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OVERVIEW

Genetic Alterations as Intermediate Biomarkers

The importance of genetic alterations in tumor development has been clearly demonstrated by the identification of specific genes—oncogenes and tumor suppressor genes—that causally contribute to the carcinogenic process. In principle, the identification of these genes should allow them to be utilized as markers of tumorigenesis and potentially exploited as biomarkers in chemoprevention studies. In addition, many tumors undergo characteristic changes in patterns of gene expression, which also may provide molecular markers of tumor development.

As discussed by G. Cooper, oncogenes are mutated or abnormally expressed versions of cellular genes that act to drive unregulated cell proliferation. They are activated in tumors by point mutations, DNA rearrangements, and DNA amplification. Their potential utility as tumor markers in chemoprevention trials is dependent on several factors, including the ease and sensitivity with which activated oncogenes can be detected, the reproducibility of oncogene activation in individual tumors of any particular type, and the stage of tumor development at which oncogene activation occurs. The *ras* oncogenes may provide the most plausible early detection markers at present, since they are frequently activated at early stages of the development of a variety of tumors and can be readily detected in small numbers of cells.

The development of colon carcinomas provides the best available illustration of the combined roles of oncogenes and tumor suppressor genes in tumor development. An overview of this multistep process which involves the activation of the *ras*K oncogene combined with the inactivation of several tumor suppressor genes (by deletion or mutation) during the adenoma-carcinoma sequence is presented by K. Cho. The tumor suppressor genes involved in these carcinomas include p53, DCC, MCC, and APC. Mutations of *ras*, APC, and MCC are most frequently found early in tumor development, and inherited mutations of APC have also been found in patients with familial adenomatous polyposis. In contrast, mutations of p53 and DCC usually occur later, in association with the progression of adenomas to malignant carcinomas. However, the order of genetic alterations is not invariant, and it appears that the overall accumulation of genetic damage is more important than the order in which these mutations occur. The complexity of genetic changes in these tumors poses a problem in terms of using these genes as biomarkers, since no single genetic alteration is necessarily associated with a given stage of carcinogenesis.

On a larger scale, alterations in the amount of cellular DNA have been identified in colonic tissue at risk for the development of cancer. Identification of aneuploidy, or an abnormal number of chromosomes per cell, was discussed by D. Ahnen. Aneuploid cell populations have been demonstrated in both adenomatous polyps and malignant colon tissue. In addition, aneuploid cells occur in normal-appearing and dysplastic mucosa of high risk individuals, such as ulcerative colitis patients. Those patients who have undergone colectomy frequently harbor multiple areas of aneuploidy throughout the remainder of the colon. Thus, aneuploidy may serve as a marker of cancer risk, although further investigation is necessary.

An alternative approach used by L. Augenlicht involves more global studies of changes in gene expression. Using computer analysis of hybridization to a reference cDNA library, it has been possible to generate a database comparing expression of a large number of genes in normal colon mucosa, adenomas, and carcinomas. Interestingly, several genes are abnormally expressed in normal colon mucosa from patients with familial adenomatous polyposis or hereditary nonpolyposis colon cancer, suggesting that abnormalities in expression of these genes may be very early markers of tumor development. One such gene has been identified as the mitochon-

drial gene encoding a subunit of cytochrome oxidase, and expression of this gene has been found to be modulated in a chemoprevention trial in which hereditary nonpolyposis colon carcinoma patients were given dietary calcium. The expression of this and other genes may thus provide useful markers for assessing the activity of agents that modulate colon cancer risk.

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