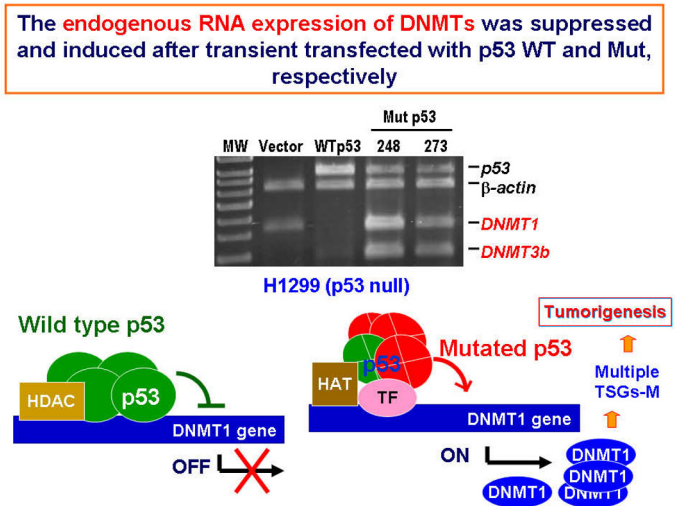
remains unclear. We performed DNMT1 promoter luciferase assay and found that wild type p53 could negatively regulate the DNMT1 promoter, whereas mutant p53 could activate DNMT1 promoter activity. The physical binding of wild type p53 and mutant p53 to DNMT1 promoters was identified by chromatin immunoprecipitation. These data suggest that deregulation of DNMTs is associated with the loss of transcriptional repression of p53. The p53 mutation results in overexpression of DNMT1 and hypermethyaltion of target tumor suppressor genes and ultimately leads to tumorigenesis.



C6-06 Cancer Genetics, Wed, 10:30 - 12:15

Gene expression signatures associated with lung adenocarcinomas in female non-smoker Chinese patients

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Female-non-smokers with lung adenocarcinomas is becoming prominent among Asian patients with lung cancer. The clinical parameters of gender, smoking habits, tumor histology, ethnic origin and EGFR mutation status were identified as predictors of clinical response to targeted therapy. The aim of this study was to identify the gene expression profiles of lung adenocarcinomas compared to normal lungs, with respect to gender difference, smoking habits and tumor EGFR mutation status among Hong Kong Chinese patients with lung adenocarcinomas. Total RNA extracted from 49 lung adenocarcinomas and 9 normal lung tissues and hybridized onto Affymetrix GeneChip HG-U133 Sets. Data were normalized and subjected to repeated iterations of unsupervised hierarchical clustering, with independent validation microarray data sets, for identification of stable sample clustering, followed by supervised analysis with Significance Analysis of Microarray (SAM) and Support Vector Machine (SVM) for identification of molecular classifiers with respect to sample clustering results. Unsupervised hierarchical clustering revealed stable clustering of adenocarcinomas vs normal lungs, female-non-smokers vs other tumors, and tumors bearing EGFR mutation at exons 18 - 21 vs wildtype tumors. Supervised analysis identified discriminatory gene classifiers that predict lung adenocarcinomas (gene classifiers = 27, prediction sensitivity and specificity of 100%), female non-smokers (gene classifiers = 22, prediction sensitivity of 65 - 85% and specificity of 84 - 94% with different independent validation sets) and EGFR mutation status (gene classifiers = 26, prediction sensitivity and specificity of 100%). Our data suggested that there is a group of Chinese female non-smokers with lung adenocarcinomas which displays gene expression profiles distinct from pulmonary adenocarcinomas from patients with other clinical characteristics. The identification of gene classifiers could provide information for further study on lung adenocarcinomas, female non-smokers with lung cancer and lung tumors bearing EGFR mutations.

C6-07 Cancer Genetics, Wed, 10:30 - 12:15

Mutations in the LKB1 tumor suppressor are frequently found in tumors from Caucasian NSCLC patients

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Background: Peutz-Jeghers syndrome has been associated with mutations in the LKB1 tumor suppressor gene. Somatic mutations of LKB1 gene have been found in human cancers including non-small cell lung cancer (NSCLC) with adenocarcinoma histology. Reports with small number of cell lines and tumors have suggested the prevalence of LKB1 mutations in NSCLC to be ~30%. Relation of LKB1 mutations to the patient gender, age, smoking history, tumor stage and outcome, and their relationship to other commonly mutated genes in NSCLC is unknown.

Methods: NSCLC tumor specimens (n = 167) with adenocarcinoma (n = 161) and adenosquamous carcinoma histologies (n = 6) were collected from surgical resections and RNA was extracted using routine methods. Some of the specimens (n = 63) were collected in Korea, while rest of the specimens (n = 104) came from Caucasian patients from the US. Tumors were screened for LKB1 mutations using the SURVEYOR-WAVE method. In SURVEYOR-WAVE method, the whole coding region of LKB1 gene was PCR amplified in two overlapping amplicons, PCR products were digested with SURVEYOR-enzyme which cleaves mismatches, and the specimens were analyzed with sensitive HPLC method for shorter digestion products. If digestion products were present, the specimen was sequenced using Sanger method to verify the mutation. Mutational analysis K-Ras, B-Raf, and EGFR hotpots were done either by SURVEYOR-WAVE method analogously to LKB1 gene analysis or by direct sequencing with Sanger method. Statistical comparisons were done using Fisher's exact test, p values < 0.05 were considered significant

Results: Mutations of the LKB1 gene were detected in twenty-two tumors (13%). Interestingly, twenty of the LKB1 mutations were detected in specimens collected in U.S. (prevalence 19%) while only two mutations (prevalence 3%) were detected in specimens from Asian origin (p = 0.004). The mutations were mainly deletions and insertions (82%) but some missense (9%), and nonsense (9%) mutations were also found. No correlation of LKB1 mutations to gender, age, or stage