

Alterations in surface TCR display are associated with the activation of naïve CD8<sup>+</sup> T cells  
Donald R. Drake III, Rebecca M. Ream, and Thomas J. Braciale  
Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908

Our laboratory and others have demonstrated that changes in the distribution of membrane TCR, reflected by a decreased binding of tetrameric MHC/peptide complexes to the surface of the T cells, can be associated with alterations in the functional competency of cytotoxic T lymphocytes. To determine whether TCR reorganization is characteristic of naïve T cell activation and differentiation, we examined tetramer binding on CD8<sup>+</sup> transgenic T cells specific for the hemagglutinin protein of the influenza A/PR/8/34 virus following antigen encounter. PR/8 infection of mice led to a significant reduction in tetramer binding to adoptively transferred HA533-specific CD8<sup>+</sup> T cells that was not dependent on a loss of surface TCR. Similar results were obtained when naïve PR/8-specific CD8<sup>+</sup> T cells were stimulated with virus-infected cells in vitro. Activation of the cells with peptide-pulsed stimulators suggested that the loss of tetramer binding was signal strength dependent since low doses of peptide could trigger a subset of the lymphocytes to proliferate and activate without losing their ability to bind specific tetramer. Confocal analyses suggested that the decreased efficiency of tetramer binding to activated HA533-specific CD8<sup>+</sup> T cells might be associated with a change in surface TCR display from an aggregated to a more diffuse organization, a pattern we have observed in other flu-specific CD8<sup>+</sup> T cell populations that show decreased binding to specific tetramer. Functional analyses suggested that the change in surface TCR array associated with a loss of tetramer binding might alter the effector activity of the HA533-specific T cells since the tetramer-low cells only weakly flux calcium and synthesize interferon- $\gamma$  following TCR ligation. Together, these results suggest that surface TCR reorganization might be a physiologic response of naïve T cells to initial antigen encounter and may function to alter the activation threshold of the cells during the early stages of their activation and differentiation program. This work was supported by USPHS grants AI15608 and HL33391 to T.J.B. D.R.D. is supported by a Cancer Research Institute Fellowship.