

Recently, a major focus of our ongoing investigations into the mechanisms(s) of asbestos transformation of human mesothelial cells has been to delineate their growth factor requirements. Quiescent cells require insulin (INS) and either epidermal growth factor (EGF), platelet derived growth factor or transforming growth factor beta to undergo one round of DNA synthesis. However, a clonal growth does not occur unless the medium also contains high density lipids (HDL). Media containing HDL, INS and either gamma interferon or interleukin-1 will also support clonal growth, but the combination of HDL, INS and EGF with any of the other factors increases the growth rate. Sustained growth of human epithelial cells in defined media containing these factors (other than INS and EGF) is unusual. Interestingly, we have also found that mesothelioma cell lines elaborate some of these mitogens indicating that these factors may play an autocrine role in mesothelial cell carcinogenesis.

LIVER CELL PROLIFERATION INDUCED BY LEAD NITRATE DOES NOT PROMOTE THE GROWTH OF GGT+ FOCI

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We have recently shown that cell proliferation induced by the mitogen lead nitrate does not achieve initiation of hepatocarcinogenesis when coupled with administration of several carcinogens. Therefore, we have investigated the effect of lead-induced cell proliferation on the promotion phase of liver carcinogenesis. The experimental protocol consisted of initiating rat liver with DENA (200 mg/kg) and treating the animals with a mitogenic dose of lead nitrate (5 micromoles/100 g, twice a month). The rats were sacrificed at 6 and 12 months and the preneoplastic lesions were identified as gamma-glutamyltranspeptidase positive foci (GGT+). The results indicate that despite the several mitogenic stimuli exerted by lead, no increase in the size and/or number of GGT+ foci, was observed when compared with that of rats treated with DENA alone.

NUCLEAR DNA CONTENT CHARACTERISTICS OF 129 HIGH GRADE MALIGNANCY NON-HODGKIN LYMPHOMAS

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We have studied the DNA-ploidy of 129 non-Hodgkin lymphomas diagnosed during the last 30 years in the Tampere University Central Hospital. The material consisted of 45 large, non-cleaved follicular centre cell lymphomas, 34 small, non-cleaved non Burkitt type lymphomas, 26 Burkitt type lymphomas (BL) and 25 immunoblastic sarcomas (IBS, Lukes-Collins classification). The analyses of archival diagnostic biopsies were done with an EPICS C flowcytometer. By using a trypsin digestion method, which yielded low CV-values (mean 5.4%, range 3.13 to 8.50), we were able to analyze about 90% of the tumour samples.

Aneuploidy as defined by an abnormal DNA Index, was seen in 1/3 of the cases. Tetraploidy was found to be characteristic for IBS (present in 53% of cases compared with 11% in other tumours, $p < 0.05$). Six Burkitt type tumours were aneuploid showing a low, near-diploid DNA-Index (mean 1.14, range 1.08 to 1.24). The BL cases had a significantly worse prognosis provided that they had near-diploid tumours ($p < 0.02$). We conclude that the DNA content characteristics described can reflect the histopathological type and clinical behaviour of high grade malignancy non-Hodgkin lymphomas.

RELATIONSHIP BETWEEN EMBRYONAL CARCINOMA CELLS AND EMBRYOS

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The stem cells of teratocarcinomas, the embryonal carcinoma (EC) cells, are multipotential cells, which may proliferate as EC cells or differentiate into a variety of directions. This has suggested that EC cells correspond to a cell type in the early embryo. In line with this, the EC cells differentiate in a way comparable to that of the embryo, EC cells can be obtained from embryos both in vivo and in vitro, and EC cells reintroduced in the embryo can participate in the formation of the tissues of the foetus. Furthermore, the EC cells share many biochemical features with early embryo cells. At present, it appears that mouse EC cells represent primitive ectoderm cells of the mouse embryo.

Upon differentiation, the EC cells lose their malignant properties. The differentiation of EC cells is connected with rapid changes in, e.g. cell surface molecules and in the organization of

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-endocrine 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 INCREASED 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 immunochemical 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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