11.043

PRENEOPLASTIC HEPATIC FOCI IN GLYCOGENOTIC, CIRRHOTIC AND CARCINOMA-BEARING HUMAN LIVERS

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During experimental hepatocarcinogenesis in rodents various types of foci of altered hepatocytes (FAH) precede the development of hepatocellular adenomas and carcinomas produced by chemicals, radiation or viruses. In order to study FAH in man we investigated 33 explanted human livers. 14 of the patients had posthepatitic cirrhosis, 8 alcoholic cirrhosis, 10 hepatocellular carcinomas, and 1 patient had glycogen storage disease type Ia (GSD, G6Pase-deficiency). In 9 (64%) livers with posthepatitic cirrhosis, in 6 (75%) with alcoholic cirrhosis, in 8 (80%) with hepatocellular carcinomas, and in the liver with GSD, hepatic foci storing glycogen in excess and showing a reduction in the activities of glycogen-phosphorylase (PHO), glucose-6-phosphatase (G6Pase), adenosine-triphosphatase (ATPase) and γ-glutamyl-transpeptidase (γ-GT) were observed. PHO and G6Pase showed a decrease in their activity in 98% and 95% of glycogen storing foci, respectively. Changes in these enzymes were the most reliable markers of FAH. Apparently, the sequential cellular changes during hepatocarcinogenesis are in principal identical under various pathological conditions and in different species.

11.044

RING-SHAPED PARTICLE (RSP): A NEW HIGHLY ACCURATE TUMOR MARKER FOR BREAST CANCER

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In a previous study published in the ASCO proc., May 1991, we demonstrated that RSP tumor marker could reliably discriminate between sera from patients with active neoplasia, and that of patients with benign disease.

In this prospective study, we have focused on breast cancer only. The study designed involved three groups: Group 1 - Normal individuals (N = 56). Group 2 - Breast cancer patients (N =38) with pathologically proven metastatic disease. Group 3-Inactive breast cancer patients (N = 100) free of disease for more than 5 years (median 9 years). All the sera were tested for RSP, CEA, and CA-15-3.

The RSP were detected using a fluorescent substrate with the antibody based sandwich reagent system developed by AMDL, Inc. All assays were conducted blind.

The RSP correctly identified 55 of the 56 normals for a specificity of 98.2% and 36 of 38 active cancer patients with sensitivity of 94.7%. The RSP also identified 90 of the 100 of the cancers in remission as negative for a specificity of 90% in this very difficult to interpret group.

When RSP was compared with CEA and CA-15-3 from active and inactive breast cancers, the sensitivity values for 38 patients with active disease were: 94.7% for RSP, 26.3% for CEA, and 71.1% for CA-15-3. The values for the CEA and CA-15-3 are consistent with published reports for metastatic breast cancer. The specificity values for the 100 inactive breast cancer patients were: 90% for RSP, 97% for CEA and 92% for CA-15-3.

Although CA-15-3 is currently recognized as the best experimental tumor marker for breast cancer, this comparative study demonstrates that RSP is a significantly more sensitive and accurate tumor marker for active breast cancer than either CEA or CA-15-3.

If ongoing serial studies support these preliminary findings, it opens the possibility for much earlier diagnostic and therapeutic interventions when the disease is more curable. Initial studies also reveal RSP level to be an effective parameter for evaluating response to therapy.

All patients in Group 3 are being serially monitored for RSP, CEA, and CA15-3 at three month intervals in an effort to diagnose relapse earlier than other current clinical, imagining & laboratory diagnostic procedures can.

11.045

Oncofetal fibronectin isoforms in human breast cancer

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Fibronectins (FN) are widely distributed glycoproteins of the extracellular matrix. Some fibronectin isoforms are present mainly during fetal development and in neoplasms (onfFN), while they have a very restricted distribution in normal adult tissues.We compared the distribution of total FN and two onfFN isoforms in normal human breast as well as in neoplastic and non-neoplastic human breast lesions. We used the mAbs IST-4 which recognizes all different fibronectin isoforms, BC-1, which recognizes all ED-B containing oncofetal FN isoform and FDC-6, which recognizes the oncofetal epitope in the IIICS region. OnfFN were present in the stroma of 72 out of 75 samples of invasive ductal carcinoma, while in invasive lobular carcinoma they were present in the stroma of 6 out of 10 samples. The intensity of the staining was much weaker in the latter type of carcinoma. The stroma of the fibroadenomas was weakly and focally positive with the mAbs BC-1 and FDC-6 in 3 out of 10 cases. Furthermore, within the same specimen, we found differences in distribution of the onfFN isoforms recognized by mAbs BC-1 and FDC-6, respectively. In non-neoplastic lesions and in normal breast sections, the onfFN isoforms were undetectable. In all samples, stroma and stroma vessels gave strong reaction with mAb IST-4. Thus, the oncofetal FN isoforms can be considered a marker of breast neoplasm, especially of invasive ductal carcinoma.

11.046

STUDIES OF NEUROBLASTOMA USING TWO NEW MONOCLONAL ANTIBODIES

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58 MoAbs to leukocytic antigens of most important clasters (CD) were screened for reactivity with neuroblastoma cells on cryostat sections. MoAb ICO-10 to Thy-1 human antigen (mol.weight of 24 KD) was selected. It reacted with a very small subpopulation of thymic cells (<5%), some cases of leukemia, and in 88% of neuroblastoma cases. In the course of generation of monoclonal antibodies to neuroblastoma MoAb ICO-63 was selected (with the mol.weight of antigen 100 KD) reacting with neuroblastoma cells, granulocyte subpopulation and platelets. Interestingly, in all Thy-1$^-$ cases, the reaction with MoAb ICO-63 was noted. These MoAbs can be applied in the studies of neuroblastoma cells and tumor metastasis to the bone marrow in combination with MoAb to CD45 common leukocytic antigen.

11.047

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Role of IL-1β and TNFa in autocrine regulation of lymphoblastoid cell lines proliferation

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B-lymphoblastoid cell lines IM-9, Wi-729 & NC-37 were cultured in serum free medium. All of them spontaneously produced 0,5-0,75 ng/ml TNFa and NC-37 also produced 50 pg/ml IL-1β. RIL-1β added in doses 10 -10^5 U/ml to cultured IM-9, NC-37 & Wi-729 cells increased their proliferation. TNFa in the same doses induced synthesis and secretion of 200-1500 pg/ml IL-1β, determined by RNA hybridization, ELISA & biotest. But after TNFa addition cell proliferation of studied cell lines decreased. Antibodies against human IL-1β inhibited proliferation of only NC-37 cells. In contrary MAB to TNFa inhibited IM-9 & Wi-729 cells proliferation. The data shows that transformed B-cell lines uses IL-1β & TNFa as an autocrine growth f-rs.

11.048

Expression of tumor markers on non-transformed human mammary epithelial cells cultured in vitro

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Normal (non-transformed) human mammary epithelial cells derived from mammoplasties have been analysed by immunocytochemistry with monoclonal antibodies to tissue-specific and onco-developmental antigens at different passage levels. A stem cell-like population of epithelial cells was defined by the marker H (type2) blood group antigen. These cells expressed a number of onco-developmental carbohydrate antigens (Le^y, Le^x, Sialyl-Le^a) and CEA, but not Thomsen-Friedenreich antigen and urokinase.The cytokeratin phenotype was CK 5,14,15,16,17 and varying minor amounts of CK 7,8,18, suggesting the derivation from basal cells of the mammary gland.