Symposium no. 4: Biology of Tumour Invasion and Metastasis

4.031

ROTATIONAL STRESS AND EFFECTIVENESS OF RAZOXANE AND CYCLOPHOSPHAMIDE IN MICE BEARING LEWIS LUNG CARCINOMA.

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The effectiveness of antineoplastic treatments require an active function of immune and natural factors of resistance of the host to tumor progression. The effects of treatment with cyclophosphamide or razoxane have been examined on spontaneous metastasis in mice implanted with Lewis lung carcinoma as a function of tumor inoculum size, of conventional vs protected housing (PH) and of the periodic application of spatial disorientation (SD). With a reduced inoculum size, tumor takes do not occur in mice kept in the PH, but occur upon application of SD. With a larger inoculum size, tumor takes occur in all of the experimental groups, and metastasis weight is significantly increased by SD. The cure rate of cyclophosphamide of 9/10 in conventional housing increases to 10/10 in the PH, and is abolished by rotational stress. The antimetastatic effects of razoxane are also reduced by rotational stress. These results indicate that housing conditions and a psychological stressor can control tumor takes and metastasis formation. They also indicate that host's antitumor resistance effecters, which are susceptible to neuroendocrine modulation by a psychological stressor, participate to determine the effectiveness of cytotoxic (cylophosphamide) and antimetastatic (razoxane) antitumor drug.

4.032

Regulation and function of metastasis-specific cell surface molecules.

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Surface molecules mediate almost all steps necessary for tumour progression. With mAbs specific for surface antigens of metastasizing cells the cDNAs for two metastasis-associated antigens were isolated. One encodes the 67k laminin receptor, the other a splice variant of the CD44 glycoprotein. The laminin receptor may be differently modified or in an altered configuration on metastasizing cells. Whereas the standard CD44 receptor is widely distributed on nonmalignant cells, splice variants, carrying additional highly hydrophilic extracellular domains, are found only on invasive tumour cells and on very few nonmalignant cells, e.g. proliferating keratinocytes, alveolar macrophages and in the proliferative zone of the crypts of Lieberkühn. Coinjection of metastasizing cells and a variant specific mAb retards metastasis formation. cDNA transfection renders nonmetastasizing cells metastatic in the rat, using the spontaneous metastasis protocol.

Reber el al., Int. J. Cancer 46 (1990) 919-927
Gunther et al., Cell 65 (1991) 13-24
Hofmann el al., Cancer Res. (1991) In press

4.033

LINOMIDE - A NEW IMMUNOMODULATOR WITH ANTI-TUMOUR AND ANTI-METASTATIC EFFECTS

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Linomide, a 3-quinoline carboxamide is at present undergoing Phase II clinical trials against kidney cancer and during autologous bone marrow transplantation after AML. In both mice and man an increase in both the number and function of NK and T cells has been found. We have investigated the effect of Linomide in various rat prostate cancer models and the mouse Lewis lung tumour. Linomide exhibits a growth inhibitory effect against the full variety of Dunning R3327-models i.e. H-hormone sensitive, AT-1 & 2-anaplastic hormone insensitive, MATLu - metastatic to lung, MATLyLu - metastatic to lung and lymphnode. In the MATLu tumour model Linomide 100 mg/kg i.p. caused a 40 % reduction in the number of rats with lung metastasis when given from day 0 and a 20 % reduction when given from day 10. The average number of metastasis/lung was also significantly reduced, e.g. Control 28 ± 3, treated 12 ± 6. In Lewis lung 100 mg/kg p.o. given from day 7-11 caused a 30 % reduction of the primary tumour and a 50 % reduction in the number of metastasis.

4.034

A FREEWAY FOR BREAST CANCER CELLS ON ROUTE TO THE AXILLA.

Unlike the blood vascular system the fine lymphatic system of the human breast, like that of skin, is potentially open-ended (Histopath. 16:533,1990). Close junctions in the walls of its finest vessels can open passively, in the presence of stromal oedema, allowing the free passage of fluid and its content into the closed drainage system. This may render active intravasation of cancer cells superfluous.

The structural relation of ductal carcinoma cells to the various parts of the fine lymphatic system will be demonstrated on light- and transmission electron microscopy of per-operative biopsy specimens. The significance of the position of the cancer cells to their possibility for further spread into the closed drainage system will be discussed.

(F. Hartveit, Dept. of Path., University of Bergen, Norway).

4.035

Antiinvasive activity of dequalinium on K1735-M2 melanoma cells in vitro.

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Signal transduction cascades involving protein kinase C (PKC) are considered to modulate cellular activities important for tumor cell invasion. In our study, we have investigated the effect of dequalinium, a potent PKC inhibitor, on K1735-M2 melanoma cell growth, directional migration and invasion in vitro. Invasiveness was tested through confrontation of melanoma multicellular spheroids with embryonic chick heart tissue. Quantitative evaluation of invasion was performed by using a computerized image analysis program. 2 μM dequalinium exhibited a considerable antiinvasive effect, which was indicated by various measuring parameters. Inhibition of invasion is suggested to be due to impairment of both melanoma cell growth and directional migration. Ultrastructural investigations showed that dequalinium caused obvious changes in mitochondria. Thus, in addition to an inhibitory effect of dequalinium on PKC the interference with main mitochondrial functions may account for the antiinvasive activity.

4.036

ALTERED TRANSPORT AND PROCESSING OF CATHEPSIN D IN HUMAN TUMOUR CELLS WITH METASTATIC PHENOTYPE

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A critical step in the metastatic cascade is the degradation of the extracellular matrix and basal membranes, a process for which proteases are required. Among such proteases cathepsin D has strongly been associated with the degree of malignancy in various tumours. We have analyzed the transport of this lysosomal endopeptidase in hepatocarcinoma HepG2, coloncarcinoma HT-29 and breast cancer MCF7 cells. The level of cathepsin D secreted into the medium ranged between 40 and 60 per cent of the total amount produced. The secreted proenzyme showed enzyme activity when assayed under acidic condition. Pulse-chase experiments indicated that secretion of procathepsin D was an early event and increased along with the time of incubation. The intracellular transport and processing of cathepsin D showed relevant differences among the cell types considered.