Symposium no. 6

Environmental Carcinogens and Relevance to Humans

6.001

O^6-alkylguanine-DNA-alkyltransferase activity in relation to the pro-mutagenic methylation damage in bladder DNA from humans predisposed to bladder cancer associated with schistosomiasis.

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O^6-alkylguanine-DNA-alkyltransferase (ATase) activity was measured in 55 bladder tissues of Egyptian patients with schistosomal bladder carcinoma (46 tumour and 9 uninvolved tissue). Alkylation damage (O^6-methylguanine; O^6-MeG) was detected in DNA from 46 of those samples (38 tumour and 8 uninvolved). ATase activity varied from 2.0 to 16.2 fmole O^6-MeG removed/µg DNA (mean+/-SD, 5.8+/-3.9) or based on tissue protein content it ranged from 27.8 to 350.7 fmole O^6-MeG removed (mean+/-SD; 117.1+/-71.4). Levels of O^6-MeG from 0.012 to 0.485 µmole/mole deoxyguanosine (dG) were detected in 44/46 samples (mean+/-SD; 0.134+/-0.10). A correlation was obtained between the level of methylation damage and ATase activity ($r=-0.62$; $p<0.001$). Higher ATase activity was observed in tumour tissue vs uninvolved ($p<0.001$). These observations implicate environmental alkylating agents in the etiology of early bladder cancer associated with schistosomiasis and the relatively low level of DNA repair suggests that the bladder is a tissue of high susceptibility to these agents.

6.002

POTENTIATION BY CAFFEINE AND ETHANOL OF TOBACCO SMOKE-GENOTOXICITY IN VIVO IN MICE

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Five times a week (90min/day) treatment of male mice BDF1 (C57BlxDBA2) with tobacco smoke (TS, 600ml/14L glass chambre) caused up to 2.0 fold increase of dead implants frequency in virgin females mated with TS-treated males. The simultaneous treatment with caffeine (500 ppm) or with ethanol (1.5%) in drinking water potentiated the TS-induced dominant lethal mutations in mouse spermatogonia stem cells. We established also a 2.6 fold potentiation by caffeine of TS-clastogen activity in bone marrow of mele and female mice. Ethanol supplementation to the drinking water did not influence micronucleus formation in bone marrow of TS-treated mice. Probably, caffeine and ethanol consumption could play an important role in the TS-genotoxicity in vivo in both somatic and germ cells in mice.

6.003

IN VIVO MODULATION OF COLONIC EPITHELIAL CELLS METABOLISM BY FECAL BUTYRIC ACID.

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Increasing content of a well defined fiber(bran)in AIN-76 rat diet,results in different amount of fecal short chain fatty acids. We show the existence of an inverse correlation only between the concentration of butyric acid and cells labelling index(L/N: ^{3}H-Thymidine-DNA pulse labelled cells L; cell number N) in total colon crypt epithelial cells and its 5 different proliferative compartments. A mathematical analysis shows that variability and complexity in our experimental data accounts only for about 47% of the trend observed.Permeability of colon cells to fecal butyric acid explains the linear correlation between their level of histone acetylation and fecal butyric acid concentration.This agent inhibits histone deacetylases,leaves acetylases unaffected,therefore playing a role in modulating genes primary structure(nucleosomal). We conclude that variation of amount of fiber in the diet,and consequently fecal transit time and butyric acid,is likely to modulate considerably the proliferative capacity of colon crypt epithelial cells,leaving their localization and state of differentiation unchanged.

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6.004

STUDY OF ADDUCTS AND MUTATIONS BY 4-NQO ON SSDNA: CORRELATION BETWEEN THE C8 GUANINE ADDUCT AND G TO PYR TRANSVERSIONS.

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4-nitroquinoline-1-oxide (4-NQO) is a base substitution mutagen which acts at guanine residues. 4-NQO in vivo and its ultimate model metabolite, acetoxy-4-hydroxyaminoquinoline-1-oxide (Ac-4-HAQO), interacting with dsDNA in vitro, form the same spectrum of adducts. Reacting Ac-4-HAQO with ssDNA in vitro we obtained a 20 fold enrichment in the dGuo-C8-AQO/dGuo-N2-AQO adducts ratio. Sequencing of mutant phage DNAs prepared after transfection of damaged DNA in E.coli revealed a 25 fold increase in G->Pyr/G->A ratio. We propose a correlation between specific guanine adducts and specific mutations, and two models to explain how dGuo-C8-AQO would generate such a type of mutations. P.C. has a fellowship from AIRC. Work partially supported by AIRC and EEC.

6.005

ALTERATIONS OF CHOLESTEROL METABOLISM IN LUNG CANCER PATIENTS

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The cholesterol content of tumor tissues and the lipid composition of the blood plasma compartment were investigated in patients affected by different histological types of lung cancer. Tumor lung tissues contained 2-fold more total cholesterol and 5-fold more esterified cholesterol than the normal tissue. The alterations in intracellular cholesterol were associated with peculiar changes of cholesterol distribution also in the plasma compartment. HDL-cholesterol levels were strongly reduced in all patients and in particular we observed a specific decrease of the HDL_3 subfraction We suggest that the decrease of HDL-cholesterol may be the consequence of a greater utilization and storage of cholesterol esters occurring in tumor lung tissues.

6.006

PLASMA LIPOPROTEIN PATTERN IN CHILDREN WITH MALIGNANCIES UNDERGOING CHEMOTHERAPY.

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Previous studies in our laboratories have shown that alterations in plasma cholesterol, mainly consisting in a decrease of HDL-cholesterol, in different experimental models of normal and neoplastic cell proliferation develop and also occur in some neoplasias in both animal and humans. The plasma lipoprotein pattern was investigated in children affected by different neoplastic diseases (leukemia and solid tumors) before any drug treatment and after remission of the disease following chemotherapy. The aim was to study the existence of any possible correlation between alterations in plasma lipoprotein and the rate of cell proliferation in children with malignancies. The level of HDL-cholesterol, strongly reduced before chemotherapy, increased during the remission of the disease.