Preclinical Research in Early Lung Cancer: Breakout Group Report

M. Mabry, T. W. Moody, and S. B. Baylin

Cancer Biology Division, The Johns Hopkins Oncology Center, Baltimore, Maryland 21231 [M. M., S. B. B.] and Department of Biochemistry and Molecular Biology, The George Washington University Medical Center, Washington, DC 20037 [T. W. M.]

The Preclinical Research breakout group committee met on April 24, 1991 in Annapolis, Maryland to discuss basic research investigational strategies relevant to detection and intervention in early lung cancer. The committee discussed high priority research approaches to study the development of lung cancer. The recommendations based on these discussions are summarized below.

Emphasis upon Studies of Bronchial Epithelial Cell Differentiation

Emphasis should be placed on the study of models of normal differentiation of lung epithelia to determine: (a) how diverse cell types which constitute the normal bronchial epithelium interact; (b) the identities of normal differentiation processes which are altered following transformation; (c) the correlation of gene expression events (for tumor suppressor genes, growth factors, and receptors, etc.) with normal differentiation events during bronchial epithelial renewal; (d) how normal differentiation patterns are reflected in, and altered in, transformed bronchial epithelial cells and how these parameters influence the biological behavior of lung cancer cells. Such studies will be essential for the identification of the best biochemical markers for early detection of lung cancer. Potential markers for non-small cell lung cancer initiated cells include hypermethylated DNA, and structural alterations of genes and chromosomes such as p53, K-ras, and chromosome 3p. Potential markers for small cell lung cancer initiated cells include hypermethylated DNA and alterations of the p53 and retinoblastoma genes, chromosome 3p, and neuroendocrine markers such as bombesin/gastrin releasing peptide.

A significant bottleneck to the above line of research is the lack of relevant model systems. Despite significant advances, within a few research groups, for establishing primary bronchial epithelial culture systems and immortalization of bronchial epithelial cells, such model systems are not being widely exploited. The provision of required human cell lines has been retarded by lack of access to primary human lung tissues for explant culture. The committee recommends establishment of either centralized human primary bronchial cell systems or a cooperative primary tissue procurement program, perhaps in association with organ transplant programs.

Establish Patterns of Genetic Alterations of Lung Cancer

The committee felt that, despite the description of large numbers of genetic abnormalities in lung cancer, there is little knowledge about the functional consequences of these lesions in established human cancers and which changes reflect the earliest events during bronchial epithelial cell transformation. There is a need to delineate, as has been emerging for colon cancer, some temporal "order" to the occurrence of specific genetic changes during the progression of lung cancer. The committee recommends the genetic characterization of precursor lesions in lung cancer. A key element of such research must be availability of well characterized, early pulmonary lesions for the study of DNA. Consideration should be given to establishing tissue repositories at key centers for this purpose. The development of panels of human tumors and linked precursor lesions from clinically well characterized patients is recommended. These would be used to study genetic lesions which have already been described in lung cancers and new ones which undoubtedly will emerge and to trace these lesions back from individual tumors to precursor lesions in individual patients.

Validation of Animal Models

A number of potentially valuable animal systems for lung cancer have been established. These animal models should be used to elucidate the role of certain tobacco-related nitrosamines such as 4-(methyleneimino)1-butanone and N-nitrosodiethylamine in carcinogenesis. Also, the effect of chemopreventive agents such as retinoic acid, β-carotene, and phenylhexylisothiocyanate should be investigated. These animal models offer the possibility of in-depth characterization of early steps in the formation of lung cancer. However, the precise relationships between each model and the steps for the human disease have not been established. For example, little is known concerning similarities or differences between the genetic alterations found in the animal models versus those in human lung cancer. Also, several potential models for understanding the role of bronchial endocrine cells in lung cancer exist, but their relationship to small cell lung cancer and stages of human lung cancer, are still in question.

The committee recommends that efforts be focussed upon existing animal model systems to establish how the stages of initiation, promotion and progression relate to human lung cancer. Particular attention should be given to determining the genetic alterations in these models, especially in the precursor lesions and early stages of carcinogenesis. The models for endocrine cell hyperplasia should be studied to determine whether this cell plays an early role in development of human lung cancer. Potential biochemical markers for early stages of human lung cancer should also be studied in the experimental animal systems. For all of these efforts collaboration between those developing animal models and molecular biologists interested in human lung cancer should be encouraged.

Establish Whether Growth Factor and Signal Transduction Pathways Act as Promoters for Lung Cancer

Factors which modulate the growth and differentiation of normal and neoplastic bronchial epithelial cells may act as promoters during the formation of lung cancer. These include bombesin/gastrin releasing peptide, insulin-like growth factor 1, and transferrin for small cell lung cancer and transforming
growth factor α/epidermal growth factor and insulin-like growth factor 1 for non-small cell lung cancer. Receptors for these growth factors and the signal transduction pathways through which they function could be intimately involved. These pathways, in turn, offer potential targets for the early intervention treatment for lung cancer. Much remains to be learned about which steps in tumor promotion occur via growth factor modulation steps. Establishment of appropriate models and the analysis of appropriate tissues to determine the roles of growth factors, growth factor receptors, and other molecules could be a primary step in the development of cohesive strategies of chemoprevention.
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