C/CwB type adenocarcinomas cases revealed any microscopic metastasis. In 34 cases, Cells/F type adenocarcinomas revealed areas of tumor opacity on mediastinal window images of air-type and solid-type tumors. In 34 cases, Cells/F type adenocarcinomas revealed microscopic evidence of metastasis (pleural involvement, vascular invasion, lymphatic permeation, or lymphnode metastasis). Whereas, no C/CwB type adenocarcinomas cases revealed any microscopic metastasis. The prognosis of C/CwB after resection is better than for Cells/F.

Conclusion: We found that ‘Air-type’ adenocarcinomas demonstrated C/CwB type, and that ‘Solid-type’ adenocarcinomas demonstrated Cells/F type. We concluded that the histopathological findings of small pulmonary adenocarcinomas could be classified into two groups:

C/CwB type and Cells/F type. The prognosis of C/CwB is better than for Cells/F.

Aneusomy by FISH analysis and histology as predictors of invasive lung cancer in bronchial biopsies from high risk subjects


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Background: The development of Lung Carcinoma (LC) is accompanied by changes in histological and chromosomal abnormalities in the airway mucosa. Neither histological grade nor markers of chromosomal abnormalities in preneoplastic epithelial lesions have been adequately evaluated as predictors of invasive LC.

Methods: Histological dysplasia score and chromosomal aneusomy measured by FISH analysis were compared as correlates of invasive LC in a case-control study of 44 individuals with LC (cases) and 90 individuals without LC (controls). We used bronchial biopsy samples from subjects found by LIFE or white light bronchoscopy to have had moderate dysplasia (MD), severe dysplasia (SD) or carcinoma in situ (CIS). Tissue samples were reviewed by the study pathologist, the grades of preneoplastic change were verified and the appropriate areas in each histological slide were selected for FISH analysis. A 4-color FISH probe was used for aneusomy detection targeting centromere 6, 5p15.2, 7p12 (EGFR) and 8q24 (CMYC).

Results: The population included 104 males and 30 females with a mean age of 64 years and a mean smoking history of 62 pack-years. There was no difference in mean age, sex distribution or pack-years of smoking between LC cases and controls, but cases had a higher frequency of current smokers (p=0.05). Thirty two had CIS as the highest histological grade of mucosal abnormality, 48 had SD and 54 MD. The strongest correlate with invasive LC was CIS by histological examination (OR=12.5, 95% CI 4.1 to 38.1). Chromosomal aneusomy was seen in 64% of the LC cases but in only 31% of the controls. (OR = 4.6, 95% CI 2.0 to 10.9). The proportion of subjects with chromosomal aneusomy increased from moderate dysplasia (22.2%) to severe dysplasia (41.7%) and CIS lesions (71.9%) and showed a similar trend for cases and controls. Presence of aneusomy slightly increased the risk for LC in MD (OR=1.91, 95% CI 0.26 to 13.8) but was a substantial impacting factor in subjects with SD (OR=7.06, 95% CI 0.82 to 60.1) and CIS (OR=5.93, 95% CI 0.5 to 69.7).

Conclusion: CIS on histological examination and abnormal FISH analysis are both associated with lung cancer cross-sectionally. Future studies need to examine these biomarkers prospectively, and to assess their interaction in predicting lung cancer risk.

SCF protein (Skp2, CUL1) regulate the E2F1 dependent transcriptional activity and cyclin E in human lung tumors

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Background: The E2F1 transcription factor is a cell cycle oncogenic protein which plays ambiguous role in promoting proliferation or apoptosis depending on histological cell type of lung cancer (Salon et al, Cell Death and Differ, 2006). Accordingly, its activity is tightly controlled by transcriptional and post-transcriptional events in which the ubiquitin-proteasome pathway mediated by SCF complexes such as Skp2 and Culil 1 (CUL1) proteins play a role in its degradation. We have previously identified differential pattern of E2F1 protein expression in human lung cancer with high expression in high grade neuroendocrine tumors, in contrast with low or no expression in non small cell carcinoma and in carcinoids (small cell lung carcinoma and large cell neuroendocrine carcinoma) (Eymin et al. Oncogene 2001). In order to investigate the role of proteasomat degradation in E2F1 expression and activity we analyzed the components of SCF complex (Skp2 and Cul1) to understand their role on expression of E2F1 and its transcriptional targets cyclin E, important regulators of cell cycle at G1-S transition.

Methods: Using immunohistochemistry and immunoblotting we analyzed 128 lung tumors of all histological types for the relationship linking E2F1 and two components CUL1 and Skp2 of the ubiquitin-protein ligase SCFSkp2 <involved in E2F1 proteolysis and the consequence on cyclin E level expression.

Results: Skp2 protein was more often overexpressed in high grade neuroendocrine (HNGE) carcinoma (46/54; 86 %) than in NSCLC (16/50; 32 %) (p<0.0001), and undetectable in 25/25 carcinoids. Overexpression of E2F1 and Skp2 proteins were directly correlated in HGNE large cell neuroendocrine carcinoma (46/54; 86 %) than in NSCLC (16/50; 32 %) (p<0.0001) and nodal metastasis (p<0.0001). There was a significant correlation between Skp2 and Ki67 across histological types (p=0.01). No correlation was found between E2F1 and CUL1. In in vitro cellular models we provided evidence that Skp2 is a novel transcriptional target of E2F1. Skp2 interacts with E2F1 and stimulates its transcription activity toward the cyclin E promoter. Consistently, we found a correlation between Skp2 and cyclin E (p<0.0001) and between E2F1 and cyclin E in neuroendocrine lung tumors (p=0.0001). In contrast, CUL1