Cancer Immunity, Vol. 5 Suppl. 1, p. 19 (6 April 2005)

CANCER
IMMUNITY
Meeting Abstract

Cross-presentation: a mechanism used by melanoma cells for the generation of a tumor-specific antigen derived from the matrix metalloproteinase 2

Francine Jotereau

INSERM Unité 601, Nantes, France

The limited efficacy and frequent side effects of cancer therapies have lead to the hope that immune strategies could improve or substitute for these, for the treatment or prevention of cancer. A major step towards this was the demonstration that various immune cells recognize tumor cells in an antigen and non antigen-specific way, and to the development of techniques for the identification of tumor antigens. A large array of melanoma antigens recognized by tumor-specific T cells has now been identified and targeted in vaccine therapies. Nonetheless, despite significant induction of tumor-specific T cells, the therapeutic efficacy of this approach remains limited, perhaps in part due to the choice of target antigens.

Our activity has been focused on characterizing antigen specific T-cell responses that spontaneously arise in human melanomas. We reported, as other groups, the frequent specificity of CD4 and CD8 melanoma TIL for the autologous tumor cells, and developed therapies based on the adoptive transfer of high numbers of TIL obtained *ex vivo*. Suggesting that some of the antigens spontaneously recognized by tumor-specific TIL could be rejection antigens, we observed a significant enhancement of tumor free survival for patients treated by tumor-specific TIL infusion, compared with patients that received non tumor-specific TIL. We therefore tried to identify the target antigens of TIL that had been infused to long-term tumor free patients. We will report here the cloning of one such antigen recognized by TIL, in the HLA-A*0201 context. Surprisingly this antigen is the self-matrix metalloproteinase-2 (MMP-2) secreted by many cells and involved, through the degradation of the extracellular matrix and of basal membranes, in a variety of physiological processes and in melanoma progression. Despite this wide expression of the protein, the MMP-2 epitope was found to be presented exclusively by melanoma cells. We will show that this results from the unique mechanism of the MMP-2 peptide generation by cross-presentation, a process so far thought to be restricted to immune cells. Remarkably, melanoma cells efficiently cross-present to HLA*0201 restricted TIL a peptide derived from secreted MMP-2, following (alpha)(omega)(beta)3-dependent endocytosis, while they did not present this peptide via the classical endogenous pathway.

As MMP-2 plays a key role in tumor angiogenesis, growth and metastasis, its efficient targeting should not allow the development of antigen-loss tumor variants, refractory to the treatment.

Furthermore, the MMP-2 peptide is contained in the (alpha)(omega)(beta)3 interacting sequence of MMP-2, whose natural and experimental anti-invasive effect has been shown. The use of this longer peptide might therefore permit to combine vaccine and anti-invasive treatments.

More generally the demonstration that melanoma cells can perform cross-presentation raises the possibility to re-direct against melanoma cells pre-existing T-cell responses specific for common environmental antigens through immunization against these proteins fused to (alpha)(omega)(beta)3 non-catalytic binding fragments of MMP-2.

Together, these data suggest that MMP-2 may exemplify a tumor antigen that may be ideal for immunotherapy of HLA-A*0201 melanoma patients.