cytoskeletal proteins. These modifications again mimic those seen in the embryo during comparable stages of differentiation.

REMODELLING OF INTESTINAL WALL CELLS - POSSIBLE CAUSE OF INTESTINAL FIBROSIS AFTER RADIOTHERAPY

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Ten beagle dogs (female and male), weight 10 to 12 kg, 1 to 2 years old were irradiated with 25 Gy (Cobalt-Phillips) onto the whole pelvis and tail for 20 days. Platinol was given in a 2 hour infusion every 5 days for 20 days during the radiation treatment. Ten dogs represented a control group. Ten days later the thoracic duct lymphocytes, peripheral blood and the large intestine were examined with the following parameters: laboratory, biochemical, histological, EM, SEM, densitometric, immunological, and LAMMA 500 examinations. Damage and remodelling of peripheral blood lymphocytes, thoracic duct lymphocytes, entero-endocrine cells, mast cells and lymphocytes in the intestinal smears of the lamina propria were found in all treated dogs. Of special interest was enhanced volume density of mast- and entero-endorcine cells, that could also reflect enhanced serotonin excretion, with hypoxia of the intestinal tissue. LAMMA 500 measurements established significant changes in the organic composition of the lamina propria cells. Immunological studies revealed significantly diminished transformation of lymphocytes with PHA and Con-A stimulation in the treated group. It is considered that the changes described represent a stimulus for fibrogen hyperproduction and collagen excretion in the treated group of dogs.

TRANSFORMING GROWTH FACTOR-BETA INDUCES INCRESED LEVEL OF PLASMINOGEN ACTIVATOR INHIBITOR mRNA IN HUMAN LUNG FIBROBLASTS

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The mechanisms behind a transforming growth factor-beta (TGF-beta) induced stimulation of production of type-1 plasminogen activator inhibitor (PAI-1) in WI-38 human lung fibroblasts have been studied using a full-length cDNA probe for PAI-1, as well as monoclonal antibodies against the inhibitor. Northern and dot blot analyses showed that TGF-beta causes an early increase in the PAI-1 mRNA level, reaching a 50-fold enhancement after 8 hr. Blocking of protein synthesis with cycloheximide caused an equally strong increase in the level of PAI-1 mRNA. Quantitative immunochenical studies of the effect of TGF-beta on PAI-1 protein levels in cell extracts and culture media were consistent with the effect on PAI-1 mRNA. The results suggest a primary effect of TGF-beta on PAI-1 gene transcription.

LOSS OF HETEROZYGOSITY IN HUMAN DUCTAL BREAST TUMOURS INDICATES A RECESSIVE MUTATION ON CHROMOSOME 13

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The genotypes at chromosomal loci defined by recombinant DNA probes revealing restriction fragment length polymorphisms were determined in constitutional and tumour tissue from 10 cases of ductal breast cancer: eight premenopausal females and two males. Somatic loss of constitutional heterozygosity was observed at loci on chromosome 13 in primary tumour tissue from three females and one male. In two cases, specific loss of heterozygosity at three distinct genetic loci along the length of the chromosome was observed. In another case, concurrent loss of alleles at loci on chromosomes 2, 13, 14 and 20 was detected, while a fourth case showed loss of heterozygosity for chromosomes 5 and 13. In each instance, the data were consistent with loss of one of the homologous chromosomes by mitotic nondisjunction. Analysis of loci on several other chromosomes showed retention of constitutional heterozygosity suggesting the relative specificity of the events. These data indicate that the pathogenesis of ductal breast cancer may, in a substantial proportion of cases, involve unmasking of a recessive locus on chromosome 13.

TWO DIFFERENT MECHANISMS BY WHICH 5-FLUOROPYRIMIDINES INDUCE DNA LESIONS

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The interaction between 5-fluoropyrimidines and DNA was investigated using an approach by which cells are lysed in dilute alkali to reveal drug-induced fragmentation of DNA. One mechanism used to induce DNA lesions is the incorporation of drug into DNA, resulting in the induction of alkali-sensitive DNA lesions. The presence of lesions results in fragmentation of DNA, which is visualized by agarose gel electrophoresis.

The second mechanism does not involve incorporation of drug into DNA. This mechanism is in all probability due to inefficient DNA repair of normally occurring defects in nucleotides.

In human colon adenocarcinoma cells treated with 5-FU one can detect both mechanisms. In cells treated with 5-FdU one can detect only the second mechanism.

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LOCALIZATION OF RADIOLABELLED MONOCLONAL ANTI-CEA ANTIBODIES AND FRAGMENTS IN COLON CARCINOMA, - DIAGNOSTIC AND THERAPEUTIC APPROACHES

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Thirty-one patients with known colorectal carcinomas were injected with Fab and F(ab')2 fragments from the monoclonal anti-CEA antibody (MAb) 35 labelled with 3 to 6 mCI of [123]I and tested by emission computerized tomography (ECT) 6, 24 and sometimes 48 hr after injection. All 23 primary tumours and local recurrences except one were clearly visualized. Interestingly, 9 of these patients had almost normal circulating CEA levels and 3 of the visualized tumours weighed only 3 to 5 g. Among 19 known metastatic tumour involvements 14 were correctly localized by ECT (Delaloye et al., J.Clin.Invest., 77: 301-311, 1986). For therapeutic purposes, seven patients with liver metastases were injected in the hepatic artery with MAbs and anti-CEA labelled with 100 mCi of [131]I. None of the 7 patients showed any significant side effects for a period of observation of 5 to 10 months. We observed good localization of intact [131]I MAb in liver metastases, as documented by ECT obtained 4 days after injection, and an estimated radiation dose to the tumour of 1000 rads, but we have not yet obtained definite evidence of tumour regression.

VACCINATION AGAINST EPSTEIN BARR (EB) VIRUS ASSOCIATED MALIGNANCIES

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We have investigated the possibility of using vaccinia virus recombinants expressing EB virus genes as potential vaccines to prevent EBV associated tumours. EB virus membrane antigen gp340 was inserted into and expressed in several strains of vaccinia virus. The gp340 produced by the vaccinia recombinants was indistinguishable from authentic gp340 by the criteria examined. Rabbits vaccinated with one of the recombinants produced antibodies that neutralized EB virus. We have also inserted the EB virus glycoprotein gB into vaccinia virus either as the authentic protein or as an in frame fusion with Hepatitis B virus surface antigen. These two constructs should present the EBgB to the immune sytem of vaccinated animals in different ways. Vaccination of rabbits is underway and should tell us whether the EBgB gene product is capable of raising EB virus neutralising antibody and also give us an idea how best to present antigens to the immune system.

RFLP ANALYSES OF c-Ha-ras LOCUS IN HUMAN TUMOURS

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A restriction fragment length polymorphism (RFLP) of the human c-Ha-ras locus has been analysed in DNA from breast tumours, leukaemic cells and lymphocytes from normal individuals by agarose gel electrophoresis and Southern blot hybridization. Examination of the allele frequencies showed three "common" alleles (6.8, 7.5, 8.3 kb) occurring with frequencies 38.2%, 36.5% and 19.2%, respectively, and several "rare" alleles (about 6%). More Ha-ras homozygotes were noted in DNA isolated from tumours than from white blood cells in normal individuals. No