A New Tumor Suppressor Gene, Selective for Lung Cancer

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The search for genes that modulate susceptibility to carcinogenesis continues to be an active and important area of research. Several years ago, Cheng and Lotan cloned a novel human gene, designated as "retinoic acid-inducible gene 1" (RAIG1) (1). The deduced RAIG1 protein sequence contained seven transmembrane domains, characteristic of G protein–coupled receptors. The ligand for this putative receptor was not identified at the time, and, indeed, this remains the case, although there has been continuing interest in RAIG1 (subsequently renamed "G protein–coupled receptor family C group 5 member A," GPRC5A) as well as several other related G protein–coupled receptors. In the original report of the cloning of GPRC5A, it was shown that by far the greatest expression of this gene occurred in human lung (among more than a dozen human tissues examined), and, moreover, the important observation was made that GPRC5A mRNA was expressed at only very low levels in human lung cancer cells (three of five head and neck squamous cell carcinoma and four of six non–small cell lung cancer cell lines). The authors hypothesized that this decrease in mRNA expression might be associated with the malignant transformation of airway epithelium. The article by Tao et al. (2) in the current issue of the Journal now provides excellent, detailed experimental evidence for this hypothesis. The key experimental tool in this article has been the use of mice (B6/129sv) in which the Gprc5a gene has been knocked out by homologous recombination.

The Lotan group is not the first to have used knockout technology to study the biology of Gprc5a in the mouse lung. Thus, in an elegant study, Xu et al. (3) used classical recombinant technology to show that Gprc5a is expressed abundantly and specifically in the lung during embryonic development and in adult mice. These authors found that the onset of Gprc5a expression in the embryonic mouse lung coincided with the onset of differentiation in the lung, and they suggested that this gene plays an important role in lung maturation and differentiation. The loss of such a differentiating function during carcinogenesis is in accord with classical concepts of cancer as a disease of differentiation (4,5). However, most notably, the lungs of 3-month-old Gprc5a −/− mice appeared histologically normal in spite of the fact that this gene is expressed at high levels in Gprc5a +/+ mice of this age, in both type I and type II pneumocytes. The reason for this lack of phenotype at 3 months of age is unclear, but the authors suggest that the expression of a related gene that regulates G protein signaling (Raig3, also known as Gprc5c) may compensate for the loss of Gprc5a. Thus, perhaps it would be necessary to lose the function of both Gprc5a and Gprc5c to elicit a lung cancer phenotype in young adult mice; to date, this apparently has yet to be done.

To carry this line of investigation even further, Lotan and colleagues have now made an important contribution to this entire story. They have kept homozygous Gprc5a knockout mice for as long as 2 years, and they now report that between 1 and 2 years of age, such −/− mice developed many more lung tumors than heterozygous or wild-type mice. Thus, only 10% of 51 wild-type mice developed lung tumors (a total of five tumors, all of which were benign adenomas), whereas in 41 Gprc5a −/− mice, they found 31 benign lung tumors and seven adenocarcinomas. These data are a striking reminder that age is one of the most critical risk factors for the development of cancer. They are also a striking reminder that it may require dysfunction of multiple genes to elicit the malignant phenotype; presumably such mutations occur with advancing age, either from exogenous or endogenous carcinogenic agents.

Another way to enhance carcinogenesis at an earlier age in these Gprc5a −/− mice would be to treat them with a chemical carcinogen, whether it be a polycyclic hydrocarbon or a tobacco-derived nitrosamine (such as NNK) (6), or even by using a simple carcinogen, such as vinyl carbamate (7). All of these agents have been shown to be highly effective carcinogens in A/J mice, which carry a K-Ras mutation and may spontaneously develop pulmonary adenomas at an advanced age, but rarely develop carcinomas in the absence of further genetic insult (8).

Given that in most cases, human carcinogenesis involves multigene damage, perhaps it is preferable to use mouse models that involve multigene damage. One can start with transgenic mice that have a defined genetic abnormality and then superimpose further damage with the use of either chemical or radiation carcinogens or the use of promoting inflammatory agents, which in turn generate further genetic damage (9). The present mouse model developed by Tao et al. (2) provides an additional excellent system for further elucidation of the multifactorial nature of carcinogenesis as well as for further testing of new chemopreventive agents that are highly effective in the lung (10). For the most effective and relevant evaluation of such agents in this new system, it would be highly desirable to add further carcinogenic insult, whether it be genetic or epigenetic. Mechanistically, the authors also comment on the possibility that activation of noncanonical Wnt signaling by Gprc5a may be involved in their observations. Given the importance of Gprc5a in both the human and mouse lung, one can expect that new advances will be forthcoming.

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