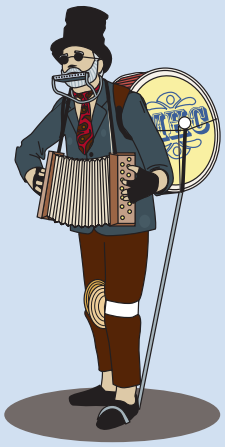
ANTIGEN PRESENTATION

Monotonous MHC sing in troubled times



Mouse Qa-1^b and its human homologue, HLA-E, are highly conserved MHC class I-like molecules that protect host cells from cytotoxic lymphocytes by presenting a single self peptide, Qa-1 determinant modifier (Qdm) from the signal sequence of classical MHC class I molecules, to inhibitory natural killer (NK)-type receptors. Now, a study by Oliveira *et al.* shows that in cells with defects in the MHC class I antigen processing pathway, Qa-1^b-bound Qdm is replaced with a diverse range of self peptides and this leads to elimination of these cells by CD8$^+$ cytotoxic T lymphocytes (CTLs).

Following immunization of mice with transporter associated with antigen processing (TAP)-deficient syngeneic cells, the authors isolated Qa-1^b-restricted CD8$^+$ T cell clones that showed cytotoxic activity against TAP-deficient cell lines. The isolated T cell clones had a classic CTL phenotype and a diverse T cell receptor (TCR) repertoire. TAP-deficient cells could not present Qdm but, instead, presented new peptides on Qa-1^b. Experiments with specific blocking antibodies ruled out the use of NK-type receptors by the T cell clones and showed their cytotoxic activity was mediated by TCR recognition of the Qa-1^b-presented peptides. Cytotoxicity of the CD8$^+$ T cells could be inhibited by exogenous loading of TAP-deficient cells with excess Qdm peptide, suggesting that in healthy cells the high-affinity binding of Qdm to Qa-1^b prevents presentation of other self peptides. Interestingly, the Qa-1^b-restricted CD8$^+$ T cell clones showed CTL activity against several tumour cell lines with known antigen-processing defects.

Using biochemical purification and tandem mass spectrometry, the authors next assessed the nature of the non-Qdm peptides presented by Qa-1^b molecules. These peptides were derived from endogenous proteins and were extremely diverse. Screening of the alternative Qa-1^b-presented self peptides identified several immunogenic peptides, which had no common amino acid motif and were derived from different housekeeping proteins — further supporting evidence of the diversity of the alternative Qa-1^b self-peptide repertoire.

Although this study focused on mouse Qa-1^b, the authors speculate that owing to the conserved structure and function of these MHC class I-like molecules, HLA-E might have a similar role in promoting human CTL activity against transformed or virus-infected tissue cells.

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ORIGINAL RESEARCH PAPER Oliveira, C. C. *et al.* The nonpolymorphic MHC Qa-1^b mediates CD8$^+$ T cell surveillance of antigen-processing defects. *J. Exp. Med.* 28 Dec 2009 (doi:10.1084/jem.20091429)