971 CHROMOSOME 11 ALLELOTYPES REFLECT A MECHANISM OF CHEMICAL CARCINOGENESIS IN HETEROZYGOUS P53-DEFICIENT MICE.

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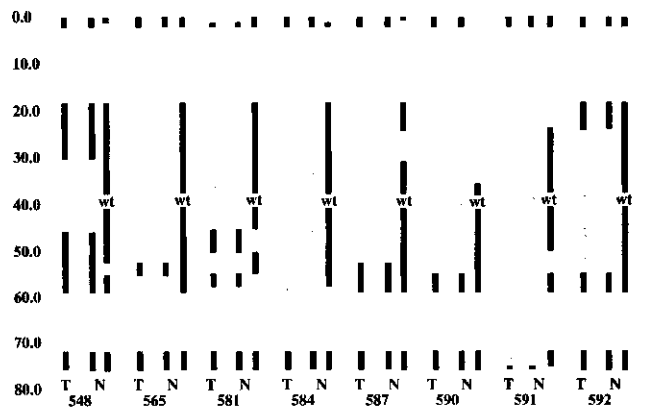
p53 (+/-) mice were administered three well-characterized carcinogens to learn more about mechanisms of carcinogenesis and to evaluate the p53-deficient mouse as a tool for identifying potential human carcinogens. Benzene-induced sarcomas, p-cresidine-induced bladder carcinomas and phenolphthalein-induced thymic lymphomas were allelotyped at the Trp53 locus and chromosome 11 simple sequence length polymorphic (SSLP) loci. Loss of Trp53 and loss of one chromosome 11 occurred in each of ten lymphomas and eight sarcomas examined. Loss of Trp53 and loss of heterozygosity (LOH) at SSLP loci were sporadic in the bladder carcinomas. However, loss of one copy of chromosome 11 was implicated in 3 of the bladder tumors where LOH occurred at 7 or more widely dispersed SSLP loci. Loss of one copy of chromosome 11 likely occurred through a p53-mediated selection process since Trp53 is located on mouse chromosome 11. The data suggest that loss occurred through a mechanism common among the three tumor types. Allelotype patterns were inconsistent with those expected from the p53(-/-)C57BL/6 (N4) X inbred C57BL/6 cross which produced the study animals. However, comparison with control tissues still allowed deduction of maternal chromosome loss. The unexpected allelotype patterns observed in normal tissues might be due to mitotic homologous recombination during embryogenesis.



972 IMMATURE RAT MAMMARY EPITHELIAL CELLS (RMECS) ARE MORE SUSCEPTIBLE THAN MATURE RMECS TO THE CYTOLETHAL, CARCINOGENIC, AND MUTAGENIC EFFECTS OF N-NITROSO-N-METHYLUREA.

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Epidemiological studies indicate an inverse relationship between age at exposure to ionizing radiation and a woman's subsequent breast cancer risk. A similar phenomenon exists in rats; immature rat mammary epithelial cells (RMECs) are more susceptible to the cytolethal effects of ionizing radiation than mature RMECs. These studies were undertaken to further explore the age-differential susceptibilities of RMECs. The age-differential survival was found through limiting dilution in vivo transplantation assays to extend to the alkylating agent N-nitroso-N-methylurea (NMU) but not to dimethylbenz(a)anthracene (DMBA). Immature RMECs were also more susceptible than mature RMECs to the carcinogenic effects of NMU; 80% of immature, *versus* 56% of mature rats, developed mammary carcinomas following 50 mg/kg (i.v.) NMU. Additionally, immature rats developed 2.3 carcinomas per rat, while mature rats developed 1.0 carcinoma per rat. Using lacI transgenic Big Blue (Stratagene) rats, it was found that immature RMECs treated with NMU harbor greater levels of persistent mutations (1, 3, and 5 weeks post-treatment) than RMECs treated when mature. The single cell gel electrophoresis (comet) assay was utilized to examine RMECs immediately and shortly following NMU treatment *in vitro*. While there were no differences immediately following NMU treatment, immature – but not mature – RMECs displayed increased single strand DNA breaks beginning two hours post-NMU. This increase, which is not due to apoptosis, can be reproduced in mature RMECs by pretreatment with the methylguanine methyltransferase inhibitor O6-benzylguanine. Such pretreatment does not alter the immature RMEC response, suggesting age-related differences in DNA repair. Therefore, immature RMECs are more susceptible than mature RMECs to the cytolethal, carcinogenic, and mutagenic effects of NMU.

973 TRANSCRIPT PROFILE DIFFERENCES BETWEEN HEPATOCARCINOGEN-SENSITIVE AND -RESISTANT STRAINS AS A BASIS FOR UNDERSTANDING MECHANISMS OF CHEMICAL-INDUCTION OF MOUSE LIVER TUMORS.

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Human carcinogen risk is commonly assessed in the B6C3F1 mouse strain, a cross between the hepatocarcinogen-resistant C57Bl/6J (B6) strain and the hepatocarcinogen-susceptible C3H/HeJ strain (C3H). The molecular basis of the susceptibility of C3H mice is not known; however, a number of hepatocarcinogen sensitivity (hcs) loci have been mapped but not identified. We hypothesize that these loci affect the expression of genes whose products play important roles in DNA repair and hepatocyte growth control. Analysis of hepatic transcript profiles comparing B6 to C3H using the Clontech Atlas mouse 1.2-II array (covering a total of approximately 1200 genes) showed 2-fold or greater differences in approximately 8% of the genes assayed. Approximately 88% of the altered genes showed increased expression in the C3H mice while the other 12% were repressed. Several of these genes are involved in the control of apoptosis and/or cellular proliferation. To determine the role of these genes in hepatocarcinogenesis, we are initiating studies to survey their expression in mouse liver tumors induced by chemicals that fall into different mode of action classes. Preliminary studies with tumors induced by WY-14,643, a peroxisome proliferator (PP), revealed significantly altered expression of PP-activated receptor γ and interferon γ-signaling pathway genes compared to surrounding (non-cancerous) and control (untreated) tissue. Definition of differences at the gene expression level in resistant *versus* susceptible mouse strains and how these differences are manifested when exposed to a chemical carcinogen will lead to a better understanding of the mechanisms of hepatocarcinogenesis in mice. This knowledge will help to determine the relevance of the mouse liver tumor response in human risk assessments.

974 ARSENIC-INDUCED GENE EXPRESSION IN URINARY BLADDER EPITHELIUM.

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Occupational and environmental exposure to arsenic has been related by epidemiological studies to development of skin and urinary bladder cancer. Although the mechanisms of arsenic carcinogenesis have not been defined, increasing evidence indicates the role of epigenetic mechanisms, including modulation of signaling pathways of cell growth. We demonstrated that arsenic exposure is associated with tissue accumulation of inorganic, and to lesser extent dimethylarsenic acid, as well as a persistent increase in DNA binding of the activating protein (AP)-1 transcription factor. The arsenic accumulation in urinary bladder tissue and AP-1 activation demonstrated dose-dependence and strong correlation. That was supported also by recovery studies. Arsenic levels as well as AP-1 binding started to decrease significantly after 8 weeks of recovery period. Consistent with the in vivo data, arsenic induced sustained MAP kinase and AP-1 activation in uroepithelial cell line. Arsenic-triggered epidermal growth factor receptor phosphorylation was involved but it was not initiation event of MAP kinase cascade. Gene expression studies using cDNA microarays, RNase protection assay, and reverse transcription - PCR indicated that arsenic alters the expression of a number of genes associated with cell growth, such as c-fos, c-jun, and EGR-1, as well as cell arrest, such as GADD153 and GADD45. Arsenic - induced gene expression might contribute to carcinogenesis in urinary bladder by dysregulation of the cell cycle events.

975 SPECIFIC SOMATIC MUTATIONS IN RENAL AND URINARY TRACT TUMOURS OF PATIENTS WITH LONG-TERM HIGH DOSE TRICHLOROETHYLENE (TRI) EXPOSURE.

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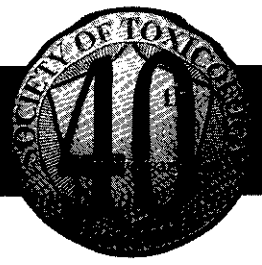
Recent epidemiological studies show that high dose occupational exposure to TRI is associated with an increase risk of Renal Cell Cancer(RCC). RCC develops as a consequence of somatic mutations of the von Hippel-Lindau(VHL)tumour sup-



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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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