukemia, colon cancer, and lung cancer. These findings suggest that miRNAs are useful diagnostic markers and therapeutic targets in human cancers, including lung cancer.

In the present study of 28 lung cancers in patients who have never smoked, miRNA microarray analyses showed high expression levels of unique miRNAs in tumor tissues and a statistically significant increase in cases with epidermal growth factor receptor (EGFR) mutations³. In particular, miR-21 was expressed at high levels in the H3255 lung adenocarcinoma cell line, which contains EGFR mutations and is hypersensitive to AG1478, an EGFR-tyrosine kinase inhibitor (TKI). The inhibition of miR-21 by antisense oligonucleotide enhanced AG1478-induced apoptotic activities in lung cancer cells, which showed intermediate levels of sensitivity to AG1478. These results suggest that aberrant expression of the miR-21 contributes, through the activation of the EGFR signaling pathway, to the development of lung cancers in persons who have never smoked. Our findings support the possibility for developing a treatment combining EGFR-TKI with a miR-21 inhibitor to prevent and reverse acquired EGFR-TKI resistance in NSCLC, an important issue of clinical relevance.

References

1. Seike M, Kondo T, Fujii K, et al: Proteomic signatures for histological types of human cancer. *Proteomics* 2005; 5: 2939–2948.
2. Seike M, Yanaihara N, Bowman ED, et al: Use of a cytokine gene expression signature in lung adenocarcinoma and the surrounding tissue as a prognostic classifier. *J Natl Cancer Inst* 2007; 99: 1257–1269.
3. Seike M, Goto A, Okano T, et al: MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers. *Proc Natl Acad Sci USA* 2009; 106: 12085–12090.