Symposium no. 4: Biology of Tumour Invasion and Metastasis

4.055

EXPRESSION AND FUNCTION OF VLA RECEPTORS IN PANCREATIC CANCER

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Cell surface receptors of the VLA family are thought to be important for invasive tumor growth and metastasis. Therefore the expression of VLA receptors in cryostat sections of normal and malignant human pancreatic tissue and 7 cell lines of human pancreatic carcinoma was examined by alkaline phosphatase immunohistochemistry. Furthermore in adhesion assays their possible contribution to cell-matrix adhesion was investigated.

VLA2, VLA5 and VLA6 could be detected in all pancreatic tissues (normal and malignant) and cell lines examined. Staining of VLA6 generally was stronger (+++) than of VLA2 (++) and VLA5 (+). While a loss of VLA6 in pancreatic cancer could not be detected, VLA2 and VLA5 were lost in 25-50% of all tumor cells. In normal pancreatic tissue all integrins were mostly confined to the basal-membrane orientated side of the cells. Whereas in pancreatic cancer the distribution was rather diffuse. In the adhesion assays VLA6 was shown to be a Laminin-receptor, while VLA2 acted as Collagen-receptor and VLA5 as receptor for Fibronectin. By using immunoprecipitation VLA6 was demonstrated to be present as $\alpha 6\beta 4$.

In pancreatic cancer a partial loss of VLA2 and VLA5 could be associated with a loss in anchorage or spatial arrangement of tumor cells. The uniformly strong expression of VLA6 in pancreatic cancer could be associated with invasive growth or metastasis.

4.056

Liver or lung colonization by F9 teratocarcinoma cells follows specific interactions with the target organ.

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When directly introduced into the blood stream by tail vein inoculation, undifferentiated F9 cells specifically colonize the liver. The lungs, despite being the first capillary network encountered by tail vein injected cells, are only very rarely colonized. On the contrary, the lungs become the main target organ for F9 cells after their differentiation has been induced by treatment with retinoic acid and cyclic-AMP.

We found that the above organ distribution pattern correlated with morphological and adhesive characteristics of differentiated and undifferentiated F9 cells, and also with their specific growth response to factor(s) present in liver or in lung.

4.057

SEMI-PERMANENT INTRACELLULAR ACCUMULATION OF LABEL BY RECEPTOR-MEDIATED ENDOCYTOSIS OF NEOGLYCOPROTEINS IN RAT COLON CANCER CELLS

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In order to study the process of metastasis of colon carcinome to the liver, we have developed a method of semi-permanent labelling of rat colon cancer cells with ^{125}I and fluorescein. The method is based on our finding that these cancer cells express membrane lectins, which bind and internalize glycoconjugates by receptor-mediated endocytosis. When conjugated with neoglycoproteins, which are ligands for these lectins, a radioiodinated, fluorescent non-degradable adduct was observed to accumulate for an extensive time period in the cytoplasm of the cancer cells. As much as 60% of endocytosed label resided in the cells after 5 days. The yield of uptake was sufficient to trace a single tumor cell in the circulation both by fluorescence and radioactivity. The endocytic nature of the uptake was evidenced by the finding that specific inhibitors of the endocytic machinery blocked the accumulation of label. Fluorescence microscopy following uptake revealed that the label accumulated in discrete vesicles, which were probably lysosomes.

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4.058

REDUCTION OF SOLID TUMOR METASTASES BY LYSOZYME: EFFECTS OF LPS. G. Sava, S. Pacor, A. Dobrina*, E. Nardon*. Institute of Pharmacology, School of Pharmacy and (*) Institute of Patology, School of Medicine, University of Trieste.

The oral administration of Lysozyme was shown capable of reducing primary tumor growth and lung metastasis formation with a mechanism involving the activation of host immunity. With the present investigation, we examine the effects of the i.v. treatment with LPS on the antitumor and antimetastic effects of lysozyme. 25 and 50 μg/mouse LPS, given on day 13 from s.c. implantation of 10^6 cells of Lewis lung carcinoma, cause a transient reduction of tumor growth, lasting 3-5 days and with a nadir at 48 hrs [reduction by 40-69%]. This effect correlates with the induction of TNF production at primary site. A similar reduction [at nadir by 49-63%] was shown in mice previously treated on days 5-12 with 100 mg/Kg /day lysozyme by oral route. LPS alone causes only marginal and not statistically significant antimetastatic effects; combined with lysozyme, LPS slightly augments the antimetastatic effects of lysozyme alone [optimal reduction by 78.8% vs 56%]. LPS thus lacks for correlations between reduction of primary tumor and inhibition of lung metastasis formation. The effects of the combined treatment with LPS and lysozyme at metastatic level are also unrelated to the reduction of primary tumor observed in this group, which is similar to that caused by LPS alone. It thus seems that the effects of LPS and Lysozyme on host immunity are independent, being only the latter capable of antimetastatic effects.

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4.059

THE ROLE OF THE IMMUNE SYSTEM IN METASTATIC SPREADING OF CANCER.

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According to our concept,cancer selectively metastasizes into the immune system,i.e. bone marrow,lymph nodes, spleen,lymphoid tissue associated with other organs (liver,lungs,etc.). In place of the existing notion about the passive transfer of the metastasizing cancerous cell together with the blood blow,and a random implantation in one of the most weak spots,it has been suggested that an active seizure of a cancerous cell by an immunocompetent cell occurs together with its programmed migration caused by the phenomenon of homing.Apparently,in some cases,immunocyte (macrophage) incorporates "a larger piece than it can swallow"and,after perishing, it forms a focus of metastatic growth in its own domain.Obviously,one should attach greater attention to the role of the immune system in carcinogenesis.

4.060

GLUCOSE STARVATION AND ACIDOSIS: Effect on Experimental Metastatic Potential. O.K. SCHLAPPACK, A. ZIMMERMANN, and Richard P. HILL, The Ontario Cancer Institute and Department of Medical Biophysics, University of Toronto, Toronto, Canada M4X 1K9. Exposure to oxygen deprivation in vitro has been reported to cause enhancement of experimental metastatic (colonization) ability of murine tumour cells (Young, S.D. et al. 1988, PNAS 85, 9533). Since the micromilieu in tumours results in exposure of the tumour cells to conditions of acid pH and nutrient deprivation, as well as hypoxia, we have examined the effect of exposure to acidosis (pH 6.5) and glucose starvation on methotrexate (MTX) resistance, cellular DNA content and the experimental metastatic ability of KHT sarcoma and B16F1 melanoma cells. Cells were exposed to these conditions for 24 and 48 hrs and tested for experimental metastatic ability or resistance to MTX either immediately following these exposures or after 24 or 48 hrs of recovery in normal growth medium. Both cell lines demonstrated an enhancement of colonization potential, which was most marked when cells were injected after 48 hrs of exposure followed by a 24 or 48 hrs recovery period. Flow cytometric analysis demonstrated an increase in the proportion of cells with excess DNA content for KHT cells but not for B16F1 cells. Despite this increase in the fraction of KHT cells with excess DNA following both glucose starvation and acidosis we observed only a small increase in MTX resistance following acidic exposure of cells and no change following glucose starvation. This study shows that transient exposure of murine tumour cells to an acidic or glucose deprived environment can cause progression in terms of metastatic potential.