increased numbers of CD4+ T cells in the spleen, compared with mice lacking either GADD45β or GADD45γ. Furthermore, sera from the *Gadd45b*$^{-/-}$*Gadd45g*$^{-/-}$ mice contained autoantibodies specific for double-stranded DNA and histones, whereas these autoantibodies were absent from the sera of *Gadd45b*$^{-/-}$ and wild-type mice.

This study indicates that GADD45β and GADD45γ are not only important for initiating immune responses but that they also provide an important control mechanism for keeping CD4+ T cells from mediating autoimmunity. Future studies will need to define the molecular mechanisms by which these molecules mediate these apparently opposing effects, and as the authors suggest, this might provide new therapeutic targets for the treatment of autoimmune disease.

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ORIGINAL RESEARCH PAPER Liu, L. *et al.* Gadd45 and Gadd are critical for regulating autoimmunity. *J. Exp. Med.* **202**, 1341–1348 (2005)

ORIGINAL RESEARCH PAPER Cohen, N. *et al.* GILZ expression in human dendritic cells redirects their maturation and prevents antigen-specific T lymphocyte response. *Blood* 17 Nov 2005 (doi:10.1182/blood-2005-07-2760)

ANTIGEN PRESENTATION

Trimming peptides for presentation

MHC class I molecules present peptides of 8–10 amino acids in length. These peptides are generated in the cytoplasm and transported through the transporter associated with antigen processing (TAP) into the endoplasmic reticulum (ER), where they are loaded onto MHC class I molecules. It recently became clear that peptides in the ER might require further processing before loading onto MHC class I molecules, and an ER-resident amino peptidase ERAAP (ER aminopeptidase associated with antigen processing, known as ERAP1 in humans), was recently identified in mice and implicated in this process. Now, two studies show that ERAAP is required for the generation of the normal repertoire of MHC class I peptides, and that ERAP1 trims precursor peptides by a 'molecular ruler' mechanism.

Hammer and colleagues analysed ERAAP-deficient mice, and showed that expression of each of the five MHC class I molecules was lower in ERAAP-deficient splenocytes than in wild-type cells. This decreased expression was due, not to quantitative differences in peptide generation, but to qualitative differences, which were assessed by measuring the stability of the peptide–MHC-class-I complexes. Interestingly, H2-L^{d}, the only MHC class I molecule that can present peptides with an internal proline residue, showed a decrease in expression that was greater than that of the other four MHC class I molecules. As optimal-length peptides containing proline residues are poorly transported by TAP, this dependence on ERAAP confirms the idea that amino (N)-terminally extended proline-containing peptides are transported into the ER through TAP and are then trimmed by ERAAP.

Next, the authors assessed the ability of ERAAP-deficient splenocytes to mediate antigen presentation of a series of specific peptides. Presentation of some peptides was decreased, while others remained unchanged or showed increased expression, showing that the lack of ERAAP disrupts the generation of the peptide–MHC class I repertoire. Peptides with an extended N terminus required ERAAP for final trimming, whereas those of optimal length were independent of ERAAP function. By introducing precursor peptides into the ER of TAP-deficient cells, the authors showed that ERAAP acts on antigen precursors in the ER itself when the precursor has an extended N terminus.

Another study, from Chang and colleagues, showed that human ERAP1 has a preference for substrates that are 9–16 amino acids in length, the same size as peptides transported into the ER by TAP. The authors tested the rates of degradation of three peptides (a 5-mer, a 9-mer and a 13-mer) containing the same repeat motif and each with the same carboxyl (C) terminus, and found that recombinant ERAP1 strongly preferred the 13-mer peptide substrate, and stopped trimming when a 9-mer chain was generated. Further experiments showed that ERAP1 prefers peptide substrates with hydrophobic C-terminal residues. Interestingly, a recently cloned human aminopeptidase termed L-RAP (also known as ERAP2), which has 49% amino acid identity with ERAP1, showed no preference for peptide length or for the C-terminal residue. Based on these studies, the authors propose that ERAP1 uses a 'molecular ruler' mechanism to assess peptide length, leading to the generation of peptides of optimal length for MHC class I binding.

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ORIGINAL RESEARCH PAPERS Hammer, G. E. *et al.* The aminopeptidase ERAAP shapes the peptide repertoire displayed by major histocompatibility complex class I molecules. *Nature Immunology* 20 Nov 2005 (doi:10.1038/ni1286) | Chang, S. C. *et al.* The ER aminopeptidase, ERAP1, trims precursors to lengths of MHC class I peptides by a 'molecular ruler' mechanism. *Proc. Natl Acad. Sci.* USA **102**, 17107–17112 (2005)