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Update on class-I restricted tumor antigens, and characterization of a novel immune escape mechanism based on tryptophan catabolism

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Abstract

The first part of the talk will present an update of the currently defined tumor antigenic peptides recognized by human CD8 T cells, mainly through an introduction to the peptide database of the *Cancer Immunity* website (1). This database lists the relevant peptide sequences, the peptide position in the parental protein, the HLA-presenting molecule with its frequency, and the bibliographic reference with a link to the Medline entry. This format has been selected to assist clinicians developing clinical trials in their choice of the most relevant antigenic targets. For the same reason, a very strict selection is applied so as to list only peptides that are fully characterized and meet a number of criteria allowing them to qualify as actual tumor antigens.

The second part of the talk will describe a novel tumor immune escape mechanism based on tryptophan degradation. It has been shown that T lymphocytes undergo proliferation arrest when exposed to tryptophan shortage, which can be provoked by indoleamine 2,3-dioxygenase (IDO), an enzyme that is expressed in placenta and catalyzes tryptophan degradation. Local tryptophan depletion by IDO expression has therefore been proposed as a natural immunosuppressive mechanism promoting tolerance of the fetus during pregnancy. Expression of IDO is also induced in many cells by interferon-gamma, and could thereby participate in the regulation of immune responses. To determine whether tumors might use this mechanism to escape T-cell mediated immune responses, we measured the expression of IDO by RT-PCR in a series of murine and human tumor cell lines. We found that many lines were positive. Moreover, when we tested a large series of human tumor samples by immunohistochemistry with an IDO-specific antibody, we observed that a vast majority stained positive, including all prostatic, colorectal, pancreatic and cervical carcinomas. Using the well-characterized model system of mouse tumor P815, where the antigen encoded by gene *P1A* is the major target of the tumor rejection response, we observed that expression of IDO by P815 tumor cells prevents their rejection by pre-immunized mice. This effect can be partly reverted by systemic treatment of mice with an inhibitor of IDO, in the absence of noticeable toxicity. These results suggest that the efficacy of therapeutic vaccination of cancer patients could be improved by concomitant administration of an IDO inhibitor.

References

1. Peptide database. URL: <http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm>