Parallel Symposium No. 2

Biology of Melanomas

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PS 2.1

PARACRINE GROWTH FACTORS IN MELANOMA PROGRESSION. Meenhard Herlyn, The Wistar Institute, Philadelphia, PA, USA

Human melanoma cells produce an abundance of growth factors. Individual cell lines have been identified expressing mRNA and protein for up to seven different factors including bFGF, TGF-α, TGF-β, PDGF-A, PDGF-B, IL-1α, IL-1β, IL-8, and MGSA. bFGF and, in few cell lines, MGSA have experimentally demonstrated autocrine growth stimulatory functions in melanoma. Melanoma-derived growth factors and cytokines also effect growth and phenotype of surrounding normal cells and regulatory networks can now be established to better understand the complex interactions between malignant and normal cells in invasion and metastasis. The different steps of the metastatic cascade are regulated by tumor-derived and normal cell-derived factors which act in concert to allow the dissemination of malignant cells. Regulatory pathways have recently been established that involve growth factors, extracellular matrix proteins and proteolytic enzymes with their inhibitors.

PS 2.2

TYROSINE PROTEIN KINASES IN NORMAL AND MALIGNANT MELANOCYTES. Dr. Ruth Halaban, Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06510, U.S.A.

The growth factors for normal melanocytes, FGF, HGF and MGF, stimulate the FGF-Receptor, Met, or c-Kit, respectively. Human melanoma cells express bFGF which continuously activates the bFGF-receptor kinase. Mutations causing white spotting, were identified in the mouse in genes encoding growth factor receptors or their ligands. Taken together, the results suggest that loss of normal melanocytes in the skin, such as in piebaldism, and uncontrolled growth of melanomas are due, in part, to deficiency in or constitutive activation of receptors with tyrosine kinase activity, respectively.

PS 2.3

GENETIC ANALYSIS OF TUMOR REJECTION ANTIGENS
T. Boon, C. Traversari, P. van der Bruggen, B. Van den Eynde and B. Lethé. - Ludwig Institute, Brussels Branch - Belgium.

We have cloned the gene coding for one of the four antigens recognized by syngeneic CTL clones on mouse tumor P815. No difference was observed when we compared the sequence of this gene, cloned from tumor cells, to the sequence of the equivalent gene cloned from normal kidney cells of the same mouse strain. The antigenicity is therefore not the result of a mutation affecting the gene expressed in the tumor. Little or no expression of the P1A gene was observed in normal tissues. Recently, we have applied a similar method to transfect the expression of one of the antigen recognized by autologous CTL clones on the human melanoma line MZ2-MEL. As a first step towards the cloning of this gene, we tried to obtain transfectants expressing the antigen. A variant of MZ2-MEL which had been selected with a CTL clone for the loss of the antigen E was cotransfected with genomic DNA of the original melanoma line and selective plasmid pSVtkneoß. The geneticin-resistant transfectants obtained were screened for their ability to stimulate the production of tumor necrosis factor by the anti-E CTL clone. A transfectant expressing antigen E was identified. When this transfectant was submitted to immunoselection with the anti-E CTL clone, the resulting antigen-loss variants were found to have lost several of the transfected pSVtkneoß sequences. This indicated that the gene coding for the antigen had been integrated in the vicinity of pSVtkneoß sequences, as expected for cotransfected DNA.

PS 2.4

MOLECULES ASSOCIATED WITH METASTASIS FORMATION IN MELANOMA. J.P.Johnson, Institute for Immunology, Goethestrasse 31,8000 Munich 2, Germany

The isolation of cDNAs encoding molecules strongly expressed on advanced primary and metastatic melanoma but only rarely expressed on benign and early malignant lesions may lead to the identification of molecules which play a role in metastasis development. The cloning of 2 such molecules (P3.58,gp89; MUC18,gp113) indicated that both appear to be cell adhesion molecules. P3.58 was found to be identical to ICAM-1 and to mediate adhesion between tumor cells and leukocytes. MUC18 is related to molecules mediating cell-cell adhesion during the development of the nervous system. The progression of primary melanomas to metastatic disease is thus characterized by the de novo expression of several molecules mediating cell-cell adhesion. The expression of such molecules provides the tumor cell with a new range of potential adhesion partners and may contribute to invasion and intra- and extravasation.