Parallel Symposium No. 9

Transgenic Mice as Tools for the Analysis of Multistage Carcinogenesis

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PS 9.1

IDENTIFICATION OF SYNERGIZING ONCOGENES IN TRANSGENIC MICE

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Mice bearing oncogenes as transgenes can contribute to our insight into transformation processes *in vivo*. These mice can serve as a starting point to search for oncogenes that synergize with the transgene in tumorigenesis. One approach entails the use of non-acute transforming retroviruses to act as insertional mutagens, thereby activating proto-oncogenes or inactivating tumor suppressor genes, while at the same time tagging these genes to allow subsequent identification. We have concentrated on the *pim*-1 oncogene, which was detected as a provirally activated gene in MuLV-induced T-cell lymphomas in mice. We have studied the role of *pim*-1, both in normal development by inactivating the endogenous *pim*-1 allele via homologous recombination in ES cells, and in lymphomagenesis by overexpressing the gene in transgenic mice. Genes that efficiently synergize with *pim*-1 in both B and T cell lymphomagenesis were identified. The nature of these genes will be discussed.

PS 9.2

Gene targeting in embryonal stem cells and its application to the study of carcinogenesis. M.L.Hooper, CRC Laboratories, Department of Pathology, University of Edinburgh.

Mouse embryonal stem (ES) cells, established in tissue culture from preimplantation embryos, retain the ability to contribute to somatic and germ cell lineages of chimaeras produced by injecting the cells into blastocysts. This makes possible an approach in which genetic modifications are introduced into the cultured cells by the techniques of somatic cell genetics, and thence via chimaeras into the mouse germ line. Mutations can be introduced into chosen genes by gene targeting, a technique in which exogenous DNA constructs introduced into cells by electroporation or microinjection undergo recombination with the endogenous gene. The application of this approach to problems in carcinogenesis will be discussed.

PS 9.3

TRANSGENIC MICE AS TOOLS FOR THE ANALYSIS OF BONE TUMORIGENESIS AND VASCULAR DISEASES

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We have been introducing growth control genes into mouse embryos and stem cells to study their causal role in oncogenesis. Data will be presented on the function of *c-fos/c-jun* in mesenchymal cell differentiation and in the development of bone tumors using transgenic mice and ES cell chimeras. I will also discuss the role of de-regulated tyrosine kinase activity exerted through overexpression of various middle T oncogenes. The specific effect of middle T on the proteolytic activity in endothelial cells and a possible mechanism for the development of hemangiomas will be discussed.

PS 9.4

EPSTEIN-BARR VIRUS LATENT GENE INDUCED NEOPLASIA IN TRANSGENIC MICE. Joanna B. Wilson, Glasgow University, Glasgow G11 5JS, U.K.

The latent membrane protein (LMP1) of Epstein-Barr Virus (EBV) is detectably expressed in many nasopharyngeal carcinomas (NPC) and in the effected tongue epithelium of patients suffering from the EBV and HIV associated syndrome oral hairy leukoplakia (OHL). In order to address the role of this protein in the EBV associated epithelial disorders, the LMP1 has been expressed in the epidermis of transgenic mice. In two lines of mice (with different transgene integration sites), expression of the LMP1 caused epidermal hyperplasia. Terminal differentiation appeared to be inhibited in these cell layers and growth induced, as evidenced by the aberrant expression of a hyperproliferative cytokeratin. This phenotypic condition is reminiscent of that observed in the tongue epithelium of OHL sufferers, as well as representing a preneoplastic state, implicating the LMP1 as factorial in both OHL and NPC. Expression of the LMP1 in other tissues in transgenic mice results in a chronic inflammatory infiltrate, which at high levels is ultimately lethal. This observation may reflect the ability of the LMP1 to induce the expression of adhesion molecules (crucial in the recruitment of leukocytes), which is presently being investigated.