Cellular and molecular changes during carcinogenesis, 
with special reference to a model of 
xenotransplanted human respiratory epithelium. 
A.J.P. Klein-Szanto, Fox Chase Cancer Center, 
Philadelphia, PA 19111, USA

Lung carcinogenesis is a complex and multistage process in which 
several genes participate in a probably additive fashion. Among the most 
important ones the following oncogenes and tumor suppressor genes seem 
to play important roles: K-ras, neu, myc, jun, p53, and Rb. In our laboratory 
and in collaboration with C.C. Harris of the Laboratory of Human 
Carcinogenesis, NCI, we have shown, using the tracheal xenograft model, 
that human bronchial epithelial cells containing ras oncogenes acquire 
invasive and metastatic abilities that correlate well with the increased 
expression and activity of type IV collagenase. We have also observed that 
many non-small cell carcinoma cell lines characterized by an advanced 
invasive-metastatic phenotype have mutations in the tumor suppressor 
gene p53. These alterations in p53 were also seen in fifty percent of 
primary non-small cell lung cancers studied and were especially prevalent in 
advanced stage tumors. Recently, using the xenograft system that consists 
in growing immortalized non-tumorigenic human bronchial epithelial cells 
(BEAS-2B cells) in deepithelialized rat tracheas, subcutaneously 
transplanted into athymic nude mice, we exposed BEAS-2B cells to either 
cigarette smoke condensate (CSC) or to the tobacco specific nitrosamine 4-
(methyl nitrosamine)-1-(3 pyridyl)-1-butanone (NNK). After 5 to 6 months 
the transplants develop tumors that were identified as invasive 
adencarcinomas. Invasiveness, similar to that seen after exposure to 
phorbol esters, was also detected after in vitro exposure of BEAS-2B cells 
to CSC. Cell lines obtained from xenografts exposed in vivo to chemicals 
exhibited several features typical of malignant lung cancer cells, such as 
increased in vivo invasiveness that correlated well with enhanced type IV 
collagenolytic activity, resistance to serum induced growth inhibition and 
increased expression of transforming growth factor alpha and its receptor. 
Collectively, these data indicate that CSC, and to a lesser extent, NNK, are 
able to induce in vivo phenotypic changes in BEAS-2B cells that are 
equivalent to the progressive changes that take place during human lung 
carcinogenesis.