CHROMOSOMAL ABNORMALITIES IN MALIGNANT PLEURAL MESOTHELIOMA

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Cytogenetic study was made of cells acquired from 32 patients (27 pretreatment) with malignant mesothelioma. The cells were obtained from fresh tumour fragments and/or from pleural effusions. Chromosome analysis was performed after various culture times by using normal G-banding technique. Metaphases were obtained from 28 mesotheliomas. In 17 specimens clonal abnormality was seen. Karyotype findings were complex and heterogenous. Correlations between cytogenetic results and clinical parameters are under investigation.

EFFECT OF AN ANTI-GAG AGENT KL-103 ON TUMOUR CELL MEMBRANES AND MICROINVASIVENESS

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KL-103, an alkylpyrimidine derivative, was shown to prevent metastatisation of highly metastatic Lewis lung tumour in vivo. Recent studies demonstrated that these cells are characterissd by high heparan sulphate biosynthesis, high sialy lation of glycoproteins and high expression of MHC antigens. Cytochemical studies demonstrated increased net negative surface charges on KL-103 treated tumour cells. There was no change in ConA binding, but an almost total disappearance of RCA-binding and MHC expression could be detected on the surface of in vitro treated cells. KL-103 was able to prevent the incorporation of radioactive precursors into GAG components and decrease the heparan sulphate/chondroitin sulphate ratio. In parallel, an immunoreactive GAG disappeared from the cell surface. As a result of these complex membrane alterations, the treated tumour cells lost their microinvasive capacity against fibroblasts in vitro. Upon KL-103 treatment there is no significant change in cell proliferation, so the anti-invasive effect of the drug is the result of the altered tumour cell surface glycoconjugate compositions (especially glycosaminoglycan).

ENDOMETIRIAL AND OVARIAN CANCER FOLLOW-UP WITH CA125 EIA MONOCLONAL

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CA125 was measured with a solid phase enzyme immunoassay based on the sandwich method (Abbott EIA CA125 Monoclonal) in a total of 39 gynaecological malignancies (17 ovarian, 13 endometrial, 9 cervical). The estimated cut-off (mean+2DS) was 27 U/ml (180 controls). Cervical carcinoma revealed elevated levels, in advanced and widespread lesions particularly, and a subsequent decrease to normal range in 2 months from surgical treatment, and an elevation subsequently in presence of relapse. Endometrial cancer showed elevated levels in stages III and IV. The data described were similar to those observed in the same patients with RIA, confirming the importance of serial determination of CA125 in the follow up of ovarian and endometrial cancer. We should stress that it is important to repeat the determinations, always, if it is possible, in the same laboratory, with the same method, for a correct clinical interpretation of the levels to be obtained.

HYDRAZINES AND DIAZONIUM IONS OF MUSHROOM ORIGIN AND CANCER

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We have undertaken a series of investigations with five nitrogen-nitrogen bond containing chemicals found in the cultivated mushroom of commerce Agaricus bisporus. In the carcino-genesis area, it was found that the N' - acetyl derivative of 4-hydroxymethylphenylhydrazine (HMPH), the salts of 4-(hydroxymethyl)benzenediazonium ion (HMBD), the hydrochloride salt of p-hydrazinobenzoic acid (HBA), β-N-[δ-L-(+)-glutamyl]-4-carboxyphenylhydrazine (GCPH) and the uncooked mushroom itself induced a variety of cancers in mice. Of the five compounds, the presence of HBA and GCPH in the mushroom was established by us. In biochemistry, various carcinogenic arylhydrazines of mushroom origin were shown to be readily metabolized in vitro by cytochrome P-450 and prostaglandin (H) synthase enzyme systems while the

non-carcinogenic agaritine was poorly converted. HMBD also reacted with adenine in vitro forming an unexpected adduct.

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ORAL TOBACCO USE AND THE POTENTIAL ENDOGENOUS FORMATION OF TOBACCO SPECIFIC NITROSAMINES UNDER SIMULATED GASTRIC CONDITIONS

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The exogenous exposure to tobacco specific nitrosamines (TSNAs), N-nitrosoanabasine (NAB), N-nitrosoanatabine (NAT), N-nitrosonornicotine (NNN) and 4-(methyl- nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in tobacco products is well documented. The potential endogenous formation of TSNAs from a variety of chewing tobaccos, oral snuffs, masheri and zarda samples was determined by extraction of tobacco samples with artificial saliva followed by incubation of extracts for 1 hr at 37° C and pH 2.0 under conditions simulating the normal fasting stomach with a constant 25µM nitrite concentration. Under the simulated gastric conditions, formation of NNN, NAB and NAT occurred. Nicotine, the major alkaloid present in tobacco and precursor to NNN and NNK was not nitrosated. The formation of NNN resulted from nitrosation of nornicotine, another alkaloid present in tobacco. Under the simulated gastric conditions, slight decomposition of NNK was observed.

The implications of the results from the model gastric nitrosations yielding NAB, NAT and NNN from various tobacco products and the additional potential exposure to TSNAs formed under in vivo conditions are being evaluated.

CYTOTOXICITY OF IL-2 ACTIVATED KILLER CELLS (LAK CELLS) AGAINST AUTOLOGOUS AND ALLOGENEIC INVASIVE BLADDER CANCER CELLS IN VITRO

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The ability of recombinant Interleukin-2 (RIL-2) activated peripheral blood cells (LAK cells) to kill autologous invasive bladder cancer cells and to kill cells from an established bladder cancer cell line, T24, was investigated.

Autologous tumour cell cultures were obtained from primary cultures derived from biopsies of transiotinal cell carcinomas. The outgrowing cells were harvested after 5 days of cultivation by trypsination (0.05%).

LAK cells were induced by incubating the peripheral blood cells (PBL) from the same patients with 50 Units/ml of RIL-2 for 3 to 6 days. PBL incubated without RIL-2 served as controls. The cytotoxic effect of the lymphocytes was evaluated by an 18 hr chromium release assay with a target:effector cell ratio of 1:50. The median tumour cell lysis induced with RIL-2 activatd PBLs was 20% for the autologous tumour cells and 35% for the T24 cells. The median lysis with the controls 4% and 6%.

EFFECTS OF NEIGHBOURING SEQUENCES ON THE SENSITIVITY OF GUANINE TO ALKYLATION LESIONS

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An important step in carcinogenesis is thought to be the initial attack on the DNA molecule by the ultimate carcinogen. An interesting class of carcinogens/mutagens are alkylating agents. It has been shown that alkylation of DNA and especially alkylation at the position O^6 of the guanine produces lesions that are associated with mutations (G- A) and neoplastic transformation. It was interesting to see if some guanines are more sensitive than others, to the mutagenic action of alkylating agents and the role of neighbouring sequences in the production of mutations.

In vitro alkylation was performed ona fragment of pBR 322 (fragment BamHI-SalI, 275 bp) containing the tetracycline resistance gene. The fragment was modified to various extents by MNU and was reinserted into the non-reacted large fragment. After transformation of E.Coli, mutants were selected for ampicillin resistance and tetracycline sensitivity. The mutants were analysed for sequence changes in the 275 bp fragment by the dideoxy method. Results, in terms of mutation distribution and neighbouring sequence effects, hae been obtained.

ESTRADIOL INDUCED PEROXIDASE ACTIVITY AS A MARKER OF HORMONE DEPENDENT HUMAN BREAST CANCER

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