Symposium no. 8

Cancer Risk Assessment

8.001

Oxidative stress in mitochondria induced by AAF and its relation to promoting activity in liver

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Chronic feeding of AAF causes a cirrhotic-like, multi-nodular transformation of rat liver after 8-12 weeks. Oval cells appear in the oxygen rich regions. They envelop increasingly peri-portal areas. At that time enzyme altered foci start to grow exponentially.
Investigations with isolated mitochondria support a new hypothesis: N-OH-AF mediates redox cycling at the inner mitochondrial membrane. This cycle is driven by the proton gradient across the membrane and O_2^- is formed. GSSG increases in mitochondria. GSSG can form mixed disulfides with protein SH-groups and CoA. Disturbance of intramitochondrial SH-group homeostasis and depletion of CoA as a cosubstrate in citrate cycle together with formation of reactive oxygen radicals cause diminished ATP synthesis and mitochondrial damage.
The described cytotoxic effects might be indirectly responsible for the increased growth of initiated hepatocytes.

8.002

MODULATION OF GENOME FUNCTIONS AND FREQUENCY OF RAT LIVER TUMORS INDUCED BY *N*-NITROSODIETHYLAMINE

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N-Nitrosodiethylamine (DEN, 80 mg/kg, i.p., once per week for 8 weeks) induced liver tumors in 90-100% of BD6 rats after 6 months. 5-Azacytidine (5 mg/kg, i.p.), a modulator of physiological DNA methylation, increased more than 2-fold ($p<0.05$) the number of tumors. Hydroxyurea (100 mg/kg, i.p.) and 5-bromodeoxyuridine (100 mg/kg, i.p.), potent inhibitors of DNA repair, had no significant influence on hepatocarcinogenesis. Nicotinamide (1.0 g/kg, i.p.), which favours DNA repair, produced a significant ($p<0.05$) anticarcinogenic effect. Out of 3 methylxanthines, acting as potent inhibitors of phosphodiesterase activity, only caffeine (600 mg/l, in the drinking water) reduced DEN hepatocarcinogenesis to a significant extent ($p<0.05$), whereas both theophylline (600 mg/l) and 2-isobutyl-3-methylxanthine (25 mg/kg, i.p.) were ineffective. L-isoproterenol (100 mg/kg, i.p.), an inducer of adenylate cyclase, was also devoid of effect on liver carcinogenesis.

8.003

CHROMATIN CHANGES RELATING WITH CARCINOGENESIS

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The nuclear matrix and the chromatin can be regarded as two interpenetrating networks, whose dynamic interaction may be involved in the activation of new cellular programs. For example, during apoptosis chromatin condenses extensively, the digestion by endogenous nucleases representing a late event. In this report we show that in rat liver carcinogenesis chromatin undergoes a large rearrangement during the emergence of persistent nodules; this process is concomitant with a sharp increase in the expression of a 39 kDa cytokeratin. In the electron microscope nucleosomal clusters appear collapsed around the nucleolus or clumped onto the nuclear lamina. The differential scanning calorimetry of isolated nuclei shows that the regular packing of the core particles, which characterizes chromatin in the normal tissue, is lost. Our results suggest that the latest steps in the nodule-to-cancer sequence are characterized by a catastrophic structural transition of chromatin, which might be modulated by alterations in the architecture and protein composition of the nucleoskeleton.

8.004

Occupational Exposure to Environmental Pollutants of Patients with Bronchial Carcinoma

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It is known that smoking is the most important risk factor for bronchial carcinoma. In addition, occupational exposure to a multitude of toxic, carcinogenic, and mutagenic compounds also favours the development of malignant tumors.
Ninety percent of the 190 patients with bronchial carcinoma included in this study were current or former smokers. 53 patients (28 %) had been exposed to occupational noxae. Clinical manifestation of bronchial carcinoma in this group was generally earlier than in patients without additional exposure to environmental pollutants.
Differentiation according to histological criteria revealed that comparatively the highest portion of patients with a history of occupational exposure was present in the groups of small cell carcinoma, large cell carcinoma, and adenosquamous carcinoma.

8.005

CYTOGENETIC STUDY IN AN ITALIAN POPULATION OF FLORICULTURISTS.

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A large part of the specialized cultivation of flowers in Italy is located in the Imperia province. The effect of occupational exposure to pesticides on the frequency of micronuclei in peripheral lymphocytes was evaluated in a population of floriculturists working in this area. Before the cytogenetic study an epidemiological survey including questions about personal data, habits, working activities, pesticides contact was made. Among thirthy different kinds of formulations belonging mainly to the chemical classes of carbamates, dithiocarbamates, and organophosphates, were used mainly in the greenhouses. A high proportion (50%) of the population has been working in floriculture for at least 20 years.
Preliminary results indicate an increment of micronuclei frequency in exposed subjects in relation to a population of floriculturists.

8.006

Are we facing increased risk of cancer at the devastated environment of heavily industrialized region of Silesia, Poland ?

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The heavily industrialized region of Silesia belongs to the most devastated region in the world. Air, water, and soil are polluted with the immence variety of organic and inorganic compounds. Airborne particulate matter was partly analyzed by Sequential Elution Solvent Chromatography (SESC) and GC-MS methods. Within polycyclic aromatic hydrocarbons a number of cancerogenic compounds was found. The total organic extract of airborne particulate matter and its SESC fractions revealed extremely high mutagenic activity in Salmonella typhimurium test. Extracts induced micronuclei and chromosomal aberrations, affected mitosis leading to mitotic arrest, exibited sister chromatic! exchange (SCE) inducing potency, and show transforming activity in chinese hamster cell line. Inhabitants of the polluted region have elevated level of DNA-adducts in WBC of peripheral blood as compared to country side controls. The geographical distribution of standardized indices of mortality on malignant neoplasia showed high parallelism to the pollution maps of the devastated region.