Cancer Immunity, Vol. 3 Suppl. 1, p. 12 (6 February 2003)

Prime-boost vaccination strategies with melanoma poly-epitope constructs

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Abstract

In order to identify strategies capable of generating a broad and long lasting tumor specific T-cell immunity, we compared vaccines based on the use of different non-cross reactive vectors encoding a string of melanoma CTL epitopes. We engineered a string of HLA-A2 (A2) and HLA-A1 restricted melanoma epitopes, which we cloned into naked plasmid DNA, vaccinia virus, Modified Vaccinia Ankara (MVA) and Semliki Forest Virus (SFV). Generation of several vectors encoding the same string of epitopes provided an opportunity to compare the ability of sequential injections of different vectors to induce effective CTL responses.

To investigate the strength and diversity of A2 restricted CTL responses to the poly-epitope vaccines, A2 transgenic mice were vaccinated with different combinations of the poly-epitope constructs. The frequency of CTL responses specific for each epitope was monitored by *ex vivo* tetramer stainings, while CTL functional activity *in vivo* was assessed by analysing the lysis of injected CSFE labelled splenocytes pulsed with relevant peptides. These assays enabled us to perform longitudinal studies of CTL responses in individual mice and provided an opportunity to compare in *ex vivo* assays the frequency and functional activity of CTL of different specificities.

Ex vivo tetramer staining of PBL from A2 transgenic mice immunized with prime-boost protocols revealed that the use of poly-epitope vaccines leads to preferential expansion of CTL with a single immunodominant specificity. Our results demonstrated that competition for antigen recognition at the surface of APC significantly skews the immune response, and strongly suggested that this competition needs to be taken into account for the development of vaccination strategies to optimally induce poly-valent CTL responses. We identified two alternative protocols for inducing polyvalent CTL responses based on the injection of either increasing numbers of APC infected with vaccinia virus encoding the poly-epitope construct, or of a mixture of viruses each encoding a separate antigen. Using these two alternative approaches we were able to prime poly-valent CTL responses and boost them independently to highly effective levels.

Preliminary results of a clinical trial in melanoma patients primed with melanoma poly-epitope constructs will be presented.