Correlative Assessment of Morphologic, Immunophenotypic, and Genetic Changes in Bronchial Epithelium of Tobacco Smokers*

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Detection of pulmonary malignancy often occurs late in the course of the disease. As a result, prognosis for lung cancer is poor. One reason for late detection is the inaccessibility of the bronchi for biopsy of tissue to study morphologic, biologic, and genetic properties of bronchial epithelium. A widely accepted paradigm for neoplastic development in the lungs holds that pulmonary carcinogenesis is the result of stepwise accretion of mutational events in bronchial epithelial progenitor cells and that widespread early genetic changes may occur in the tracheobronchial tree (“field effect”) before the onset of overt invasive carcinoma. If the important early mutational events in pulmonary carcinogenesis could be found, it should be possible to better identify patients at increased risk for lung cancer by genetic analysis of bronchial epithelium at a time when intervention may reduce the risk and lessen the mortality of this tumor. We have attempted to identify early bronchial lesions by sputum cytology screening of patients with a smoking history of more than 40 pack years and COPD. Patients with moderate or worse dysplasia then undergo laser-induced fluorescence emission (LIFE) bronchoscopy (Xillix, Inc.) and biopsy. Biopsies are studied by conventional histologic techniques and by immunohistochemistry for the expression Ki-67 and p53. Dysplastic cells are microdissected from biopsied sections and analyzed by polymerase chain reaction (PCR)-based techniques for loss of heterozygosity in chromosome 3p using a large number of primer sets for microsatellite repeats and for mutation of the p53 gene, exons 5-9, by single-strand conformation polymorphism using nested primers. We have studied 25 patients with bronchial epithelial dysplasia of varying severity by these methods. We have observed frequent increases in the vascularity of metaplastic and dysplastic submucosa, sometimes with papillary vascular epithelial projections into the bronchial lumina. Increased expression of Ki-67 was observed in all dysplasias; p53 expression was found in patients with severe dysplasia. Loss of heterozygosity (LOH) at 3p was documented in a narrow region at 3p13-14 in 4 of 6 cases in which adequate material was available for microdissection. p53 mutation was not observed in any of the 6 microdissected biopsies. We conclude that bronchial squamous dysplasia is a frequent finding in patients with a long smoking history, that this histologic change is accompanied by LOH at 3p and increased cell turnover (as reflected by increased Ki-67 expression), and that these latter changes frequently occur before overexpression or mutation of p53 is detectable.

Chrysotile Asbestos Induces PDGF-A Chain-Dependent Proliferation in Human and Rat Lung Fibroblasts In Vitro*

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Inhalation of asbestos in a rat model results in the predominant deposition of fibers onto alveolar duct bifurcations, where a fibrotic lesion develops. The lesion that remains 1 month following a single exposure is primarily composed of increased numbers and volume of mesenchymal cells and macrophages. Mesenchymal cell number and volume is increased by 25% and 40%, respectively. We now know that lesions persist for at least 6 months following a series of 3-h exposures on 3 consecutive days. The mechanisms driving lung mesenchymal cell proliferation in response to inhaled asbestos fibers is under investigation in our laboratory.

Although investigators have proposed that polypeptide mediators secreted by stimulated alveolar macrophages, such as platelet-derived growth factor (PDGF), are responsible for the mesenchymal cell proliferation following asbestos inhalation, this hypothesis has not yet been proved. It also is unclear why nonfibrogenic particles, which stimulate macrophage growth factor release in vitro, do not result in fibrosis following in vivo exposure. We have observed that fibrogenic asbestos fibers are translocated into the interstiti*

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