LUNG CANCER SUSCEPTIBILITY

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Abstract: Substances in tobacco smoke and environment are risk factors for lung cancer. The project elucidates the mechanism between carcinogenic substances in tobacco/environment and genetic/epigenetic factors in lung cancer development. Sequence variations in genes involved in metabolism of carcinogens or DNA repair have been investigated to determine whether they could predict risk of lung cancer. GWA studies have provided evidence that common variations at 5p15.33, 6p21.33 and 15q25.1 influence lung cancer risk. We have recently shown that 4 SNPs in the 15q25 locus is associated with PAH-DNA adducts in normal lung tissue and TP 53 mutations in the tumor. The role of inflammation in lung carcinogenesis has become more evident, interleukins regulate the expression of several molecules and signaling pathways involved in inflammation. Our studies suggest an association between lung cancer risk and single nucleotide polymorphisms (SNPs) in the regulatory regions of IL1B, IL6 or IL8. We recently reported that SNPs in the regulatory region of the IL1B gene affected the mRNA levels by changing the binding affinity of transcription factors or by creating novel binding sites. IL1B-SNPs at -3893, -1464, -511 and -31 positions formed a specific risk haplotype (GGCT) with near complete linkage in the patients, but not in cancer-free controls. The risk haplotype (GGCT) was present in 65% of cases compared to 36% of controls and correlated with significantly higher IL1B mRNA levels in the lung of lung cancer patients. We further characterized the specific transcription factor binding to the IL1B -31 T/C polymorphism which is localized in the TATA box at the core promoter region. DNA-protein interaction analysis using EMSA and human lung cells lines evidenced that the transcription factor Yin Yang (YY1) bound preferentially to the C variation at -31. The binding of YY1 to the C SNP was further confirmed using ChiP assay and was found to affect the expression of IL1B. In order to get a better understanding of the regulation of the CYP1A1 gene in lung cancer, we studied CYP1A1 enhancer DNA methylation in normal lung and in adenocarcinomas. We found that in normal lung from lung cancer patients that smoking and age (pyrosequencing of bisulfite-DNA) affected CYP1A1 DNA methylation. We found inverse associations between methylation and CYP1A1 gene expression and DNA adducts in normal lung tissue and TP53 and K-ras mutations in tumor tissue (matched pair). We also found increased methylation in adenocarcinomas compared with normal lung, which is related to significantly reduced gene expression in the tumor. These results indicate overall that the CYP1A1 enhancer methylation may affect the initiation of lung carcinogenesis. Furthermore, our data indicate a role of epigenetic modification in the regulation of expression of key cytokines involved in inflammatory responses during lung cancer development.

Keywords: Lung cancer, susceptibility, inflammation, epigenetics, DNA adducts

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