Immunobiological Analysis of TCR Single-Chain Transgenic Mice Reveals New Possibilities for Interaction between CDR3α and an Antigenic Peptide Bound to MHC Class I

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Abstract

The interaction between TCRs and peptides presented by MHC molecules determines the specificity of the T cell-mediated immune response. To elucidate the biologically important structural features of this interaction, we generated TCR β-chain transgenic mice using a TCR derived from a T cell clone specific for the immunodominant peptide of vesicular stomatitis virus (RGVYQGL, VSV8) presented by H-2K^b. We immunized these mice with VSV8 or analogs substituted at TCR contact residues (positions 1, 4, and 6) and analyzed the CDR3α sequences of the elicited T cells. In VSV8-specific CTLs, we observed a highly conserved residue at position 93 of CDR3α and preferred Jα usage, indicating that multiple residues of CDR3α are critical for recognition of the peptide. Certain substitutions at peptide position 4 induced changes at position 93 and in Jα usage, suggesting a potential interaction between CDR3α and position 4. Cross-reactivity data revealed the foremost importance of the Jα region in determining Ag specificity. Surprisingly, substitution at position 6 of VSV8 to a negatively charged residue induced a change at position 93 of CDR3α to a positively charged residue, suggesting that CDR3α may interact with position 6 in certain circumstances. Analogous interactions between the TCR α-chain and residues in the C-terminal half of the peptide have not yet been revealed by the limited number of TCR/peptide-MHC crystal structures reported to date. The transgenic mouse approach allows hundreds of TCR/peptide-MHC interactions to be examined comparatively easily, thus permitting a wide-ranging analysis of the possibilities for Ag recognition in vivo.