Symposium no. 4: Biology of Tumour Invasion and Metastasis

4.049

Alteration of intracellular Ca^{2+} modulates MTS1 and NM23 gene expression in B16 murine melanomas. C. Parker and G.V. Sherbet, Cancer Research Unit, The Medical School, Newcastle upon Tyne, U.K.

MTS1 is a metastasis associated gene highly expressed in high metastasis tumours. NM23 is a putative metastasis suppressor gene. A modulation of metastatic behaviour by agents such as retinoic acid and melanocyte stimulating hormone (MSH) resulted in the modulation also of the expression of the MTS1 and NM23 genes in the B16 melanoma. Thapsigargin, which raises intracellular Ca^{2+} levels, and verapamil, which blocks Ca^{2+} influx, both down regulated these genes.

Verapamil and MSH enhanced melanisation. However, these agents had opposite effects on MTS1 expression. These data suggest that signalling pathways for melanisation and MTS1 regulation are different.

4.050

THE EFFECTS OF LAMININ ON SCLC IN RELATION TO THE PATTERN OF EXPRESSION OF LAMININ RECEPTORS

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The expression of laminin receptors was investigated on 11 small cell lung cancer (SCLC) cell lines. The integrins VLA-1, 3 and 6 and the 67 KDa monomeric receptor were found on 10 cell lines, with different levels of expression, whereas the VLA-2 receptor was absent on all cells tested. Only the NCI-H446 cell line did not express any of these laminin receptors. The adhesion of cells with large amounts of $\alpha_6\beta_1$ and 67 KDa receptors to laminin was partially or completely inhibited by the anti-VLA-6 G0H3 MAb, but not by the anti-67KD MAb, which indicated that the in vitro adhesion was mainly mediated by the VLA-6 integrin. Laminin was also found to enhance the SCLC growth in nude mice. However, none of the studied receptors seem to be involved in the laminin-induced increase of cell proliferation. In fact, the NCI-H446 cell line, which did not express any of the laminin-receptors, was also stimulated to grow in vivo by laminin.

4.051

CORRELATION BETWEEN SERUM AND TISSUE MCA IN BREAST CANCER. Quaranta M, Micelli G., Simone G., Donadeo A, Petroni S, Muncipinto A, Sepia MG. Oncology Institute – Via Amendola, 209 – 70126 BARI – ITALY.

MCA is a glycoprotein recognized by the monoclonal antibody b12 on cytosol and in the serum of breast cancer patient(pts) and recently, also on tissue with the immunohistochemical technique (ICA).A good correlation exists between MCA plasma and cytosol measurements, providing information on locoregional extension or distant metastases.Its use for early diagnosis has yet to be demonstrated and could be related to the lack of correlation between serum and ICA markers.We studied 23 ductal infiltrating carcinoma pts who underwent radical mastectomy(N+ 20 and N- 3).The ICA method was used for MCA assay on tissue frozen at -80°C and the immunoenzymatic method for MCA serum evaluation (cut-off:11 U/ml).The ICA method demonstrated the presence of ER, PgR, oncoprotein p53 and Ki67(antigen associated with cell proliferation).Serum MCA/ICA correlation was 70%(p=0,07), with 16/23 breast cancer pts and 4/6 control pts with benign tumors.Serum MCA/ICA showed a weak correlation with ER(39%) but a higher correlation with PgR(61%), p53(56%) and Ki67 (50%).Correlation between serum MCA/ER was 41% and higher for PgR(54%), p53 and Ki67(50%).Our data indicate, therefore, a difference between MCA in situ and its serum levels, which limits the validity of this marker in preoperative diagnosis of breast cancer.

4.052

Plasminogen activator can also act as an activator of glioma cell secreted metalloproteinase. Alison Reith, George Milne and Garry J. Rucklidge, The Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB, U.K.

Rat glioma cell lines BT4C and BT5C display a destructive mode of invasion in vivo and in a model system of invasion in vitro. This has been attributed to a secreted metalloproteinase which has been affinity purified in a latent form from conditioned culture medium. The enzyme is activated by the action of the aminophenylmercuricacetate in vitro but the mechanism of activation in vivo has not been identified. Zymogram analysis of the culture medium of these cell lines indicates that they also secrete plasminogen activators. Using a radiolabel release assay we have shown that plasminogen activator converts glioma cell metalloproteinase from the latent to the active form in vitro and propose this as a mechanism for a similar activation in vivo contributing to the degradative invasion properties of these cell lines.

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4.053

Anti-invasive properties of extracellular matrix proteins using an in vitro model system. Alison Reith[1], Garry J. Rucklidge[1] and Rolf Bjerkvig[2]. [1]The Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB, U.K. [2]The Gade Institute, Department of Pathology, University of Bergen, Bergen, Norway.

Fetal rat brain cells, cultured in agar coated flasks, aggregate to provide the target tissue and rat glioma cells form spheroids, which provide the tumour material in a three-dimensional system for the study of brain tumour invasion. Brain aggregates are confronted with the glioma spheroids and the invasion process observed. Ependymal cell clusters within brain aggregates contain laminin, fibronectin and collagen type IV and these areas are resistant to invasion by glioma cells. For two glioma cell lines the addition of laminin prevented the invasion of spheroids into fetal brain aggregates. The spreading of glioma spheroids on laminin-coated plastic was also inhibited compared to fibronectin and collagen type IV. Additional studies show that fetal rat brain cells do not aggregate if laminin is present. Laminin therefore appears to play a key role in the prevention of glioma invasion in vitro.

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p53 wild-type differentially affects murine metastatic variants.

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p53 was originally considered to be an oncogene, but several convergent lines of research have indicate that the wild-type gene product actually functions as a tumor suppressor gene. In transfection studies, the wild-type murine p53 gene has been shown to inhibit the transforming ability of mutant p53 genes in rat embryo fibroblasts. To determine whether p53 w.t. expression could influence the metastatic phenotype we have produced transfectant clones from some murine metastatic variants. In particular low (BC215) and high (C87) metastatic lines derived from Lewis Lung Carcinoma (3LL) have been transfected with a plasmid containing human p53 w.t. gene under the SV40 promoter. Clones derived from the two metastatic variants transfected with p53 w.t. have been studied for proliferation capacity. Our findings indicate that both recipient cell types transfected with wild-type p53 cDNA form five to ten fold fewer colonies than those transfected with vector without p53 cDNA. In addition, colony formation by wild-type p53 transfectants occurred with reduced efficiency in low metastatic BC215 cells. These results suggest that the wild-type p53 gene inhibits the clonal growth of both cells (C87 and BC215) and that the more malignant cells (C87) may be less sensitive to the inhibitory effects of wild-type p53.

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