Introduction

The papers in these proceedings were selected from a conference entitled, "Innovations in the Multimodality Therapy of Lung Cancer," held in Denver, Colorado, April 3 to 4, 1992. The conference was jointly sponsored by the University of Colorado Cancer Center, the Lung Cancer Institute of Colorado, The Rocky Mountain Oncology Society, the Metro Denver Oncology Nursing Society, and the CME office of the University of Colorado School of Medicine. The goals of the conference were to bring together all disciplines involved in the study and management of lung cancer, including basic scientists, pathologists, social scientists, pulmonologists, thoracic surgeons, radiation oncologists, medical oncologists, nurses, and other professionals. Topics included molecular genetics of lung cancer, risk factors and primary prevention, pathogenesis and biology, early detection, chemoprevention, and treatment of all disease stages, including combined-modality therapy, supportive therapy, and quality-of-life issues.

The organizers of this conference believe that the optimal diagnosis, prevention, and treatment of lung cancer in the 1990s requires close interactions between the disciplines described above. It is also believed that the scientific advances described in these proceedings will lead to decreased lung cancer mortality and to improved survival and cure rates in the next decade.

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Overview of Genetic and Molecular Events in the Pathogenesis of Lung Cancer*

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Research on dominant oncogenes and tumor suppressor genes has characterized differences in genetic lesions between small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC) and identified associations with clinical parameters. More than one half of all lung cancers contain a mutation of the p53 tumor suppressor gene. There does not appear to be an association between the presence of this mutation and survival. A ras family oncogene was found to be mutated in approximately 20 percent of tumors and tumor cell lines from patients with NSCLC in contrast to none of 45 tumors and tumor cell lines from patients with SCLC. The presence of a K-ras mutation was determined to be an adverse prognostic factor for survival in retrospective studies of patients with NSCLC. Mutations of K-ras are more common in tumors from smokers than nonsmokers and have not been detected in lung cancers resulting from occupational exposure to radon. Mutations in the p53 gene and K-ras oncogene are most commonly G to T transitions in lung cancer vs G to A transitions in other cancers. Prospective studies of these mutations in resected tumor specimens taken from patients with accurate follow-up may continue to provide important clues about their potential clinical and biologic significance.

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The characterization of genetic abnormalities in lung cancer cell lines and tumors has been extensive. This article will review recent published data on tumor cell lines and tumors from patients with lung cancer where initial clinical and follow-up information has been compiled. In particular, it will focus on both a tumor suppressor gene (p53) and a dominant oncogene (K-ras) that provide clinical insight into the biology of lung cancer, its histologic classification, and patient outcome.

p53 Gene Mutations In Lung Cancer

Mutations of the p53 gene are currently the most common genetic alteration identified in human cancers. The p53 gene is a tumor-suppressor gene that normally codes for a nuclear phosphoprotein that binds to the large T antigen of the DNA tumor virus, simian virus 40 (SV40), to form an oligomeric complex. The large T antigen of SV40 is needed to maintain a transformed or malignant phenotype in cell culture. Normal p53 negatively regulates cell growth and division, whereas mutated forms can stimulate cell division. The p53 mutations may therefore function to promote growth of cancer cells.

Recent research has focused on abnormalities of the p53 tumor suppressor gene in tumors and tumor cell lines from patients with non–small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The p53 mutations occur throughout the entire length of the gene, although they tend to occur more commonly within the regions that bind the large T antigen.** The p53 mutations have been found in 100 percent of 25 established cell lines from patients with...
SCLC, as well as in 27 of 35 SCLC tumor specimens (77 percent). Some p53 gene abnormalities have also been reported in 57 of 77 tumor cell lines (74 percent) and 27 of 55 tumor specimens (49 percent) from patients with NSCLC. There are no obvious associations between p53 mutations in NSCLC and a patient's smoking history, gender, histologic subtype, tumor stage, or duration of survival.

The p53 nucleotide mutations in lung cancers tend to differ from those in other cancers that are not as tightly linked to cigarette smoking. The former mutations are most commonly a G to T transversion (change from a purine to a pyrimidine), whereas the latter are typically a G to A transition.

The p53 gene has recently been studied in 19 patients with lung cancer who had been exposed to radon, another environmental agent associated with the development of lung cancer, while working underground as miners. Tumor specimen studies revealed p53 mutations in 7 of 19 patients (37 percent). None of these mutations were the G to T transversions commonly seen in lung cancer, probably because the genetic lesions in these tumors were associated with a different environmental pathogen (radon) than the lesions typically found in patients who develop lung cancer after chronic cigarette smoking.

K-ras Oncogene Mutations in Lung Cancer

K-ras (also known as K-ras-2) is one of three human ras oncogenes (K-ras, H-ras, and N-ras) that code for 188 or 189 amino acid proteins with a molecular weight of 21,000. The ras proteins normally bind guanine nucleotides (guanosine triphosphate or diphosphate), have guanosine triphosphatase activity, and play a role in the transduction of signals across cellular membranes, thereby regulating cellular proliferation. Mutations of the ras proteins, which most commonly occur at the 12th, 13th, or 61st amino acid, contribute to the development of cancer. A ras oncogene is mutated in approximately 20 percent of NSCLC tumors and 30 percent of NSCLC cell lines. In contrast, none of 45 SCLC tumors or tumor cell lines studied had such mutations. The ras mutations are found in up to 30 percent of patients with adenocarcinoma of the lung vs 4 percent and 10 percent of patients with squamous cell and large cell lung carcinomas, respectively. In NSCLC, mutations of K-ras are most frequent, accounting for 90 percent of such mutations identified in adenocarcinomas of the lung. In contrast to p53 mutations, which can occur throughout the length of the gene, 85 percent of K-ras mutations in adenocarcinomas of the lung occur at the 12th codon (normally CTT, which codes for glycine). Mutations are most commonly the result of a G to T transversion in the first two bases. The resulting mutant codons, TGT and GTT, represent approximately 70 percent of the mutations identified at the 12th codon of the K-ras oncogene and code for cysteine and valine, respectively.

K-ras Mutations in Smokers, Nonsmokers, and Patients With Occupational Exposure to Radon

K-ras oncogene mutations found in lung cancers of smokers are different from those found in lung cancers of nonsmokers and patients who have had occupational exposure to radon. A retrospective study of adenocarcinomas of the lung found K-ras mutations occurred more frequently in smokers (eight of 27) than in nonsmokers (two of 27, p = 0.044). In addition, one of the two mutations found in the nonsmokers was unusual in that the mutant 12th codon CGT, which codes for arginine, resulted from a G to C transversion rather than the more common G to T transversion seen in the tumors of smokers. The G to C transversion is most commonly found in pancreatic adenocarcinomas.

K-ras mutations in the lung cancers of 19 uranium miners who had been occupationally exposed to radon have been analyzed. While 18 of these 19 patients were also cigarette smokers, none had tumors with a K-ras codon 12 or 13 mutation. Thus, it appears that patients with different risk factors for lung cancer have distinct patterns of K-ras mutations in their tumors.

In contrast to lung cancer, K-ras oncogene mutations in gastrointestinal (GI) malignancies, specifically colon and pancreatic cancer, do not typically have G to T transversions in the first position of the 12th codon. Gastrointestinal cancers, however, are not as strongly correlated with smoking as is lung cancer. Thus, despite a similar histologic appearance (adenocarcinoma) and mutation of the same oncogene (K-ras), the pattern of K-ras mutations in lung cancer differs from that found in GI malignancies. This difference may relate to the degree of association with smoking and the mutagenic properties of tobacco smoke.

Clinical Outcomes of Patients With NSCLC and K-ras Mutations

Two retrospective studies have associated identification of K-ras mutations in NSCLC tumors and tumor cell lines with shortened survival. In the first, Slebos et al found 19 K-ras codon-12 mutations in 69 tumors from patients with early-stage adenocarcinoma of the lung (45 stage I, 14 stage II, and seven stage IIIA), in whom surgical resection was performed with curative intent. Patients with tumor mutations lived a significantly shorter period of time than those without mutations (median actuarial survival, two years and four years, respectively, p = 0.002).

Mitsudomi et al studied the K-ras oncogene in tumor cell lines from 66 patients with NSCLC, most of whom had advanced-stage disease. Twenty-one had stage I, II, or IIIA disease treated with surgical resection (19) or chest irradiation (2), and 45 had stage IIIB or IV disease treated with chemotherapy, palliative radiotherapy, or supportive treatment. Eleven of 66 (17 percent) tumor cell lines from these patients had mutations in the 12th codon of the K-ras oncogene. Those who had this specific mutation lived a shorter time than those who did not (p = 0.03). Subset analysis of the 21 patients with stages I, II, and IIIA NSCLC, a group similar to the patients in the Slebos et al study, also revealed an association between K-ras mutations in tumor cell lines and shortened survival (p = 0.005). Therefore, K-ras oncogene mutation appears to be an adverse prognostic factor for patients with both early and late stages of NSCLC. However, in contrast to the Slebos et al study, patient survival in this study was measured from the time tissue was obtained for cell culture rather than from the time of diagnosis. Prospective studies will need to be performed to confirm these retrospective findings.

Pathogenesis of Lung Cancer (Johnson, Kelley)
CONCLUSION

The studies of p53 and K-ras have provided important clinical insights into the biology of lung cancer. Although over one half of all patients with lung cancer have mutation of the p53 tumor suppressor gene in their tumor specimen, there has been no association identified between the presence of a p53 mutation and survival. In contrast, a ras family oncogene is mutated in approximately 20 percent of tumors and tumor cell lines from patients with NSCLC and the presence of a K-ras mutation is an adverse prognostic factor for survival in two different retrospective studies of patients with NSCLC. Prospective studies of these and other genes in tumors from resected specimens taken from patients with accurate follow-up may continue to provide important clues about the potential clinical and biologic significance of these genetic abnormalities.

REFERENCES