THE INCORPORATION OF 5-FLUOROURACIL INTO RNA OF NORMAL TISSUES AND AN ADENOCARCINOMA TRANSPLANTED INTO THE LIVER OF PROTEIN DEPRIVED RATS

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Liver metastases of adenocarcinoma are commonly treated with 5-fluorouracil (5-FUra). A main effect is due to its incorporation into RNA. At protein deprivation, common in human cancer, the incorporation of cytidine into RNA is increased in the liver in rat. We have examined the effect of dietary protein on the incorporation of 5-FUra into RNA of tumour and normal tissues in rat.

Method: An N-methyl-nitrosoguanidine-induced adenocarcinoma of the colon of rat was transplanted to the liver. The rats were given either a 25% or 0% casein diet and some of the latter amino acids parenterally for one week. The rats were given 600 nmol [3]H-5-FUra/100 g body weight in a 2 hr infusion by the hapatic artery and killed after one further hr. Amounts of labelling in the acid-soluble fraction, RNA and DNA were determined in tumour and several normal tissues.

Results: Protein deprivation increased specific RNA labelling significantly in liver, kidney and ileum. Parenteral amino acids largely eliminated this increase and increaed the RNA/DNA ratio in the liver. Protein deprivation also increased the specific RNA labelling in tumour, but the increase was not statistically significant. There was no change in bone marrow.

Conclusion: Protein deprivation alters the incorporation of 5-FUra into RNA in several tissues. Trials are in progress to decrease the incorporation of 5-FUra into normal tissues.

A TUMOUR CELL-ASSOCIATED PLASMIN-INDEPENDENT PATHWAY FOR UROKINASE PROENZYME ACTIVATION

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It has been shown by several authors that human tumour cells normally produce and secrete the single-chain proenzyme form of urokinase plasminogen activator, which can be activated by plasmin to the active two-chain form. For example, using inhibitory monoclonal antibodies to plasmin we have shown that such a pathway operates in cultures of human colon tumour cells.

However we now report that a human macrophage-like call line (RC2A) consistently secretes the DFP-sensitive two-chain form of urokinase, which is formed by a cell-associated non-plasmin pathway. The active urokinase product is also recognised by the fast-acting PAI-2 class of specific inhibitor.

ANTI-IDIOTYPIC IMMUNITY AND TUMOUR DORMANCY IN A MOUSE B-CELL LYMPHOMA

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Immunization of mice with purified idiotypic IgM rescued from the BCL1 lymphoma specifically protects against tumour challenge with approximately 30% of mice surviving for more than 6 months. Spleens from long-term survivors with no visible tumour were examined for tumour cells using monoclonal anti-idiotypic antibody. Dormant tumour cells were detectable which on passage into naive mice gave rise to tumour in the usual time span.

In long-term survivors which eventually showed emergent tumour, the pattern of surface idiotype expression was variable, ranging from normal to completely negative, but cytoplasmic idiotype was always present. This alteration was partly due to immunoselection of a variant tumour which fails to express idiotype but has intracellular idiotype.

Host mechanisms involved in tumour suppression appear to include anti-idiotypic antibody and reactive T cells which respond in vitro to idiotypic IgM.

SCANNING CYTOPHOTOMETRIC DETERMINATION OF DNA IN P3X63-Ag8 PLASMOCYTOMA CELLS

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The IgG1 producing murine plasmocytoma cell line P3X63-AgB established from MOPC 21 has been used for fusions in hybridoma technology. Intraperitoneally transplanted cells (not fused) were investigated on smears by scanning cytophotometric measurement after Feulgen staining. Only

cells with a single nucleus but not multinucleated or giant cells were determined. The DNA content and nucleus area showed a time dependent change 10 to 18 days after transplantation with hypotetra-to octaploidal pattern. The increasing DNA content and the behaviour of aneuploidy has been suggested as the result of endoreduplication or nuclear fusion in the environment of host defense.

IMMUNOMODULATING EFFECT OF COPOLYMERS OF METACRYLIC ACID

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The immunomodulatory effect of six copolymers of metacrylic acid (MA) were investigated in $BD2F_1$ mice. The copolymer of MA with acrylamide (MAA) was selected for further investigation. MAA applied i.p. was able to enhance (as compared to the control) by 147% the plaque-forming cell response, by 100% rosette-forming cells response, by 142% the delayed type hypersensitivity reaction, as well as 10 times the NK activity of spleen cells. Suppression of humoral immune response induced by some bacteria could be reduced by MAA pretreatments. In L1210 leukaemia-bearing mice MAA exhibited some synergistic therapeutic effect when combined with BCNU.

EFFECTS OF BETEL EXTRACT AND RELATED COMPOUNDS IN CULTURED HUMAN BUCCAL CELLS

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Effects of aqueous betel nut extract and several betel-specific alkaloids and N-nitroso compounds were investigated in cultured human buccal epithelial cells and fibroblasts. The extract decreased both colony forming efficiency and clonal growth rate of epithelial cells to less than 50% at 10 µg/ml. Exposure to higher concentrations also caused both dose-dependent depletion of thiols and formation of DNA single strand breaks. Of eight betel nut-associated compounds investigated, 3-(methyl-nitrosamino)propionaldehyde was the most potent on a molar basis and significantly decreased both cellular survival and thiol content and also caused DNA damage in buccal cells between 0.1 and 0.3 mM. More than 10-fold higher concentrations of arecoline, guvacoline or N-nitrosoguvacoline were required to cause similar effects. Arecaidine, guvacine, N-nitrosoguvacine or 3-(methylnitrosamino) propionitrile up to 6 mM did not affect the cells significantly. The induction of cyto- and genotoxic effects by extract and several betel nut-specific compounds may be of importance for understanding the relationship beteeen betel chewing and carcinogenesis in the human buccal epithelium.

POLY-L-LYSINE AS DIFFERENTIATION INDUCER IN FRIEND ERYTHROLEUKAEMIA: STUDIES IN VITRO AND IN VIVO

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The ability of the synthetic cationic polypeptide poly-L-lysine (PLL) to induce differentiation was examined in Friend murine erythroleukaemia cells. Like other membrane-interacting agents, PLLs of different molecular weights were found to be good inducers of differentiation. These polymers enhanced differentiation produced by suboptimal concentrations of dimethylsulphoxide (DMSO). Since PPL was inactive as an initiator of maturation of DMSO-resistant cells, it is likely that some events (presumably membrane-related effects) involved in the multistep stimulation process are common to polar-planar solvents and to this polycationic polymer. A PLL of 2,700 MW was selected to examine the induction of differentiation process in animals bearing Friend erythroleukaemia. Although no increase in the survival was observed, the pattern of differentiation in erythro- and granulocytopoietic series in the myelograms of treated animals showed evidence of some cell maturation.

HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS AND CERVICAL SQUAMOUS CELL CANCER

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Current data implicating the role of HPV in squamous cell carcinogenesis of the uterine cervix can be summarized as follows: (1)cervical HPV infections are a sexually transmitted disease (STD), shown to represent an increased risk for cervical