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Structural Basis for Recognition of a Mutated Human Melanoma Antigen by an Anti-Tumor T Cell Receptor. Lu Deng^a, Ries Langley^a, Suzanne L. Topalian^b, Roy Mariuzza^a, ^aCenter for Advanced Research in Biotechnology, Univ. of Maryland, Rockville, MD20850, ^bSurgery Branch, NCI, NIH, Bethesda, MD20892.

CD4⁺ T cells play an important role in generating and maintaining immune responses against cancer. T cell receptor (TCR) E8, isolated from tumor-infiltrating CD4⁺ T cells, recognizes a melanoma antigen restricted by the MHC class II molecule HLA-DR1. The mutated antigen is a peptide derived from the glycolytic enzyme triosephosphate isomerase (TPI₂₃₋₃₇) with a single amino acid substitution (Thr28Ile). Here we present the crystal structures of TCR E8 in free form, and of the trimolecular complexes E8/wild type TPI₂₃₋₃₇/HLA-DR1 and E8/mutant TPI₂₃₋₃₇/HLA-DR1. The structures show substantial conformational changes for CDR3 α of E8 upon binding to peptide/MHC. E8 primarily recognizes the central to N-terminal portion of TPI₂₃₋₃₇, in contrast with both anti-microbial and alloreactive TCRs which focus on the peptide center, and autoimmune TCRs, which recognize the N-terminal peptide segment. This study provides the structural basis of the dramatically altered T cell stimulation capacities of the wild type and mutant TPI peptide, and offers insights into CD4⁺ T cell responses to MHC class II-restricted tumor antigens in general.

This research is supported by NIH grant AI36900 to RAM.