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THE FUNCTION OF CD44 VARIANTS IN PSYCHOLOGY AND METASTASIS

M. Zoller, German Cancer Research Center, Hiedelberg, Germany

CD44 originally described as a lymhocyte homing receptor comprises a family of membrane integrated glykoproteins, which differ by posttranslational modifications as well as the primary aminoacid structure. By alternative splicing, up to 10 additional exons can be inserted in the extracellular part of the smallest isoform of CD44 (CD44s), which is found on lymphcytes, connective tissue and many epithelial cells, while larger isoforms (CD44v) are predominantly expressed on tumor cells. One of these additional exons, exon v6, was shown to be of particular importance in the process of tumor progression. In a variety of rat tumor models, exon v6 was expressed on all lines, which metastasize via the lymphatic system, but not even on one line, which grows non-invasive. The importance of exon t6 for metastasis formation was confirmed by induction of the metastatic phenotype via transfection of non-metastasizing tumor cells with cDNA or CD44v. The functional relevance of exon v6 was sustained by blocking metastatic progression with a monoclonal antibody (1.ASML). Anti-CD44v apparently interferes with tumor progression by inhibiting embedding of tumor cells in the draining lymph node. Preliminary studies support the hypothesis that CD44v may not act via ligand interaction, but by interfering with ligand interactions of the invariant part of the molecule. The observation that exon v6 is not only involved in metastasis formation, but plays a functional role during lymphocyte activation, will help to unravel the function of this unique molecule, whose expression suffices to transfer the metastatic phenotype.

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INTEGRINS AND METASTASIS

Imhof, B.A.#, Ruiz, P.#, Friedrichs, K.*, Franke, F+, Terpe, A.+, Dunon, D#.
#Basel Institute for Immunology, Grenzacherstrasse 487, Basel, Switzerland.*Department of Gynecology, Medical School, University of Hamburg, Hamburg, Germany; +Department of Pathology, Medical School, University of Giessen, Giessen, Germany

Metastasis of transformed cells involves the detachment of cells from the primary tumor, their transport through the blood circulation or the lymphatics, adhesion to the vascular endothelium, extravasation and their lodgement to secondary tissue sites. Since tumor cells invade normal healthy tissue, they use vascular adhesion molecules normally involved in homing of circulating hemopoietic cells. The EA-1 antibody recognizes α6 integrins on the apical surface of vascular endothelium and blocks cell-cell interaction. At present α6 integrins are described as laminin receptors responsible for cell-extracellular matrix contacts. Contrary to our expectation, the EA-1 antibody solely blocked cell-cell but not cell-laminin adhesion. This suggests the existence of a new ligand for α6 integrins besides laminin. At present we are producing chimeric soluble α6 intgerins in order to identify this alternative ligand. The EA-1 antibody blocked the adhesion of invasive tumor cells to frozen sections. Furthermore, in an in vivo metastasis model, it prevented experimental lung metastasis by blocking the adhesion of invasive melanoma cells to the luminal side of the vascular endothelium.

Using antibody EA-1, expression of α6 integrin was studied in tumor specimen of 119 breast cancer patients. These tumors were evaluated for clinically relevant risk factors (Tumor size, node status, histological grading, steroid receptor level). High α6 integrin expression correlated with adverse prognosis. In comparison with the established risk factors α6 integrin expression was of superior prognostic significance concerning overall survival. We consider α6 integrin expression as a novel potential marker for poor prognosis in breast cancer.

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RECEPTORS FOR LAMININ AND METASTATIC PROCESSES

P.M. Martin

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E-CADHERIN VERSUS TUMOR INVASION

Van Roy, F.[1], Vleminckx, K.[1], Berx, G.[1], Keirsebilck, A.[1], Bracke, M.[2], Deman, J.[2], Vandenbossche, G.[2] and Mareel, M.[2]
[1]Laboratory of Molecular Biology and [2]Laboratory of Experimental Cancerology, University of Ghent, Belgium

E-cadherin (uvomorulin) is a Ca^{2+}-dependent epithelial cell-cell adhesion molecule with potent morphogenic action. Compelling evidence was obtained for an invasion suppressor role of E-cadherin in carcinomas: E-cadherin-specific neutralizing antibodies and antisense plasmids induce invasiveness, whereas efficient expression of sense cDNA plasmids counteracts invasiveness (Van Roy and Mareel, 1992, Trends Cell Biol. 2:163-169). In order to detect and identify mutations in the E-cadherin genes of malignant tumors, an extensive structural analysis of the human E-cadherin gene was undertaken. Besides E-cadherin inactivation by irreversible genetic defects, transient downregulation of E-cadherin may occur in invasive tumor cells. Accumulation of E-cadherin mRNA and protein was found to be reversibly sensitive to microenvironmental influences such as tumoral growth *in vivo* and cytokines *in vitro*. Tyrosine phosphorylation of cadherin-associated cytoplasmic catenins and exposition of large proteoglycans at the plasma membrane are other means to neutralize the E-cadherin function and induce invasiveness. Alternatively, administration of specific drugs or factors (IGF-1) can upregulate E-cadherin functionality and inhibit invasion.

FVR and GV are, respectively, Research Director and Research Assistant with the N.F.W.O., Belgium. AK holds an IWONL fellowship. Research supported by FGWO, ASLK, SVTK and Belgian Cancer Association.

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ADHESION RECEPTORS AND LYMPHOMA DISSEMINATION

C.J.L.M. Meijer, Department of Pathology, Free University Amsterdam

Lymphocyte migration and recirculation of lymphocytes between the lymphoid organs and other tissues is thought to be essential for effective immunologic surveillance and dissemination of the immune response. In addition, lymphocyte recirculation may also be important in the segregation of lymphocytes with particular functions in the different lymphoid tissues. Furthermore, insight in the molecular basis of these processes may help us to understand lymphoma spreading and metastatic invasion of carcinoma cells.

Lymphocyte migration involves 3 steps:

a) lymphocyte-HEV interaction
b) lymphocyte extracellular matrix interaction mainly mediated via the β integrins (VLA 1,2,3,4,5,6)
c) lymphocyte motility

The existence of specific homing receptors mediating lymphocyte-HEV interaction has been supported by the development of monoclonal antibodies that inhibit lymphocyte binding to endothelium in man and rodents. The lymphocyte plasma membrane antigens involved in the recognition and adherence of HEV are called homing receptors. Their counterparts on HEV, which are in fact tissue specific position markers on endothelial cells, are called vascular adressins.

Homing receptors and adressins belong to 4 different families of adhesion receptors :

1. Selection
2. Integrins
3. Ig superfamily
4. CD_{44} group

The expression of homing receptors and vascular adressins are dependent on the activation and differentiation status of the lymphoid and/or endothelial cell. Lymphoid leukemias and NHL represent the malignant counterparts of normal lymphoid cells in different steps of activation with which they share many characteristics, including the expression of various adhesion receptors. In this paper the expression of the different families of adhesion receptors and their purative role in lymphoma dissemination is discussed.

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ASSOCIATION BETWEEN THE EXPRESSION OF CELL ADHESION MOLECULES AND THE DEVELOPMENT OF METASTASES IN MELANOMA.

Johnson J.P., Sers C., Rothbächer U., Riethmüller, G. Institute for Immunology, Goethestrasse 31, 80336 Munich 2, Germany

In order to identify molecular changes which accompany the development and progression of human cutaneous melanoma, we have isolated monoclonal antibodies which show differential reactivity in situ with benign and malignant melanocytic lesions. Two of the antibodies identified antigens which were only rarely detected on benign lesions but which were present on more than 70% of advanced primary tumors and metastases. Interestingly, early thin primary tumors which have only a low probability of developing metastases expressed these two antigens from a melanoma of cDNA expression library revealed at both are cell surface molecules. One of the antigens ICAM-1, molecule known to mediate the adhesion of leukocytes to other cell types. The second molecule which we have called MUC18, is most closely related to molecules which mediate cell analyses of a large number of primary tumors indicates that the expression of both ICAM-1 and MUC18 by human melanoma cells is associated with their ability to metastasize in nude mice. Thus the de novo or increased expression of cell adhesion molecules mediating heterotypic interactions may be an important step in the development of metastatic lesions by solid tumors.