Col 07

LIVER LECTINS AS RECEPTORS FOR METASTASIS

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After the discovery of vertebrate lectins by Ashwell and his group it has been postulated by us, that these organ-characteristic lectins (e.g. the galactose-specific Hepatic-Binding-Protein, HBP) may play a role in the metastatic process of tumors, because they could act as acceptors for cryptic carbohydrate receptors of circulating tumor cells. Earlier in vitro-experiments with human hepatocytes and various tumor cells support this hypothesis as rosette formation of these cells (initial step of metastasis) could be avoided by low concentrations of glycoconjugates with terminal galactose, which block the liver lectins and inhibit the adhesion of tumor cells. Recent in vivo-experiments (with BALB-c mice) confirmed our in vitro-results. For the very first time we succeeded in altering the organotropy of metastasis from lung exclusively to lung and liver by a neuraminidase treatment of the tumor cells, which removes the terminal sialic acid to expose penultimate galactose residues. However, regular application of arabinogalactan, a high-molecular weight polysaccharide with abundant galactose residues avoided the settling of liver metastases by blocking the liver lectin)HBP), whereas the application of mannan did not alter the initial pattern of metastasis which demonstrates the importance of the HBP in the metastatic process. For the future it might be possible to inhibit the metastatic process (e.g. during surgical operations) by blocking organ lectins by appropriate carbohydrates.

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Col 08

COMPARISON OF THE TUMOR MARKERS CA 19-9, CA 12-5, CA 15-3 AND CA 50

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Ca 19-9, Ca 12-5, Ca 15-3 and Ca 50 have some structural similarities in common: 1) They belong to O-glycosidically bound carbohydrate chains of mucins (serum,saliva,seminal plasma,amniotic fluid, milk,gastric juice). 2) Sugar determinants Ca 19-9, Ca 15-3 and Ca 50 are also components of glycolipids, whereas Ca 12-5 is found exclusively on mucins. 3) N-acetylneuraminic acid is an antigenic determinant of all these carbohydrate antigens. 4) N-acetylneuraminic acid is linked either α2→3 to the terminal galactose residue (Ca 19-9, Ca 50) or α2→6 to an internal N-acetylglucosamine (Ca 12-5). The antibodies Ca50 and Ca 19-9 have probably partial identical epitop structures, namely sialylated type 1 chains: NeuAcα(2→3)Galß(1→3)GlcNAc. The striking biochemical similarity between Ca 19-9 and Ca 50 can be demonstrated by analyzing the sera from tumor patients in pancreas carcinoma and carcinoma of the gastrointestinal tract and in inflammatory processes (chronic pancreatitis). Ca 15-3 has a similar distribution in certain organs (amniotic fluid, human milk,ovarian cyst fluid) as the markers Ca 19-9 and Ca 12-5 show, but in addition it is found on milk fat globules and on cells of the pancreatic gland. This marker has no organ specificity for breast cancer, in pancreatic carcinoma it could be used as an additional marker.

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Col 09

GCA-2: A NEW MARKER FOR GASTROINTESTINAL TRACT CANCER

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Monoclonal antibodies (mAb) against three newly established biliary adenocarcinoma cell lines (A.Knuth et al., J.Hepatol.1, 579, 1985) were generated to define new antigens of clinical or diagnostic relevance for this group of tumors. 1850 hybridoma supernatants were screened for restricted reactivity with the immunizing biliary adenocarcinoma cell lines by ELISA techniques (ALP, POX, beta-galactosidase). From the initial screening of 31 cell lines of malignant and non-malignant human tissues 5 monoclonal antibodies were selected for further testing. MAb GCA-2 showed a restricted pattern of reactivity with the immunizing biliary adenocarcinoma cell line SK-ChA-1 and weak crossreactivity with a colorectal cancer cell line and a hypernephroma cell line. On frozen sections of 47 different malignant and non-malignant human tissues GCA-2 reacted with biliary tract cancer, pancreatic cancer, and stomach cancer. Colorectal cancer was weakly positive in 1/8 tested samples. MAb GCA-2 has been useful for the detection of single tumor cells in malignant effusions. Normal gall bladder epithelium and 1/3 normal tissue samples from pancreas reacted with GCA-2. All other tested normal tissue samples were GCA-2-negative. The antigen defined by this monoclonal IgM antibody GCA-2 is heat stable. ABH blood group absorptions were negative. Partial absorptions were seen with the blood group precursor substance OG (Ii specificity) isolated from ovarian cyst fluid and Lewis^a blood group preparations (T.Feizi et al., J.Exp.Med.133, 39, 1971). GCA-2 is not crossreactive with the tumor marker CA 19-9, defining a sialyl-Le^a antigen. The GCA-2 defined antigen is shed from biliary adenocarcinoma cell lines into tissue culture supernatants as detected by a recently developed radioimmunoassay. In various sera from tumor patients with biliary adenocarcinoma, pancreatic, stomach, and colorectal cancer antigen was detectable with GCA-2. Specificity and sensitivity of GCA-2 in screening sera for gastrointestinal tract cancer still needs to be determined by testing series of sera from healthy individuals and patients with other cancers. The biochemical characterization of the GCA-2 defined antigen is under way.

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Col 10

EPITHELIAL (EPM-1) AND EXOCRINE (EXO-1)CELL MARKERS DEFINE GASTROINTESTINAL TUMORS

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The biology of gastrointestinal tumors and of the corresponding normal tissues is not so well understood. New markers for gastrointestinal tumors can now be defined by the use of cultured human tumor cell lines and the hybridoma technology. Our interest was, to define new markers on pancreas carcinoma and normal pancreas cells. Hybridomas were generated, screened and established after immunization of Balb/c mice with Capan-1 pancreas carcinoma cells. Three antibodies, which had reacted only with the three cultured pancreas cancer cell lines and not with a panel of 10 cultured non-pancreatic cancer and normal cells were analyzed on 200 tissue samples (fresh frozen) of tumorous and normal origin by indirect immunoperoxidase staining.
A common epithelial cell marker (EPM-1) was defined by two monoclonal antibodies (Pa-25/42) and a marker for exocrine cells by monoclonal antibody (Pa-G14). EPM-1 was detected on all 73 tissue samples of 18 different normal epithelial cell types and on 34/38 epithelial tumor tissue samples, including 7 exocrine pancreatic carcinomas. 59 non-epithelial cultured tumor and normal cells and 49 tissue samples of nonepithelial origin did not react with Pa-25/42. Antibody Pa-G14 defines the exocrine cell marker Exo-1, because it reacted with all 30 normal and most neoplastic adenoid cells and tissues, but not with 120 samples of non-exocrine origin (normal and neoplastic). Exo-1 was identified biochemically as a polar neutral glycolipid by thin layer chromatography. Both markers EPM-1 and Exo-1 were detectable in human saliva, bronchial, pancreatic and intestinal secretions by an ELISA test. In preliminary studies at least EPM-1 can also be found in human serea. Both markers EPM-1 and Exo-1 represent novel antigens for gastrointestinal tumors and may be important clinically for histological grading, detection of epithelial cells in effusions and as serum markers./I.Med.Mainz