THE USE OF ORGANOMERCURIAL COMPOUNDS IN THE TREATMENT OF TRANSPLANTABLE RENAL ADENOCANCER.

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Nephrotoxic mercury chloride has been shown to produce tumour destruction in renal adenocancer (RC) which was associated with severe toxicity. Organomercurials (OM) were studied in the same RC model after establishing the lethal dose (LD) of phenylmercury (PM) in groups of 10 tumour-free Balb/c mice treated for 10 days with 2-10 mg/kg. Treatment of RC-bearing animals (tumour takes: 100%) was started at day 21 for 10 days. With increasing PM, a therapeutic activity (TA) of 25% was achieved (groups received 0,0.2,0.4,0.6,1.0 and 1.2 mgPM/kg). Loss of animals was however high in the group receiving 1.2 mg/kg (LD75). Low dose PM (0.6 mg/kg) was tested in combination with other cytotoxic compounds (cycloleucin, CL; ceruleinin, CR; hydrea, HD) which show anti-tumour activity in the RC model. The TA was increased to 50% in animals treated with a combination of 0.6 mgPM/kg and 20 mgCL/kg and 30 mgCR/kg. To maintain PM nephrotoxicity, a modified OM was studied: 2-(ethyl-mercury-mercapto) -benzooxazol-5-carboxylic-Na displayed a selective anti-growth effect using transplantable rat RC in the nude mouse as compared with bladder cancer. Nephrotoxicity in tumour-free animals was significantly below that of 50% TA levels (1.2 compared with 8.5 mg/kg). Toxicity was lowered by simultaneous injection of 200 mg/kg of 4-hydroxypyrazolo (3,4-d) pyrimidine, and combination with vincristine distinctly improved TA without prolongation of survival.

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PREFERENTIAL ALKYLATION OF REITERATIVE DNA SEQUENCES BY CHEMICAL MUTAGENS/CARCINOGENS

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The aim of this work has been to investigate if DNA sequences with different complexities can be differentially alkylated after treatment with monofunctional alkylating (methylating and ethylating) agents. Growing mammalian cell cultures were exposed to different doses of mutagens/carcinogens and their DNAs were analyzed by density gradient ultracentrifugation, hydroxylapatite fractionation, and gel electrophoresis after restriction enzyme treatment. Analysis with labelled mutagens (MNNG and ENU) has shown that there is a non-random distribution of the adducts in DNA sensitive sites recognizable as A-T, G-C rich satellites and highly repetitive sequences. Analysis with restriction enzymes showed that both methyl and ethyl groups influence the restriction pattern of enzymes such as Hpa II and Msp I that recognize specific endogenous DNA methylation. This data shows that alkylating agents may induce changes in DNA regulatory regions. Inhibition of restriction enzyme activities suggests, as a subsequent mechanism, a modification in the pattern of the normal endogenous methylation of the 5-methylcytosine.

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IMMUNOBIOLOGICAL CHARACTERISTICS OF LECTIN-RESISTANT VARIANTS OF MOUSE LEWIS LUNG CARCINOMA CELLS.

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From the Lewis Lung Carcinoma cell line, $LL_2$, two variant sublines $LL_25$ and $LL_28$, were selected in vitro with wheat germ agglutinin. In comparison with the parental line, cells of both sublines exhibited markedly reduced metastatic potential. $LL_25$ subline also had diminished tumourigenicity and was more resistant in vivo to the cytotoxic effect of NK cells. Cell surface carbohydrate composition, lectin binding and expression of H-2 specificities were examined. $LL_25$ subline displayed relatively higher expression of appropriate specificities of $H\text{-}2^b$ haplotype, and in addition, the presence of antigenic specificities from inappropriate $H\text{-}2^k$ and $H\text{-}2^d$ haplotypes was detected.