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Immunophenotyping of human tumor antigens

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Abstract

Current concepts of active immunization procedures employing cancer vaccines focus on two main antigenic targets: MDAs (Melanocyte Differentiation Antigens) and CT (Cancer Testis) antigens. MDAs are normal constituents of melanocytes. Their presence in melanomas, the malignant counterpart of melanocytes, appears as a logical consequence of lineage associated aberrant growth. As their name implies, CT (Cancer Testis) antigens are present in germ cells of the adult testis and the fetal ovary as the only normal tissues and in a variety of cancers.

The concept of immunotherapy is based on the assumption that antigenic structures expressed in tumors can be used for therapeutic approaches employing the autologous immune system or by the application of immunotherapeutic reagents. Based on this concept, there is a great need to gain profound knowledge of the actual protein/antigen expression and its distribution pattern within normal tissues and neoplasms. Current molecular antigen/target isolation techniques almost instantaneously provide the necessary data to conduct distribution pattern analyses at the mRNA level, while analysis of antigen protein expression rests on the availability of serological reagents, e.g. polyclonal or monoclonal antibodies (mAbs).

For both groups, MDAs and CT antigens, we have generated several mAbs for protein expression analyses. For the analysis of MDAs, we have generated mAb A103 to Melan-A (MART-1) and mAb T311 to tyrosinase. HMB45, a previously generated commercially available mAb is reactive to gp100, another MDA.

We and others have analyzed the expression pattern of tyrosinase, Melan-A and gp100 in normal tissues, benign lesions and tumors on the protein and mRNA level. These data confirm the melanocyte-associated expression pattern of these antigens. It should be noted, that besides serving as targets for immunotherapy in melanomas, these antigens and their detecting mAbs are important tools in surgical pathology for categorizing tumors. However, there are differences among the antigens as to their incidence and staining pattern in various lesions. In malignant melanoma, Melan-A and tyrosinase appear to be the most often and most homogeneously expressed antigens, though there are differing opinions. Most importantly there are drawbacks to each antigen and its detection. While HMB45 appears to be melanocyte-specific, gp100 -albeit at low levels- is detectable by RT-PCR in many normal tissues. Melan-A mRNA expression is restricted to tissues containing melanocytes and tumors thereof, but mAb A103 is reactive with normal tissues and tumors which are negative for Melan-A mRNA. Though not true for melanomas, tyrosinase appears not to be expressed in some lesions at all.

With regard to CT antigens, our group has generated mAbs to various CT antigens and tested them on a wide variety of normal and tumor tissues. Our CT mAb panel includes mAb MA454 to MAGE-1, mAb M3H67 to MAGE-3, mAb ES-121 to NY-ESO-1, mAb CT7-33 to CT7, and mAb SC554 to SCP-1. Another mAb used in our analysis, mAb 57B, was generated against MAGE-3 by Dr. Giulio Spagnoli and appears to have reactivity for more than one MAGE antigen.

As the name implies, CT antigens are present in normal testis, but absent in other normal tissues. Immunohistochemical analysis with our CT antibody panel confirms this expression pattern. In testis, staining can be seen solely in germ cells. We could also confirm the expression of CT antigens in placenta, known to be mRNA positive for some CT antigens. Though adult ovary is consistently negative for the expression of CT antigens, embryonic and fetal ovary shows an intense reactivity in germ cells undergoing maturation. In human cancers, extensive RT-PCR typing has been carried out for CT antigen expression, and immunohistochemical analysis shows a generally similar pattern of CT expression at the protein level. Some tumors, e.g. colorectal and renal cell carcinomas, are only rarely immunoreactive, confirming results of mRNA typing. In tumor types with a higher frequency of CT mRNA expression, immunohistochemical analysis gives a complex picture of antigen distribution, both with regard to different lesions as well as within the same lesion. In the majority of cancers, the pattern of CT antigen expression is heterogeneous, and homogeneous antigen expression throughout the tumor mass is the exception. This applies to a variety of tumors, such as head and neck carcinoma, hepatocellular carcinomas, mammary carcinomas, urothelial carcinomas and ovarian carcinomas. Even in melanomas, a tumor type with a high frequency of CT antigen expression, the pattern of antigen expression is mostly heterogeneous. The basis for this striking heterogeneity in CT antigen expression is unknown. There are only a few exceptions to this rule of heterogeneity of CT antigens.

Synovial sarcomas are high-grade tumors, which are often associated with a poor prognosis. In our study, a high percentage (approx. 80%) of synovial sarcomas were strongly and homogeneously immunoreactive with mAb 57B and mAb ES-121, whereas mAb CT7-33 and mAb MA454 showed little or no reactivity. CT antigen expression was found in both morphological types, monophasic and biphasic synovial sarcomas, and in both underlying genetic alterations, the SSX1 and SSX2 translocation types.

Currently new serological reagents to additional CT antigens are being developed, and studies are under way to determine the temporal sequence of different CT antigen expression in germ cell development and in tumor progression.

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