Importance of Chromosome 9p Loss in Human Lung Cancer

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The race to determine the genetic steps in the progression of lung cancer has recently intensified, in large part because of the launch of new translational multidisciplinary initiatives by the U.S. National Cancer Institute known as SPORE (Specialized Projects of Oncology Research Excellence) grants. Thus, the molecular genetics of an often-ignored major killer, lung cancer, are now being unraveled by several groups. In this issue of the Journal, a pioneering group in lung cancer genetics (1) describes loss of chromosome 9p in preneoplastic lesions in patients with non–small-cell lung cancer. Initially described as a rare event in preliminary allelotypes (2), chromosome 9p loss now represents the most common genetic change in non–small-cell lung cancer and in many other types of human neoplasms.

Deletions of chromosome 9p21 originally identified a putative tumor suppressor gene locus in leukemia (3). Moreover, genetic linkage studies demonstrated that the familial melanoma locus also resided on chromosome 9p21 (4). Subsequent studies in primary tumors and cell lines began to reveal the presence of deletions, including homozygous deletions at chromosome 9p21 in various tumor types such as those of the lung (5-7), head and neck (8), bladder (9), and many others. These studies began to demonstrate that 9p loss was among the most common genetic events yet described in human cancer.

The finding of chromosome 9p21 loss in preneoplastic lesions and lung cancer now extends and confirms these observations. Previously, 9p loss was found to be an early event in the initiation and progression of bladder cancer and head and neck cancer (8,9). Thus, lung cancer is now added to the list of neoplasms in which 9p loss occurs in the earliest detectable lesions. Moreover, recent evidence suggests that the frequencies of 9p loss in lung cancer are probably underestimated because many of the deletions are actually quite small (<500 kilobases) (10). As many as one third of the hemizygous and homozygous deletions in this region would not extend to the two markers tested in the study by Kishimoto et al. (7) (D9S171 and interferon alfa [IFNA]). Even with this slight limitation, Kishimoto et al. firmly establish the role of 9p loss in lung cancer progression and its occurrence early in apparently benign, preinvasive lesions.

On the basis of a derivation of Knudson's hypothesis, chromosome loss represents one step in the inactivation of tumor suppressor genes. Thus, the identification and characterization of the critical suppressor gene on 9p21 have been high priorities in many laboratories. As mapping studies continued on chromosome 9p21, p16 was identified and characterized as a potent cyclin/CDK inhibitor involved in the G1/S transition of the cell cycle (11). Kamb et al. (12) identified p16 within the deleted region in several hundred cell lines derived from a broad range of human cancers. Although only a few of these lines contained inactivating mutations within the p16 gene, these investigators found that p16 was homozygously deleted in a majority of these cell lines.

Parallel studies in primary tumors revealed a similar paucity of point mutations in p16 (13). Although only a small percentage of sporadic tumors were found to harbor point mutations, patients with familial melanoma were found to harbor germline mutations of p16 (14). The absence of point mutations in many tumor types pointed to an alternative mechanism of p16 inactivation. We have found that homozygous deletions are present in many of these tumor types (10). Moreover, p16 is often included within these homozygous deletions in a substantial number of primary tumors, including non–small-cell lung cancers. Furthermore, methylation of a 5' CpG island leading to transcriptional inactivation also appears to be a common mechanism of p16 inactivation in cell lines and primary human tumors (15).

In small-cell lung cancer, however, homozygous deletions and methylation of p16 are rare despite a high frequency of loss at 9p21 (10). Although a second tumor suppressor gene locus very close to p16 cannot be ruled out, it is probable that p16 is at least one of the major targets in this region for most neoplasms with loss of chromosome 9p. This notion has been strengthened by complementary functional studies demonstrating suppression of growth after introduction of normal wild-type (WT) p16 into cells with inactivated p16 (16,17).

Kishimoto et al. (7) also describe multiple preneoplastic lesions, geographically and morphologically distinct in the same patient, that harbor the identical chromosome 9p loss seen in the invasive tumor. They refer to this as allele-specific loss and speculate that an unknown mechanism may lead to preferential loss of one allele in tumors from these patients. This group has also described a similar pattern of 3p loss in the same preneoplastic lesions of the lung (18). Indeed, some preference for allelic loss based on parental origin has been seen in various tumor suppressor genes (19-22). Investigators have described preferential gene mutations in the paternal allele with preferred loss of the second maternal (WT) allele in inherited syndromes. These preferential losses, however, are not absolute and do not approach the 100% concordance seen in these lesions. Moreover, the mechanism for preferential loss in these inherited cancer syndromes has not been elucidated.

Although Kishimoto et al. (7) discount the possibility of clonality (i.e., many of these apparently distinct lesions arising

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