was not produced. Thus, these compounds may possibly be toxic carcinogens. To test this hypothesis estradiol and catecholestradiols were administered to Sprague-Dawley rats. An increase in prostate mass was observed. In human hyperplasia of the prostate we found that the catecholestrogen concentration was three times higher in malignant tumours than in benign growths.

INOSITOL PHOSPHATES AND PHOSPHOINOSITIDES IN RAT LIVER NODULES

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We have investigated the inositol phosphate turnover system in liver nodules from rats. These nodules, considered to be preneoplastic lesions, have many histological and biochemical alterations, e.g. a larger growth fraction and an altered response to growth factors.

The total amounts of phosphoinositides and inositol phosphates were measured in normal and nodular liver, as well as the turnover rate of the different compounds after stimulation with vasopressin.

Consistent with earlier findings, the basal level of phosphatidyl inositol was roughly doubled in the nodules, though neither the polyphosphoinositides nor the inositol phosphates showed any marked differences.

The nodular cells responded to vasopressin with a quicker than normal elevation of the inositol trisphosphate amount, but to the same level as the normal liver. The normal cells showed a six-fold increase of inositol tetrakisphosphate, which we have not been able to show in nodular cells.

INDUCED DIFFERENTIATION IN HUMAN LEUKAEMIA/LYMPHOMA CELL LINES. A SHORT OVERVIEW

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In recent years cell lines representative of most types of human leukaemia and lymphoma have been established in vitro. Such lines have been found to be instrumental in studies aimed at understanding (1) whether the differentiation block, typical of leukaemia/lymphoma in vivo, is reversible in vitro and if so, whether the induced differentiation will be terminal, i.e. associated with a G1/G0 cell cycle block, and (2) the deranged genetic control of proliferation/differentiation in leukaemia/lymphoma. These studies clearly show that at least for non-lymphoid cell lines (HL-60, U-937, K-562, MEL, Ku 812, M 1-2, THP-1) induction of terminal differentiation is indeed possible by e.g. phorbol ester, vitamin D3, retinoic acid, interferon, and that several protooncogenes are regulated during this process.

ANTI-MELANOMA PROPERTIES OF CHEMICAL INDUCERS OF DIFFERENTIATION: IN VITRO AND IN VIVO STUDIES

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The effects of three chemical inducers of cell differentiation, sodium butyrate, dimethylthiourea (DMTU) and tetramethylurea (TMU), were studied on mouse and human melanoma cell lines and B16 melanoma tumours. Sodium butyrate, dimethylthiourea (DMTU) and tetramethylurea (TMU) were found to inhibit melanoma cell growth, clonogenicity in soft agar and tumourigenicity in syngeneic mice. Sodium butyrate, DMTU or TMU also induced morphological and biochemical changes in melanoma cell lines. These changes include cell enlargement, development of endoplasmic reticulum and golgi complexes, and enhancement of NADPH cytochrome c reductase and γ-glutamyl transpeptidase activities. These phenotypic alterations are in part compatible with a more differentiated phenotype. Systemic administration of sodium butyrate, DMTU or TMU to mice inoculated with B16 melanoma cells resulted in delayed tumour appearance and prolonged survival of the mice. These studies form a basis for further evaluation of the potential therapeutic use of chemical inducers of differentiation in solid tumours.

This study is supportd by an ICRF-grant.

DOWN REGULATION OF NK CELL ACTIVITY IN MoLV LEUKAEMOGENESIS: EVIDENCE FOR TUMOUR CELL MEDIATED SUPPRESSION

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The role of natural killer (NK) cells in retrovirus induced leukaemogenesis was studied. Neonate BALB/c mice infected the Moloney murine leukaemia virus (MoLV) develop leukaemia. The MoLV infected mice showed a progressive loss of endogenous or augmented NK activity, correlated with the development of the leukaemic state. Mixing of spleen cells from tumour bearing mice with NK augmented splenocytes, resulted in suppression of NK activity. In addition, mixing of T cell lines isolated from MoLV induced tumours with augmented splenocytes also resulted in the down regulation of NK cell activity. It is postulated that after MoLV infection, the progression of virus transformed T cells to a fully developed tumour depends on the ability of these cells to down regulate NK cell activity and thus evade immune surveillance.

REGULATION OF MAMMALIAN DNA REPAIR ENZYMES DURING THE CELL CYCLE

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We have studied the regulation of mammalian DNA repair enzymes as a function of the cell cycle. Synchronous populations of L-929 cells in early G1 were obtained using centrifugal elutriation. Synchronous populations of early G1 cells were reestablished in culture and harvested at different intervals during the cell cycle. Enzyme extracts were prepared by a high salt wash of purified nuclei. The results indicate that DNA repair enzymes redoxy-endonuclease, ^{3}Me-adenine-DNA-glycosylase, uracil-DNA-glycosylase and Ap-endonuclease all have an increased activity in late G1 prior to the onset of DNA synthesis. The O^{6}-Me-guanine transferase activity, however, was present at the same level in all stages of the cell cycle studied. We conclude from these experiments that the majority of mammalian DNA repair enzymes are cell cycle dependently expressed.

BIOLOGICAL AND MOLECULAR PROPERTIES OF p53

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p53 is a cellular protein found in elevated levels in a variety of tumour-derived and *in vitro* transformed cells. To investigate the possible role of p53 in transformation, we cloned p53-specific DNA and used it to construct p53 expression plasmids. The introduction of such plasmids into non-transformed cells, either alone or together with Ha-*ras*, led to neoplastic conversion, thus implicating p53 as an oncogenic protein possessing *myc*-like activities. This notion was also confirmed by experiments indicating that p53 can serve as a competence factor in the control of normal cellular proliferation. Finally, p53 was shown to form a tight complex with a major heat-shock protein, raising the possibility that stress proteins may also play a role in proliferation-related processes.

CORRELATION BETWEEN HLA-A,B,C EXPRESSION ON HUMAN UROTHELIAL CELL LINES AND TRANSFORMATION GRADE *IN VITRO*

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Various characteristics of human urothelial cell lines permit a classification of these cell lines according to grade of transformation (TGr) *in vitro*. Of special interest here is that the slightly transformed (TGrI) and pre-tumourigenic (TGrII) cell lines all express the appropriate HLA-A,B epitopes in contrast to the tumourigenic (TGrIII) cell lines. Using the immunofluorescence test and a complement dependent cytotoxicity test we have investigated 3 TGrII and 7 TGrIII cell lines for their expression of the monomorphic part of HLA-A,B,C antigens. We provide evidence that the apparent loss of HLA-A,B epitopes observed in TGrIII cells is due to a significantly (4 to 6 fold) lower concentration of HLA-A,B,C antigens on TGrIII cells as compared to that on TGrII cells. Furthermore, treatment of TGrIII cells with neuraminidase partly restored the expression of HLA-A,B,C antigens.

THE EFFECT OF CELLADAM ON EHRLICH AND S180 TUMOURS

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A new anticancer and immunostimulant