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New TRP-2-derived T helper epitopes identified in HLA-DRB1*0301 transgenic mice elicit spontaneous T cell responses in HLA-DRB1*03 and HLA-DRB1*04 melanoma patients

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Antigen-specific cytotoxic CD8+ T lymphocytes (CTLs) are effective mediators of destructive anti-melanoma immunity but primary CTL-sensitisation and establishment of CTL-memory are dependent on the helper activity of antigen-specific CD4+ T lymphocytes. Therefore, active immunotherapy of melanoma patients should ideally target antigen-specific CD8+ and CD4+ T cells in order to achieve effective anti-tumor CTL immunity. Identification of tumor antigen epitopes is a prerequisite for specific T-cell targeting in the course of vaccination and for vaccine evaluation. But in contrast to HLA-class I restricted peptide ligands only a few HLA-class II-presented epitopes are characterized. We used computer algorithms and HLA-DRB1*0301 (HLA-DR3) transgenic mice to identify epitopes derived from the differentiation antigen tyrosinase-related protein-2 (TRP-2). Three potential HLA-DR3-restricted epitopes were predicted from the TRP-2 protein sequence, two of the corresponding synthetic peptides exhibited HLA-DR3 binding capacity, but only one sequence (Pep1) specifically activated CD4+ T cells in HLA-DR3 transgenic mice after peptide immunization. Processing of an epitope located in the Pep1 sequence from the TRP-2 antigen was subsequently demonstrated by TRP-2 protein immunization. Pep1-specific CD4+ T cells could also be induced *in vitro* in human T cell cultures obtained from the peripheral blood of normal HLA-DRB1*0301 donors. Interestingly, *in vivo* sensitized Pep1-specific T cells were also detectable in the peripheral blood of HLA-DRB1*03 and HLA-DRB1*04 melanoma patients verifying Pep1 as a target of spontaneous T cell responses.