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Natural and vaccine-induced immune responses to cancer-testis antigen-derived peptides

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Abstract

The isolation of CD8+ cytolytic T cells (CTL) reactive to the autologous tumors in cancer patients has allowed, during the last decade, the identification of several categories of tumor-associated antigens that can be the target of tumor-specific immune responses. Among them, one of the most relevant for the development of cancer vaccines is the group of the so-called Cancer-Testis (CT) antigens, which are expressed by tumor cells but not by most somatic adult tissues, with the exception of testis. Because of their expression commonly found in tumors of various histological types, CT antigen-derived peptides recognized by tumor reactive CTL are relevant candidates for generic vaccination of cancer patients.

In the last two years, we have analyzed the natural response to four CT antigen-derived HLA-A2 restricted epitopes recognized by tumor reactive CTL. Three of them correspond to the previously described peptides from MAGE-A10 (254-262), NY-ESO-1 (157-165) and CAMEL (1-11). The fourth peptide corresponds to the first identified SSX-2 (41-49) derived epitope, which has recently been defined in our laboratory. For each peptide natural responses were analyzed in circulating lymphocytes of melanoma patients bearing or not antigen expressing tumors, as well as in healthy donors. The results obtained indicate that the repertoire of specific CD8+ T cells available for each of these peptides is composed of T-cell clones able to recognize the antigen with different functional avidity. In each case, avidity of antigen recognition directly correlated with the efficiency of tumor recognition. Both high and low avidity CTL could be isolated from either melanoma patients or healthy donors. However, isolation of high avidity CTL was significantly more frequent from patients bearing antigen-expressing tumors. Natural responses to the four peptides were also found among tumor infiltrating lymphocytes (TIL) and tumor infiltrated lymph node cells (TILN) from some patients bearing tumor lesions expressing the corresponding antigens. Interestingly, in each case, specific CTL isolated from TIL or TILN displayed high avidity of antigen recognition and tumor reactivity. These results indicate that both high and low avidity CTL specific for the analyzed peptides are a normal constituent of the repertoire of CD8+ T cell available for these antigens and that high avidity, tumor-reactive CTL are selectively expanded during spontaneous immune responses to antigen expressing tumors.

On the basis of these results, clinical trials of cancer patient's vaccination with CT antigen- derived peptides have recently being undertaken with the aim of either inducing or boosting natural tumor-specific immune responses. In a trial that in currently ongoing at the Ludwig Institute Clinical Trial Center (New York Branch at Division of Medical Oncology, Columbia University, New York), we analyzed the CD8+ T-cell response to a NY-ESO-1 peptide vaccine in three sarcoma patients bearing NY-ESO-1 expressing lesions and with no specific immune

response detectable prior to vaccination. The vaccine consisted of the 9-mer NY-ESO-1 157-165 and the 11-mer 157-167 administered together with granulocyte-macrophage colony-stimulating factor (GM-CSF) as systemic adjuvant. Consistent with the results of previous studies, we detected, in these patients, a significant CD8+ T-cell response to the vaccine. By analyzing this response more in detail, however, we found that the largest part of the vaccine elicited CD8+ T cells were directed against multiple distinct epitopes in the 157-167 region and were non tumor reactive. Only a minor fraction of elicited CD8+ T cells directed against the 9-mer 157-165, and of sufficient high functional avidity, recognized the naturally processed target on NY-ESO-1+ tumor cells. In a separate study conducted at the Division of Clinical Onco-immunology of the Ludwig Institute for Cancer Research, (Lausanne Branch, Switzerland), a single patient with metastatic ocular melanoma received vaccination with four melanoma antigen derived peptides, including the 9-mer NY-ESO-1 157-165, administered with Montanide. Peptide NY-ESO-1 157-165 was remarkably immunogenic in this formulation and induced a CD8+ T-cell response detectable *ex vivo* at an early time point of the immunization protocol. The vaccine-induced CD8+ T-cell response decreased upon dismissed peptide administration, but was boosted by further peptide injections. Importantly, vaccine-elicited CD8+ T cells specifically lysed NY-ESO-1 expressing tumor cells. Together, the results of these studies underline that, because of the complexity of the repertoire of CD8+ T cells that can be elicited by vaccination with synthetic peptides, a precise definition of the targeted epitope and, hence, of the corresponding peptide to be used as immunogen, is required to ensure a precise targeting of the tumor.