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Analysis of the B-cell repertoire against human cancers

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Abstract

The SEREX approach, the serological analysis of antigens by recombinant expression cloning, is based on the concept of "autologous typing" which was developed by Dr. Old's group in the late 70s. Like "autologous typing", SEREX exploits the patients' B cell repertoire for the identification and characterization of human tumor antigens that are immunogenic in the autologous host. The first human tumor antigen was identified by SEREX in 1993, when HOM-RCC-3.1.3, a new human carbonic anhydrase was shown to be overexpressed and immunogenic in a subpopulation of renal cancers. Since then, >2000 antigens have been defined by SEREX, demonstrating that most, if not all human cancers express multiple genes coding for proteins that are immunogenic in the autologous host. The specificities of tumor-associated antigens span the wide spectrum from strictly tumor-specific over differentiation antigens, products of mutated and viral genes, genes overexpressed or amplified in tumors to antigens which show the wide-spread distribution of common autoantigens without any differential expression between normal and malignant tissues. It has become evident that being presented in the context of "danger" (i.e. by a neoplasm) is of greater importance for the antigenicity of a molecule than its more or less restricted expression in a malignant tissue. From the clinical point of view, however, only antigens with a specific or preponderant expression in tumors are attractive candidates for vaccine strategies. Of the latter, the group of cancer testis antigens (CTA) has attracted special attention. With prominent members being the originally T-cell defined MAGE, BAGE and GAGE antigens, CTA represent a rapidly growing group of gene families that are expressed in a wide spectrum of human tumors, but not in normal tissues except for testis. Using reverse T-cell immunology, preexisting T-cell clones could be shown to react with several of SEREX-defined CTA, e.g. NY-ESO-1 and HOM-MEL-40, and we expect all SEREX antigens to be shown to elicit T-cell responses if only looked for carefully enough. Moreover, we have just started to learn about the functional role of some antigens in the pathogenesis of malignant tumors, thus gaining important insights into their biologic relevance. The availability of monoclonal antibodies will reveal the expression of antigenic products at the single tumor cell level. While the repeated detection of certain antigens suggests that the number of human tumor antigens is limited, we should aim at extending the coverage of currently 50% of the most common tumors with one and 30% with two antigens, to close to 100% of all human tumors with three or more specific antigens during the next years to provide the molecular basis for multivalent vaccine approaches for the majority of patients. Finally, carefully designed clinical studies will have to evaluate the role and susceptibility to therapeutic interventions of humoral and cellular immune responses to the molecularly defined antigens in correlation with the biology, clinical evolution and responses to therapy in antigen-positive and antigen-negative tumors.

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