Parallel Symposium No. 4

Biology of Tumour Invasion and Metastasis

Chair

Volker Schirrmacher
Deutsches Krebsforshungszentrum, Heidelberg

Co-Chair

Silvio Parodi
Istituto Nazionale per la Ricerca sul Cancro, Genoa

PS 4.1

Epidermal Growth Factor Receptor (EGFR) in Mammary-Carcinoma Metastasis.

R.B.Lichtner#, A.Kittmann, M.Wiedemuth, A.Ullrich*, V.Schirrmacher and K.Khazaie.
German Cancer Research Center, Heidelberg, D-6900; #Research Laboratories of Schering AG, Berlin, D-1000; *Max Planck Institute for Biochemistry, Martinsried bei München, D-8033

High expression of EGFR in metastases of human breast tumors as compared to the primary tumor suggests a contribution of EGFR to metastatic potential. In the 13762NF rat mammary tumor highly metastatic clone MTLn3 cells express functional EGFR while low metastatic clone MTC cells express only residual amounts. Using retroviral vectors we introduced a full length cDNA of the human EGFR into these cells. Expression of human EGFR was stable and receptors were functional with respect to surface expression and EGF-stimulated phosphorylation. Implantation of MTLn3 and MTC cells into female nude mice resulted in the same pattern of metastasis as in syngeneic rats. The relative metastatic potentials of the transfected cell lines in nude mice and rats are compared.

PS 4.2

INVASION OF A RECONSTITUTED BASEMENT MEMBRANE BY TUMOR CELLS AND ITS MODULATION

Adriana Albini
Istituto Nazionale per la Ricerca sul Cancro, 16132 Genova, Italy

Invasion of basement membranes is a critical step in the metastatic process. We have established an in vitro assay which uses a reconstituted basement membrane (Matrigel) coated on top of chemotaxis filters in a Boyden chamber assay. We and other investigators have found a very good correlation between malignant behavior in vivo and cell invasiveness of Matrigel (chemoinvasion) in vitro. This assay has also proven useful for studying the modulation of the invasive phenotype. We will summarize some of our most recent results using the chemoinvasion assay: Transfection of activated ras oncogene in recipients of different origin (3T3, low metastatic murine melanoma and breast epithelial cells) induces the invasive phenotype 3T3 cells transformed with chemical carcinogens also become invasive. Invasion can be inhibited by certain biological response modifiers (interferons, vitamin A) and other compounds such as suramin and TIMP-2 (tissue inhibitor of metalloproteinase). TIMP-2 is effective at concentrations as low as 10-20 μg/ml. We have also adapted this assay to the study of angiogenesis; cells derived from the angiogenic lesion, AIDS-associated Kaposi's sarcoma, induce endothelial cells to cross the reconstituted basement membrane. The Matrigel invasion assay represents a useful model for the "pre-screening" of potential anti-invasive, anti-angiogenic and anti-metastatic agents. *CNR n°90.00.140PF70*

PS 4.3

FUNCTION OF THE FIRST DOMINANT METASTOGENE: A NEW SURFACE GLYCOPROTEIN CONTROLS A METASTASIS-SPECIFIC GENETIC PROGRAM.

Margot Zöller, Martin Hofmann, Helmut Ponta, Sigfried Matzku, Peter Herrlich
Deutsches Krebsforshungszentrum Heidelberg, Institut für Radiologie und Pathophysiologie. Im Neuenheimer Feld 280. D-6900 Heidelberg, Germany and
Kernforshungszentrum Karlsruhe, Institut für Genetik und Toxikologie, P.O. Box 3640, D-7500 Karlsruhe 1.

Rat and human tumor cells express a range of different splice variants of the glycoprotein CD44, making use of at least nine exons in addition to those of the standard CD44 protein (sCD44 which is expressed on a variety of cells, e.g. T and B lymphocytes). A variant derived from a highly metastatic rat pancreas adenocarcinoma cell line, when overexpressed in any one of several non-metastasizing rat tumor cells, confers full metastatic properties in the spontaneus metastasis assay. An active minimal version of the gene carries the sequence of only one additional exon in the frame of CD44. The new dominant genes control a complex genetic program obviously required for metastasis formation. We, therefore, suggest its classification as metastogene. These metastogenes add to the complexity of dominant and recessive oncogenes known to date.

References:
Gunthert et al., Cell 65, 13-24, 1991
Hofmann et al., Cancer Research, 1991, in press.

PS 4.4

GENE TRANSFECTION AND THE IMMUNE RESPONSE TO TUMORS.

PHILIP FROST, M.D. PH.D., UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER, HOUSTON, TX.

We have demonstrated that the transfection of murine tumor cells with the gene coding for the hemagglutinin antigen of influenza virus can confer an immunogenic phenotype on such cells. Not only do these cells fail to grow, but they can also protect against a systemic challenge with non-transfected parental cells. Similar findings will be described regarding transfection of tumor cells with lymphokine genes, including IL-2, IL-4, IL-5, and with the cytokine gene for interferon-γ. These results offer a reason for cautious optimism regarding the potential usefulness of such approaches in the immunotherapy of neoplasia. An outline of such applications will be presented.