Analysis of the correlation between HLA phenotype and prognosis of non-small cell lung cancer patients in Japan

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Background: Lung cancer is one of the most common malignant disease and its incidence and mortality continue to increase worldwide. The prognosis for patients with non-small cell lung cancer (NSCLC) remains extremely poor, thus the analysis of genetic and epigenetic alterations in the pathogenesis of lung cancer has extensively researched recently. The present study was undertaken to investigate the correlation between HLA phenotype and the prognosis of patients with NSCLC.

Methods: We reviewed the medical records of 695 NSCLC patients who underwent surgical resection from January 1996 to December 2005 at University of Occupational and Environmental Health and Kitakyushu municipal medical center. Serological typing of HLA class I was performed using a microcytotoxicity test of lymphocytes or PCR-sequence-specific oligonucleotides (PCR-SSO). The correlation between HLA phenotypes and clinicopathological features was analyzed. The survival curves were calculated by the Kaplan-Meier method, and then the comparison of the survival curves was carried out using Log-rank test. Multivariate analysis was performed by Cox’s proportional hazard model.

Results: The frequency of HLA-A11 in patients with NSCLC was higher, whereas the frequencies of B13 and B51 were lower as compared with the control population of each HLA phenotype. The 3-year and 5-year overall survival rate of the 695 patients underwent complete resection was 72.1% and 64.9%. The 3-year and 5-year disease free survival rate (DFI) of entire patients was 62.4% and 54.4%. The correlation between the prognosis (overall survival or DFI) and each HLA class I phenotype was analyzed in these patients. The 5-year overall survival rate was 73.6% in HLA-A2 positive patients (A2(+)) (n=156) and 83.0% in HLA-A2 negative patients (A2(-)) (n=249) at stage I. The 5-year DFI was 65.7% in A2(+) and 75.4% in A2(-) at stage I. HLA-A2(+) group at stage I showed the unfavorable prognosis significantly than A2(-) group both in overall survival (p<0.05) and DFI (p<0.05). The 5-year overall survival rate was 38.8% in A24(+) (n=181) and 56.8% in A24(-) (n=109) at stage II and III. Although there was no significant difference at stage I between HLA-A24(+) and HLA-A24(-) groups, HLA-A24(+) group at stage II and III showed poorer prognosis than HLA-A24(-) group in overall survival significantly (p=0.01).

Conclusions: Expression of HLA-A2 was considered as one of the unfavorable prognostic factors in NSCLC patients at stage I. HLA-A24(+) group also showed significant unfavorable prognosis at stage II and III. These results suggested that HLA-A2 and HLA-A24 were the prognostic factors in NSCLC patients.

Prognostic significance of p16INK4A, DAPK and RASSF1A promoter hypermethylation in non-small cell lung cancer (NSCLC)

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The epigenetic inactivation of tumor suppressor genes may play an important role in the development and progression of many cancer types, including lung cancer. Therefore, we investigated association of the aberrant promoter methylation of p16INK4A, DAPK ((Death-Associated Protein Kinase) and RASSF1A (Ras Association Domain Family 1A) genes (by methylation-specific PCR), with clinicopathological features and prognosis in 102 radically resected NSCLCs (62 stage I/II and 40 stage IIIa).

Hypermethylation of the p16INK4A, DAPK and RASSF1A promoters was found in 42 (41%), 38 (37%) and 29 (28%) of the tumor DNA samples, respectively. 23 tumors (22%) exhibited hypermethylation of all three tumor suppressor genes. Regarding different clinicopathological features of NSCLCs, there was a significant association between methylation of the genes and an advanced TNM stage (p=0.05 for p16INK4A, p=0.02 for DAPK, p=0.03 for RASSF1A, Fisher’s exact test), as well as between adenocarcinoma and squamous cell carcinoma for RASSF1A (p=0.04) and for p16INK4A (p=0.05) hypermethylation. Univariate analysis of survival (logrank test) demonstrated a significant trend of poorer prognosis for patients with methylated p16INK4A, DAPK, and RASSF1A genes. Multivariate analysis of survival (Cox proportional hazard model) indicated that p16INK4A and DAPK promoter hypermethylation was the stronger independent predictor factors for early stage I-II (p=0.04 and p=0.02), whereas RASSF1A promoter hypermethylation was the independent prognostic predictor for stage IIIa (p=0.04). In conclusion, hypermethylation of p16INK4A and DAPK genes is a common abnormality associated with poor survival and aggressiveness of early-stage NSCLC, whereas RASSF1A methylation is a profound prognostic factor for patients with locally advanced NSCLC.

Expression of cellular retinol binding protein-1 is associated with poor prognosis of stage I non-small cell lung cancer

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Background: Cellular retinol binding proteins act as carriers for retinol and influence the trafficking, metabolism, and storage of retinoids in the cytoplasm. Alteration of cellular retinol binding protein-1 (CRBP-I) expression in lung cancer is not known in terms of their association with lung carcinogenesis.