Mel 05

FLOW CYTOMETRIC (FCM) STUDIES ON THE BIOLOGY OF MALIGNANT MELANOMAS AND PREMALIGNANT LESIONS

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FCM DNA-measurements were done in 434 primary melanomas, 480 melanoma metastases and 59 congenital melanocytic nevi. Abnormal DNA-stemlines were detected in 41 % of the primary tumors, in 75 % of the metastases and in 8 % of the congenital nevi. The occurrence of abnormal DNA-stemlines proved to be an indicator of poor prognosis. 37 % of the primary tumors were multiclonal thus denoting tumor cell heterogeneity.
Sequential measurements were possible during the course of the disease in 105 patients. Genetic instability - that means changes of the DNA-index in the tumor cell lines to higher or lower values - was observed in 62 % of the patients evaluated. The course of the disease in these cases was more progressive, resulting in a shorter survival time. Compared with tumor cell heterogeneity, genetic instability seems to be a superior prognostic criterion indicating poor prognosis. These results obviously confirm NOWELL's hypothesis (Science, 194, 23 - 28, 1976) that genetic instability may select more progressive cell lines.
The occurrence of abnormal DNA-cell lines in congenital melanocytic nevi probably is an indicator of a premalignant condition in cases where histologic examination does not reveal any evidence for malignant melanoma.

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Mel 06

EXPRESSION OF CLASS I AND CLASS II HLA ANTIGENS IN PRIMARY AND METASTATIC MELANOMA: RELATION TO PROGNOSIS

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Class I HLA(ABC) antigens are necessary for interactions of cytotoxic T cells with target cells. Class II HLA (DR, DP, DQ) antigens that are constitutively expressed on antigen-presenting cells can be induced in a variety of cells by y interferon.
Normal melanocytes bear low amounts of class I and lack class II HLA antigens. Immunohistological studies on benign and malignant melanocytic tumors with monoclonal antibodies against class I and II HLA antigens revealed that HLA ABC was absent or low in dermal nevi, and strongly expressed by nevi with mononuclear cell infiltrates. Nevi, however, lacked considerable amounts of HLA-DR, DP and DQ antigens. Primary melanomas broadly expressed HLA-ABC antigens in most cases. Considerable expression of class II HLA was found in 40% of primary melanomas, and increased in proportion to invasiveness of the tumors. HLA-DR (and DQ) expression in primary melanoma was significantly associated with the amount of intratumoral T cell infiltrates. The peritumoral infiltrate was not related to the class II phenotype of the tumors. Independently from tumor thickness, expression of HLA-DR on more than 10% of tumor cells was significantly associated with metastatic spread of primary tumors.
In melanoma metastases, we found a lack of HLA-ABC in advanced stages (visceral metastases). This feature, when present in locoregional metastases, was an adverse prognostic sign. Even worse, however, was broad expression of HLA-DR antigens in locoregional metastases. Metastases expressed more often HLA-DR and -DP antigens than primary tumors.
Our data suggest that loss of class I HLA-antigens and increased expression of class II antigens are associated with poor prognosis of melanoma.

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Mel 07

CHARACTERIZATION OF CELL SURFACE ANTIGENS DISTINGUISHING BENIGN AND MALIGNANT HUMAN MELANOCYTES

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A considerable number of monoclonal antibodies directed against melanoma associated antigens have been described. However, most of these antigens were found to be expressed on benign melanocytic lesions in essentially the same way as on melanoma cells. Recently we have described two glycoproteins, gp75 and gp89, which are differentially expressed on benign and malignant melanocytic lesions.

In a more extended study 42 benign nevi and 56 malignant melanomas were investigated by immunohistochemical methods. Whereas 76% of the melanomas expressed gp75 and 89% gp89, only 2% of the nevi were positive for gp75 and 14% for gp89. The expression of both antigens was not homogeneous within a given lesion but revealed distinct subpopulations. Staining of nevi was usually weaker than melanomas and less cells were labelled.

For further investigation of these antigens, molecular cloning of gp89 was approached by DNA transfection into mouse L-cells. Clones from the second round of transfection were obtained which express gp89. Attempts to isolate the gene for gp89 by hybridization with human DNA probes are in progress.

In addition, structural variation of gp89 observed in different cell lines is being further investigated.

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Mel 08

SENSITIVITY, SELECTIVITY, AND SPECIFICITY OF MONOCLONAL ANTIBODIES DIRECTED AT TUMOR ASSOCIATED ANTIGENS FROM METASTATIC MELANOMA

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Melanoma as any other cancer develops biological heterogeneity from a single clone origin. This heterogeneity manifests itself as a phenotypic variation with alteration of cellular morphology, varying sensitivity to immune defences, varying growth rates, variable metastatic potential including organotropy and varying susceptibility to therapeutic interventions.
Members of the EORTC-MMCG have recently developed a number of MAB directed against various melanoma associated antigens using a common bank of 140 melanoma cell lines. 30 purified antibodies were testes within the group and the most efficient selected for further development.
Melanoma metastases from regional lymphnodes and various organs, bone marrow, normal human and metastatic tissue and from a variety of ectodermal, entodermal, and mesenchymal tumors were examined. Imprint as well as aspiration cytology was prepared before freezing the material and preparing cryostat sections.
The results show a wide variety of interesting crossreactions against normal and neoplastic human tissue, particularly with neurectodermal differentiation antigens and ontogenetically similar tumors.
It appears possible to reproducibly characterize the quality and sensitivity of MAB directed against melanoma associated, which is a conditio sine qua non for their use in clinical medicine. It has become possible to use a panel of MAB-conjugated markers for in vivo and in vitro tumor imaging as well as conjugated cytostatic agents for a specific therapy.

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