Plenary Lecture

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Tumor antigens recognised by T lymphocytes

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Many genes of the MAGE family are expressed by tumors of different histological types and not by normal cells except for male germ-line cells, which do not express MHC molecules. The antigens encoded by *MAGE*-type genes are therefore strictly tumor-specific. We have identified recently the first *MAGE*-encoded epitopes presented by HLA class II molecules to CD4+ T lymphocytes. Monocyte-derived dendritic cells were loaded with a MAGE-3 recombinant protein and used to stimulate autologous CD4+ T cells. We isolated CD4+ T cell clones that recognised two different MAGE-3 epitopes, both presented by the HLA-DR13 molecule, which is expressed in 20% of Caucasians. This procedure ought to be applicable to other proteins. The defined epitopes will be useful for the evaluation of the immune response of patients immunized with proteins or with recombinant viruses carrying entire genes coding fur tumor antigens. The use of antigenic peptides presented by class II in addition to peptides presented by class I may also improve the efficacy of anti-tumor vaccination.

To increase the range of patients eligible for therapy with peptides, it is important to identify additional MAGE epitopes recognized by cytolytic T lymphocytes (CTL). Candidate peptides known to bind to a given HLA have been used to stimulate T lymphocytes *in vitro*. In some instances, CTL clones directed against these peptides have been obtained but they often failed to recognize tumor cells expressing the relevant gene. we designed a method, which selects naturally processed peptides. Dendritic cells infected with a canarypoxvirus (ALVAC) containing the *MAGE-A1* gene were used to stimulate CD8+ cells from individuals without cancer. Responder cells that lysed autologous cells expressing MAGE-A1 were cloned using stimulator cells either transduced with a retrovirus coding for MAGE-A1 or infected with recombinant Yersinia-MAGE-A1. This led to the identification of five new MAGE-A1 epitopes recognized by CTL clones on HLA-A3, A28, B53, Cw2 and Cw3 molecules. All these CTL clones recognized target cells expressing gene *MAGE-A1*.

A distant relative of the previously identified *MAGE* genes is expressed in many normal tissues. This gene is located in Xp11. Its exon-intron structure is completely different from that of the other *MAGE* genes. None of the 20 MAGE antigenic peptides presently known to be recognized by T lymphocytes is encoded by the new *MAGE* gene. Therefore, this finding leaves intact the tumoral specificity of the antigens encoded by the *MAGE* genes that are expressed only in tumor and germline cells.

Thirty-nine tumor-bearing patients with metastatic melanoma were treated with three subcutaneous injections of the MAGE-3.A1 peptide at monthly intervals. No toxicity was observed. Of the 25 patients who received the complete treatment, 7 displayed significant tumor regressions. Three regressions were complete and two of them led to a disease-free state which persisted for more than two years. No evidence for a CTL response was found in the blood of the four patients who were analyzed, including two who displayed complete tumor regression. Our results suggest that injection of the MAGE-3.A1 peptide induces tumor regression in a significant fraction of the patients, even though no massive CTL response is produced.