Inhalation Cancer Bioassays of Benzene in Tg.AC and p53+-/- Mice

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Human cancer models developed in transgenic mice are being proposed for use as short-term carcinogenicity bioassays. Two transgenic mouse tumor models, one carrying an activated form of the ras oncogene (Tg.AC v-Ha-ras) and another with an inactivated copy of the p53 tumor suppressor gene (p53 heterozygous “knockout” mice: p53+-/- mice) are being proposed as alternatives to traditional 2-year rodent bioassays. This project assessed the use of Tg.AC and p53+-/- mice as short-term cancer models using a prototype genotoxic carcinogen, benzene. An accelerated incidence of thymic lymphomas occurred in greater than 80% of p53+-/- mice exposed to 100 ppm benzene for 34 weeks compared to 4% incidence in p53+/+ mice. A high incidence (> 90%) of these thymic lymphomas showed loss of the functional p53 allele, loss of heterozygosity at multiple chromosome 11 microsatellite markers, and the retention of two copies of the disrupted p53 allele. These data indicate that benzene-induced thymic lymphomas are due to genetic recombination at chromosome 11 likely mediated by benzene-induced DNA strand breaks. The overall hypothesis of these studies is that benzene-induced thymic lymphomas are initiated in the bone marrow stem cells by DNA strand break induced aberrant recombination resulting in genomic instability and accelerated tumor development during T-cell maturation in the thymus. Gene expression profiles in the bone marrow from p53+/+ and p53+-/- mice exposed to benzene for 15 weeks were determined to identify early response biomarkers associated with tumor development in the p53+-/- mouse model. This research focused on expression of genes that are part of the p53-mediated DNA damage response pathways involved in cell cycle arrest (p21, gadd45, and cyclin G) and apoptosis (bax, bcl-2) and in the regulation of p53 itself. Gene expression was assessed by quantitative RT-PCR methods.

Collaborative Effort: These studies were part of a collaborative effort between scientists at the NIEHS and CIIT examining short-term cancer bioassay models.


Presentation(s):


This abstract was prepared by the principal investigator for the project. Please see www.USLRI.org for more information about the LRI.


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Dean, S. W., Brooks, T. M., Burlinson, B., Mirtsalis, J., Myhr, B., Recio, L., and Thybaud, V. (1999). Transgenic mouse mutation assay systems can play an important role in regulatory

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