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Reproducible HLA class I altered phenotypes found in different metastasis of two patients immunized with tumor specific peptides

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The HLA class alteration of five different metastasis obtained from two patients immunized with Melant/A-MART 1, Tirosinase and gp100 tumor peptides have been characerized. In the first patient, it was obserbed the presence of a dual population of melanoma cells in the three metastasis i.e. one HLA positive and the other with lost of heterozigocity at chromosome 6p region and therefore with and HLA haploype loss(A2,B60,Cw1).

The absence of HLA A2 could explain why this patient did not respond to the immunization protocol since this HLA molecule is the restriction element for the tumor peptides used. The primary tumor of this melanoma patient presented an LOH located at the 6q chromosomal region, but only in the vertical growth phase (VGP) of the lesion. This analysis revealed that whereas LOH at 6q could be detected in DNA of VGP of the primary lession, LOH at 6p was obserbed only in DNA from metastasic material.

The second patient presented also two metastasic lessions with the same HLA molecular defect i.e. an HLA B locus downregulation (HLA B51,B70). In this patient one lession positive metastasis regressed while the other progressed rapidly. These data provide the first indication that multiple metastasis generated in the same host could have identical altered HLA class I phenotypes.

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Modulation of tumor necrosis factor (TNFα) in cancer therapeutics

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When given systemically, TNFα has marked antitumor activity in mice but cannot be used effectively in humans because of severe limiting toxicity. Its antitumor action in humans has been demonstrated, however, as by limb perfusion and intracarotid administration TNFα is effective against limb sarcoma or melanoma and glioblastoma, respectively. It would be important to improve the therapeutic index of TNFα. Based on the exploitable immunomodulating effects of Adriamycin (DOX), combination regimens of DOX plus TNFα at non-toxic doses were designed which were markedly synergistic and caused complete immunity-dependent cures of lymphoma EL4 and breast adenocarcinoma EO771 in syngeneic C57Bl/6 mice. The curative effects on EL4 were T-cell dependent and were accompanied by the development of marked immunological memory.

A different approach is also being pursued in this laboratory to modify the actions of TNFα. A previously unknown protein, TNFα inhibitory protein (TIP-B1), has been identified, purified to homogeneity and partially characterized. TIP-B1 is activated/induced by TNFα and prevents the apoptotic effects of TNFα plus cycloheximide after preincubation of target cells. TIP-B1 does not bind nor destroys TNFα and does not affect TNFα binding to its receptors. A partial cDNA has been expressed and found to encode a protein which exhibited part of the activity of the natural TIP-B1. Antibodies against this partial rTIP-B1 cross react with the natural protein. TIP-B1 is present in specific areas of a variety of normal tissues such as lymphoid organs or breast tissues under different physiological conditions; it is present in the cytoplasm of target cells but is found in the membrane fractions after exposure of the cells to TNFα. The potential exploitation of TIP-B1 in cancer therapeutics is expected to be based on an antagonism of TNF action in those tissues where TNFα has growth promoting activity; conversely antibodies against TIP-B1 may increase the antitumor effects of TNFα in these tissues where the cytokine has apoptotic effects.

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