Abstract of the 2011th Maruyama Memorial Lectures of the 80th Annual Meeting of the Medical Association of Nippon Medical School

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The Abstract of the 2011th Maruyama Memorial Research Fund Prize Memorial Lecture

Molecular Targeted Therapy of Lung Cancer and the Development of a Molecular Predictive Model

Akihiko Miyanaga

Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School

Lung cancer remains the leading cause of cancer death worldwide, despite improvements in chemotherapy. Recently, new therapeutic strategies targeting specific tumor-related genes have been developed for non-small cell lung cancer (NSCLC). For example, epidermal growth factor receptor (EGFR) inhibitors, such as gefitinib and erlotinib, have shown dramatic antitumor effects in patients with NSCLC and an EGFR mutation. Furthermore, tumors featuring EML4-ALK fusion constitute an NSCLC subtype that is highly sensitive to ALK inhibitors. However, only a small proportion of patients with NSCLC will benefit from these molecularly targeted therapies. Therefore, it is desirable to find novel therapeutic agents targeting lung cancer and to develop a molecular predictive model.

We have previously used Affymetrix GeneChip to perform gene expression profile analysis of a set of lung cancer cell lines[1]. Correlation analysis with a modified National Cancer Institute program revealed a correlation between drug activity patterns and gene expression patterns.

Histone deacetylase (HDAC) and histone acetylase catalyze deacetylation and acetylation, respectively, of histone in eukaryotes, and their dynamic balance is important for accurately regulating gene expression. Inhibitors of HDAC effectively up-regulate expression of tumor suppressor genes and thereby reduce tumor growth and induce programmed cell death. These drugs have inhibited the proliferation of a wide variety of transformed cells *in vitro*, including lymphoma, myeloma, leukemia, and NSCLC.

We examined the sensitivity of a series of NSCLC cell lines to HDAC inhibitors[2]. Two HDAC inhibitors, trichostatin A and suberoylanilide hydroxamic acid (vorinostat), both displayed strong antitumor activities in a proportion of 16 NSCLC cell lines and suggest the need for predictive markers to select patients for this treatment. We performed a gene expression profiling study using complimentary DNA arrays on the same set of cell lines and studied the relationship between the cytotoxic activity of trichostatin A and the gene expression pattern. Next, we performed pathway analysis using the genes to provide insights into the biological function of the genes and removed 10 of the 19 imported genes. We used 9 genes (*PDCD4*, *HNRPDL*, *NQ01*, *SEC23A*, *PSME2*, *MYL6*, *PSME5*, *TM9SF1*, *TM9SF1*), which were identified with gene-drug sensitivity correlation

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and pathway analysis, to create a support vector machine algorithm model by which sensitive cell lines could be distinguished from resistant cell lines. The prediction performance of the support vector machine model was validated by an additional 9 cell lines, resulting in a predictive value for the response to HDAC inhibitors of 100%. Therefore, this 9-gene classifier is useful for predicting sensitivity to HDAC inhibitors and may contribute to achieving individualized therapy in patients with NSCLC[2].

Whereas there is no evidence of a molecularly targeted gene of small cell lung cancer (SCLC), a promising target is the mammalian target of rapamycin (mTOR), which is activated in many cases of lung cancer. Therefore, targeting mTOR is an attractive strategy for developing therapeutic agents against lung cancer. Everolimus is an orally administered mTOR inhibitor that has been approved for the treatment of advanced renal cell carcinoma. Recently, a phase II study evaluated everolimus in patients in whom SCLC had relapsed after treatment.

We analyzed the antitumor effects of 3 mTOR inhibitors, temsirolimus, everolimus, and rapamycin, in a panel of 9 SCLC cell lines to examine the possibility of treating SCLC with mTOR inhibitors. The 3 mTOR inhibitors showed strong activity against 2 (SBC-5 and H69) of the 9 SCLC cell lines. The responsiveness to the 3 mTOR inhibitors was strongly correlated in the panel of 9 SCLC cell lines tested. To investigate the mechanism of the resistance of SCLC cells to everolimus, we established an mTOR-resistant cell line by exposing the drug-sensitive SBC-5 cell line to everolimus for about 2 months. In addition, we performed gene and receptor tyrosine kinase phosphorylation profiling on the same set of cell lines to identify the molecules associated with the sensitivity of SCLC to everolimus. The level of phosphorylated EGFR expression was found to be elevated in receptor tyrosine kinase phosphorylation expression patterns. Selecting patients on the basis of mTOR inhibitor resistance might be useful for developing therapies for SCLC.

References

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