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Identification and characterization of target molecules for antigen-specific cancer immunotherapy

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Abstract

The CRI/LICR cancer vaccine collaborative can be viewed as operating in two modes, a discovery mode and a clinical trials mode. The discovery mode can be further subdivided into studies aimed at antigen identification and characterization, and those investigations focusing on understanding tumor immunity and immune escape. Both aspects of the discovery mode feed into the clinical trials mode. With regard to the identification of antigenic targets, 2 approaches have been utilized: *an analysis of the autologous immune response to cancer* (e.g. T-cell epitope cloning, serological expression cloning) and *an analysis of differential gene expression* (representational difference analysis, microarray analysis, database mining). The goal of both approaches is to identify gene products that are expressed predominately in cancer, which can be used as targets for cancer vaccines.

Serological expression cloning or SEREX is a method of immunoscreening tumor-derived cDNA expression libraries with sera from cancer patients in order to identify those antigens reactive with high titer IgG. We have recently applied the SEREX technique to sarcoma and identified a new seroreactive cancer/testis antigen with immunotherapeutic potential, termed NY-SAR-35, which was expressed exclusively in normal testis, as well as melanoma, lung cancer, breast cancer and gastric cancer. These studies focused on the serological response of individual sarcoma patients. We have also focused on serological responses present in populations of cancer patients. In a recent study, serum samples from 75 colon cancer patients and 75 normal individuals were screened for serum antibody reactivity to a panel of 77 SEREX-defined antigens. Fourteen of these 77 antigens reacted only with sera from cancer patients, and not with sera from normal individuals, indicating that the immune response was cancer-related. Expression analysis showed that transcripts encoding 1 of the 14 antigens, NY-CO-58/KNSL6, was highly expressed in normal testis with low to trace levels of mRNA expression in all other normal tissues tested. NY-CO-58/KNSL6 was also highly expressed in 9/9 cases of colon cancer, ranging from 4 to 43 times the level detected in normal colon tissue, indicating its potential as a cancer vaccine target.

We have also applied non-immunological techniques, such as database mining, to the identification of target antigens. In order to identify new cancer/testis antigens the Unigene database was searched for genes that have homologous expressed sequence tags (ESTs) derived exclusively from normal testis and cancer-derived EST libraries. 1300 genes were identified and 140 of them were tested by RT-PCR in a panel of normal tissue and tumor-derived cDNA preparations. Four of the genes tested were expressed exclusively in testis and a variety of tumor types and are considered newly defined cancer/testis antigens, termed CT15, CT16.1, CT17 and CT22.

During the course of our investigations, several questions have arisen. One major question is; what properties contribute to a target's immunotherapeutic potential? Answers include expression, immunogenicity and function. In terms of expression, is differential expression enough (e.g. NY-CO-58) or is restricted expression required (e.g. cancer/testis antigens)? The answer may lie in the level of expression necessary to maintain tolerance/induce an immune response, i.e., an immunologically relevant level of expression. With regard to immunogenicity, are those antigens associated with spontaneous immunogenicity in cancer patients (e.g. SEREX defined antigens) or those antigens with immunogenic potential (e.g. antigens defined by database mining) better target antigens? This question may only be answered in the context of clinical trials. Finally, antigens with functions that are essential to cancer cell survival cannot be selected against in the course of tumor evolution, and are therefore attractive targets. These functionally important antigens must still be differentially expressed and immunogenic in order to maintain their targeting value.

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