supporting the notion, that lymphocytes could be used as a model for primary target tissue, e.g. lungs. However, we have not seen any significant differences in lymphocyte AHH activity and inducibility between lung cancer patients and controls.

We have also studied whether MO activities predict the in vivo or in vitro formation of benzo(a)pyrene diolepoxide (BPDE)-DNA adducts, the model lesion for PAH-induced carcinogenesis. We have shown that the nature of P450 isozyme is of importance for the activation ability, whereas the magnitude of activity seems to be of lesser importance. This was demonstrated with the aid of monoclonal antibodies (MAb) to different P450 isozymes. For example, the MAb to rat MC-induced liver P-450 inhibited AHH in placenta, but not in liver. It readily inhibited the in vitro formation of BPDE-DNA adducts in placenta, but not in liver. The MAb to phenobarbital-induced isozyme did not have these effects.

THE EFFECT OF INHIBITION OF MITOCHONDRIAL PROTEIN SYNTHESIS ON THE GROWTH KINETICS OF A RAT LEUKAEMIA

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Mitochondria (mt) contain DNA coding for several subunits of components of the oxidative phosphorylation system and a specific system to transcribe and translate this DNA. Inhibition of the expression of mt-genes finally diminishes the capacity for oxidative phosphorylation to an extent that cell functions (e.g. proliferation) become impaired. This has been demonstrated already in several tumour systems. Specific and continuous impairment of mt-protein synthesis by treatment with tetracyclines results also in growth inhibition of a leukaemia in the rat - it even leads to its disappearance. Cytostasis is achieved more rapidly and the rat of cytolysis is faster when tetracycline treatment is started in later stages of tumour progression. Our studies indicate that this is due to interference of tetracyclines with the cytostatic and cytolytic effects of corticosteroids on the growth of this tumour. As tetracycline treatment has lasted longer, the anti-tumour effects of (endogeneous) corticosteroids become less. It is suggested that mt-protein synthesis is required for the action of corticosteroids on leukaemic cells.

PROVIRUS INTEGRATION IN [90]Sr -INDUCED OSTEOSARCOMAS OF CFF1 MICE

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The development of [224]Ra and [90]Sr induced osteosarcomas in mice is accompanied by the expression of endogenous retroviruses in bone tissues of the treated animals in the early latency period, and later in the osteosarcomas. Using the Southern blotting procedure, we have studied the presence of somatically acquired proviruses in genomic DNA isolated from seven primary [90]Sr induced osteosarcomas and one osteosarcoma cell line (0-127a1) of the CF1 mouse strain. Newly integrated ecotropic proviruses were detected with specific hybridization probes in four primary tumours. In contrast, genomic DNA from cultured osteosarcoma cells harboured additional ecotropic recombinant (MCF-related) proviruses. No integrations were found in the vicinity (22 kbp) of c-myc. The c-myc locus is amplified in two out of eight tumour DNAs. According to our data, detectable integrations of activated retroviruses do not appear to be an essential requisite for the development of radiogenic osteosarcomas in mice, but in some cases, clonal or oligoclonal integrations might have been responsible for the deregulation of a nearby putative oncogene, allowing cells to escape normal growth control in vivo.

REVERTANTS OF METHIONINE-DEPENDENT H-ras-1 ONCOGENE-TRANSFORMED CELLS

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Methionine-dependence is a metabolic defect reported to be exhibited by many transformed and malignant human or animal cells (Mechan et al, BBRC, 117: 429, 1983). This defect is characterized by the inability of cells in culture to grow in a medium where methionine has been replaced by its immediate metabolic precursor, homocysteine. The biochemical basis of this phenomenon is not understood. We have shown recently that the activated H-ras-1 oncogene, derived from the EJ human carcinoma line, induces methionine-requirement after transfection in

epithelial non-transformed immortalized rat cells of the Clone 9-3 line (Vanhamme and Szpirer, Exp. Cell. Res., 169: 120, 1987). Here we report that several of the H-ras-1-transformed methionine-dependent clones can yield methionine-independent revertants at a high frequency. We analyzed these revertants for several of their properties, including cloning-efficiency in soft agar to determine whether reversion of the methionine-dependent character is associated with full reversion of the transformed phenotype. Methionine-independent revertant clones were found to retain their ability to grow in agar, indicating only partial reversion of the H-ras-1 induced transformed phenotype.

REACTIVITY OF ANTIBODIES TO DNA MODIFIED BY BENZO(A)PYRENE IS DEPENDENT ON THE LEVEL OF MODIFICATION - IMPLICATIONS FOR QUANTITATION OF BENZO(A)PYRENE-DNA ADDUCTS IN VIVO

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Antibodies specific for DNA modified by (±) trans-7,8-dihydroxy-anti-9,10-epoxy-7,8,9,10 tetra hydroxybenzo(a)pyrene (BPDE) have been used in an enzyme-linked immunosorbent assay (ELISA) to quantitate the products of BP covalently bound to DNA. The antibodies were made by immunizing rabbits and mice with BPDE-modified DNA (2% modified) complexed with methylated bovine serum albumin. The resulting polyclonal and monoclonal antisera showed a high reactivity towards single-stranded BPDE-DNA, but had a lower reactivity for double stranded BPDE-DNA. The free N2-deoxyguanosinyl adduct of BPDE was less well recognized and no affinity was detected for BPDE-tetrols or DNA modified with N-acetoxy-AAF. A high cross-reactivity was found with DNA modified with (±) trans-1,2-dihydroxy-anti-3,4-epoxy-1,2,3,4-tetrahydrochrysene (CDE).

The antibody-reactivity towards BPDE-DNA depended on the level of modification; in the competitive ELISA as little as 4 fmol BPDE-DNA (42 pmol/µg) was sufficient for 50% inhibition, whereas 17 fmol of adduct was requird when [3]H-BPDE of a low level of modification (1 to 10 fmol/µg) was used as inhibitor. Samples of [3]H-BP-DNA isolated from the livers of mice treated with various doses of [3]H-BP were examined by ELISA. The binding values, calculated from the immunoassay, were in good agreement with the values from radioactivity measurements. The combination of standards of a low level of modification and highly specific antisera in a competitive ELISA is a valuable tool in the detection and reliable quantitation of human exposure to PAHs.

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EXPRESSION OF c-sis IN HUMAN MALIGNANT MESOTHELIOMA CELL LINES

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Malignant mesotheliomas are mesodermally derived tumours. Occasionally a reactive connective tissue growth occurs. The expression of mRNA of PDGF A and PDGF B (c-sis) was studied in malignant mesothelioma cell lines and normal mesothelial cells. From five patients with confirmed malignant mesotheliomas, seven malignant mesothelioma cell lines were isolated. All were found to have chromosomal aberrations. Normal mesothelial cells were derived from patients without a malignant mesothelioma and had a normal karyotype. All malignant mesothelioma cell lines were found to express the 4.2 kb c-sis mRNA abundantly while the normal mesothelial cells did not express this messenger. The PDGF A chain was expressed by normal as well as malignant mesothelial cells. These studies indicate that the c-sis oncogene may possibly play a role in this type of malignancy.

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RECESSIVE MODE OF INHERITANCE OF MELANOMA FORMATION IN XIPHOPHORIN FISH

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Studies on oncogenes provide evidence that the transformed phenotype is conferred onto cells in a dominant fashion. Studies on retinoblastoma, Wilms tumour, etc. show contrary evidence, i.e. tumours are due to homozygosity or to a total loss of recessive genes. Some of this controversy in interpreting genetic mechanisms in tumourigenesis could best be resolved in an