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4.067

FUNCTIONAL CHARACTERIZATION OF THE LAMININ - BINDING DOMAIN OF THE 67 kDa LAMININ RECEPTOR.

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The interaction of tumor cells with laminin (LM) is a critical step in metastasis. Among the different LM receptor present on the surface of tumor cells, the 67 kDa receptor is unique for its high affinity and for its association with the malignant behaviour of tumor cells. We have identified the LM binding site of this receptor. Different synthetic peptides deducted from the cDNA sequence of the receptor have been studied, as well as their corresponding affinity purified polyclonal antibodies. A 20 aminoacid peptide has been identified that binds to LM with affinity and specificity similar to the whole receptor. We have used this peptide to examine the role of the 67 kDa receptor in LM-mediated cell functions, and particularly in the metastatic process.

4.068

HUMORAL MEDIATORS FOR CACHEXIA IN HEPATOMA-BEARING RATS

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Rats bearing the Yoshida ascites hepatoma AH-130 show an early and sharp loss of body weight as well as skeletal muscle protein, particularly due to enhanced protein catabolism. A redistribution of amino acids favoring the tumor growth is also observed. Marked perturbation of the hormonal homeostasis and production of cytokine-like factors occur soon after tumor implantation. Tumor necrosis factor (TNF)-like activity is detectable in the blood of AH-130-bearing rats. An elevation of plasmatic prostaglandin E_2 (PGE_2) is also observed during tumor growth. The hepatoma AH-130 cells, cultured for few days, release both IL-1 and TNF bioactivities, together with PGE_2. These mediators, probably involved in the development of cachexia, also seem to be correlated with the tumor cell proliferation rate.

4.069

RELATIONSHIP BETWEEN HLA ANTIGEN EXPRESSION IN GASTRIC ADENOCARCINOMA AND TUMOR STAGING

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Relationshp between HLA class I and II antigens detection and gastric adenocarcinoma progression is the subject of controversial debates. MoAbs to monomorphic determinants HLA-I (W6/32, ICO-53, Bral3/1), HLA-II (ICO-1, Bra series), epithelial antigens (Egp34, MoAb HEA 125; HMFG-1; CEA, MoAb HEA 19) were used. During examination of 59 adenocarcinoma cases on cryostat sections 3 patterns of MoAb reaction with the tumor were identified: negative, mosaic, monomorphic. Interrelationship between HLA class I and II molecule expression on the tumor was revealed. Loss of monomorphic HLA I and II determinants was more frequent for tumors of larger size, T4 according to TNM classification. In HLA-DR+ tumors N_0 TNM cases were predominant, in HLA-DR$^-$-N_1 cases (46 and 23%). Clinical stage III proved typical in HLA-DR$^-$ group (12 out of 13 patients).

4.070

Involvement of endothelial cell mannose-binding surface molecules in the adhesion of B16 melanoma cells to mouse liver sinusoids.

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We have demonstrated that liver-metastasizing tumor cells arrest and grow in the periportal segments (PPS) of the sinusoidal microvasculature. By microfluorimetry and confocal microscopy of FITC-conjugated ovalbumin (OVA) intraportally perfused in liver, we show that mannose receptor distribution is zone-related, with twice the density in the PPS as in the perivenous segments. We next studied the in vitro adhesion kinetics of 51-Cr-labelled B16 melanoma cells to endothelial cell monolayers derived from liver sinusoids, and the effect of endothelial cell pre-incubation with saturating concentrations of OVA (500 ug/ml, 2h) on tumor-endothelium adhesion. The tumor adhesion to OVA pre-incubated endothelium was significantly inhibited at 15 min (21%), 30 min (28%) and 60 min (47%) with respect to that in OVA-unexposed endothelium. We suggest that the specific mannose receptor of the sinusoidal endothelium may play a role in the adhesion of B16 melanoma cells to the PPS, the sinusoidal area preferred by liver-metastasizing tumors.

4.071

AUGMENTATION OF A TUMORIGENIC AND METASTASIZING POTENTIAL OF LOW-MALIGNANT SPONTANEOUSLY TRANSFORMED HAMSTER EMBRYO CELLS BY IN VITRO SELECTION WITH ACTIVATED MACROPHAGES (MP)

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MP may play an essential role in in vivo tumor selection and progression. We have shown that by in vivo passage of the low-malignant spontaneously transformed in vitro cells of STHE strain, highly susceptible to cytotoxic activity (CTA) of activated MP, variants resistant to CTA of the MP may be selected. In order to examine the possible role of the host MP in tumor progression we studied the ability of normal (resident) and LPS-activated peritoneal MP of Syrian hamsters to select malignant STHE tumor cells in vitro. The only STHE cell variants thus in vitro selected with activated MP were significantly more resistant to CTA of both, activated MP and hydrogen peroxide, and simultaneously they were more tumorigenic and more metastatic.

4.072

MECHANISM OF PANCREATIC CANCER CELL INDUCED PLATELET AGGREGATION.

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The aggregation of host platelets by circulating tumor cells (TCIPA) has been recognized as an important step in the metastatic process of tumor cells. We studied TCIPA in two cell lines of ductal human pancreatic cancer (PaCa 3, PaCa 44). Both cell lines were able to induce the aggregation of human platelet rich plasma in vitro. The aggregation could not be inhibited by apyrase, ASS or collagenase, suggesting that it was not ADP-, thromboxane- or collagen-dependent. Hirudin, a thrombin-antagonist was able to completely inhibit TCIPA, showing that TCIPA in pancreatic cancer is a thrombin-dependent process. Furthermore pretreatment of the tumor cells with trypsin or neuraminidase had no effect on TCIPA, suggesting that the thrombin generating activity of pancreatic cancer cells is not confined to the cell surface. Blocking receptors for adhesive proteins on the cell surface, which previously could be shown to facilitate tumor cell-platelet adhesion in vitro, with appropriate antibodies (anti-GPIIb-/IIIa, -VLA5 and VLA6) or RGD had no effect on TCIPA. This indicates that pancreatic carcinoma cell induced platelet aggregation does not require direct tumor cell-platelet contact.
We conclude that pancreatic carcinoma cells induce platelet aggregation through thrombin activation without direct tumor cell-platelet contact.