Ablerrant methylation of IL-12Rβ2 gene in lung cancer

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Background: Interleukin-12 receptor β (IL-12Rβ2) knock-out mice develop lung adenocarcinoma, and epigenetic silencing by CpG methylation leads to loss of this gene in B-cell malignancies. The aim of this study was to determine whether IL-12Rβ2 methylation is a common feature in human lung cancer.

Methods: We examined mRNA expression of IL-12Rβ2 in lung cancer cell lines, and normal bronchial, and tracheal epithelial cells using RT-PCR, and we examined the methylation status of IL-12Rβ2 in primary lung cancers.

Results: Loss of expression was found in 10 of 13 (77%) NSCLC cell lines, and 2 of 5 (40%) SCLC cell lines compared with normal bronchial or tracheal cells. Treatment of 11 expression-negative cell lines with a demethylating agent restored expression in all cases. Ablerrant methylation status of IL-12Rβ2 gene was reversely concordant with its mRNA expression. IL-12Rβ2 methylation was detected in 96 of 230 NSCLCs (42%) and 3 of 6 SCLCs (50%). IL-12Rβ2 methylation correlated with poorer prognosis in lung adenocarcinomas (hazard ratio = 2.33, p = 0.0059).

Conclusions: We conclude that epigenetic silencing of IL-12Rβ2 is a frequent event in lung cancers. Ablerrant methylation of this gene seems to be a useful predictor of long-term outcome for adenocarcinoma of the lung.

The role of gene mutations and amplifications involved in epidermal growth factor receptor pathways in non-small cell lung cancer

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Background: Activation of the epidermal growth factor receptor (EGFR) in cancer cells has been shown to promote processes involved in tumor cell proliferation, angiogenesis, invasion, and metastasis, and to inhibit apoptosis. The purpose of the present study is to verify the role of genetic alterations involved in the EGFR pathways in non-small cell lung cancer (NSCLC) development.

Methods: We analyzed mutations of the EGFR, KRAS and PIK3CA genes and amplification of the loci corresponding to those genes in primary tumors from 96 patients with NSCLC. Mutation analyses of EGFR (exon 19 and 21), KRAS (exon 2 and 3), and PIK3CA (exon 9 and 20) were performed by the PCR-direct sequencing method. Gene amplification analyses were performed by the fluorescent in situ hybridization method.

Results: EGFR, KRAS, and PIK3CA gene mutations were found in 22 (23%), 2 (2%), and 3 (3%) of 96 NSCLCs, respectively. The copy number gains of these genes were 26 (27%), 10 (10%), and 19 (20%) of them, respectively. On the whole, 55 (57%) of the 96 NSCLCs had one or the other gene alterations. The gene alterations were evenly found in cases with early stage disease as well as in those with advanced disease. It is suggested that these gene alterations play essential roles in the initial step of lung carcinogenesis. EGFR gene mutations were preferentially detected in females (34.1%, 14/41), non-smokers (50.0%, 14/28), and adenocarcinomas (35.1%, 20/57), with statistical significances (Chi-square test, P < 0.05), which confirmed previous observations. In contrast, PIK3CA gene amplification were preferentially detected in males (29.1%, 16/55), smokers (34.1%, 16/51), and squamous cell carcinomas (41.3%, 12/29) (Chi-square test, P < 0.05). It is suggested that certain carcinogens in the tobacco smoke might have caused PIK3CA gene amplification to promote squamous cell carcinoma development.

Conclusions: The pathway mediated through EGFR, KRAS and PIK3CA gene has critical role in the development of NSCLC. NSCLCs can be divided into specific molecular subsets according to the genetic alterations in this pathway.