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Dissertations-Kurzfassung

Identification of a new HLA-A*01 restricted T cell epitope derived from the melanoma differentiation antigen tyrosinase related protein 2

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For the development of effective antigen-based cancer therapies and also for monitoring T cell responses in the course of vaccination, the identification of MHC class I restricted epitopes from immunologically relevant tumor antigens is required. Tyrosinase related protein 2 (TRP2) is an attractive target antigen for immunotherapeutic treatment of human melanoma. Until now no TRP2 peptide presented by HLA-A*01 (HLA-A1), the second most common HLA allele among the Caucasian population, has been described.

In the present study, a new HLA-A1 restricted T cell epitope from the TRP2 differentiation antigen was identified by applying the "reverse immunology" strategy based on the prediction of potential epitopes derived from the antigen protein sequence. The peptide with the highest prediction score, $TRP2_{181-190}$ (VYDFFVWLHY), elicited antigen-specific T cells repeatedly from healthy $HLA\text{-}A1^+$ donors. In vitro induced T cell lines recognized peptide-pulsed target cells as well as $HLA\text{-}A1^+$, $TRP2^+$ melanoma cells after IFN-γ treatment. $TRP2_{181-190}$-specific CTLs also recognized dendritic cells (DCs) loaded with a 28mer polypeptide containing the $TRP2_{181-190}$ sequence or DCs infected with a recombinant modified vaccinia virus Ankara encoding TRP2 (MVA-TRP2). Proteasome inhibitors blocked $TRP2_{181-190}$ processing from endogenously expressed TRP2 protein indicating that the proteasome is involved in the generation this epitope. In addition to HLA-A1, peptide $TRP2_{181-190}$ could also stimulate HLA-A2-restricted T cells. These T cells recognized MVA-TRP2 infected DCs and cross-reactively recognized target cells loaded with $TRP2_{180-188}$, an already known HLA-A2 restricted epitope, indicating that both peptides bind to the HLA-A2 molecule in a similar conformation. Consequently, $TRP2_{181-190}$ has the capability to bind to different, widely expressed HLA molecules, suggesting that it might be a valuable tool for vaccination and immunomonitoring of melanoma patients.