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Histology

COMMENTARY

Viral Interactions With the p53 Gene in Human Cancer: NCI Workshop

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Cancer is a multistep process that is usually preceded by the accumulation of mutations in an assortment of genes. Until recently, the tumorigenic mutations that have been studied in detail are those that activate oncogenes. The discovery of antioncogenes, or tumor suppressor genes, by which inactivating mutations elicit tumorigenesis, has added a new dimension to the understanding of neoplasia. The retinoblastoma susceptibility gene (RB) is the prototype tumor suppressor gene and has been shown to suppress the transformed phenotype for several different cancers. The p53 gene is a growth-control gene that plays a key role in the suppression of abnormal cell proliferation and tumor development. Mutations in the p53 tumor suppressor gene are the most common genetic alterations associated with human cancers. They occur with high frequency in almost all cancers studied, including those of the breast, cervix, colon, liver, lung, and prostate (*1-5*). Until recently, however, little was known about the normal functions of p53. Although p53 was originally thought to be an oncogene, it is now considered to be a tumor suppressor gene in its normal form. Wild-type p53 negatively regulates cell growth and division, but some mutant forms of p53 gain the ability to stimulate cell division. It is perhaps because of the gain-of-function mutations, which can act in the heterozygous state, that p53 mutations are so common in human cancers. The normal physiological role of p53 appears to be in the regulation of the cell cycle. The p53 protein is phosphorylated in a cell cycle-dependent pattern by cdc2 kinase, reaching maximal levels of phosphorylation during mitosis (*6*). The p53 protein may regulate cell growth by regulating the initiation of DNA replication or by acting as a transactivator of transcription (directly or indirectly), either by stimulation of growth inhibitory genes or by repression of growth stimulatory genes. p53 has also been implicated in playing a role in programmed cell death, or apoptosis (*7*). Three different DNA tumor viruses (simian virus 40, adenovirus, and papillomavirus) produce oncogene products that target p53, eliminate its activity as a transcription factor, and initiate transformation.

To review and assess the recent advances in p53 research and to suggest future areas of research emphasis, the Biological Carcinogenesis Branch, Division of Cancer Etiology (DCE), National Cancer Institute (NCI), Bethesda, Md., sponsored a workshop on December 18, 1992, to address viral interactions with p53 in human cancer. The workshop chair was Webster Cavenee (Ludwig Institute for Cancer Research, San Diego, Calif.), a member of the DCE Board of Scientific Counselors. The co-chair was Carol Prives (Columbia University, New York).

David Livingston (Dana-Farber Cancer Institute, Boston, Mass.) presented an overview of the functional analysis of the RB gene product and related proteins. The RB gene is the prototype tumor suppressor gene and is an important regulator of cell proliferation. Functional inactivation of this gene is typically linked to the appearance of a neoplastic phenotype in vivo. Cells of several common epithelial tumors (e.g., breast, bladder, prostate, and small-cell lung cancer) often lose RB function (*8*). Several lines of evidence suggest that the RB gene product acts to constrain growth in normal cells and that its loss permits the unconstrained growth characteristic of cancer cells. Three DNA tumor viral proteins—simian virus 40 (SV40) large T antigen, adenovirus E1A, and the human papillomavirus (HPV) E7 protein—have been shown to associate with RB and to modulate its growth-suppressive function (*9-11*). There is a discrete RB domain, termed the "pocket," which is the prime interaction site for these viral proteins, and, from the results of various genetic analyses, the functional integrity of this domain is essential to the maintenance of RB growth suppression action. RB also uses this pocket to bind a series of cellular proteins, such as the E2F transcription factor (*12,13*). Viral oncoproteins may be structural mimics of these cellular proteins, thereby preempting interaction of RB with its normal cellular partners. In his presentation, Livingston described the functional consequences of RB–

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See "Notes" section following "References."