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ANTIGEN PROCESSING

Another ingredient to the mix

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A molecular mechanism by which thiol-based redox reactions regulate the editing of the MHC class I peptide repertoire has been revealed in *Cell*. The process that results in the presentation of optimal, high-affinity peptides on MHC class I molecules to $CD8^+$ T cells is complex, and there is still much to learn about how this process works on a molecular level. This paper identifies a new member of the peptide-loading complex, and provides insight into how peptide editing occurs on MHC class I molecules.

After they reach the cytosol, antigens are digested by proteolysis. Those peptides that are not completely degraded are translocated into the endoplasmic reticulum (ER) by the transporter associated with antigen presentation (TAP). Once in the ER, the peptides can follow various fates, including binding to MHC class I molecules. This ensures that only very recently acquired and high-affinity peptides are available for binding. Peptide loading occurs with the help of the peptide-loading complex, which consists of the MHC class I heterodimer, TAP and several chaperones. These chaperones are necessary to ensure that newly synthesized MHC class I molecules do not escape ER quality control, which would allow suboptimal MHC class I molecules to reach the surface of the cell.

The authors first set out to investigate how optimal-peptide loading occurs. They identified a new component of the peptide-loading complex, protein disulphide isomerase (PDI), which is an ER enzyme necessary for the correct formation of disulphide bonds in proteins. Knockdown of PDI in HeLa cells by RNA interference inhibited the cytolytic activity of $CD8^+$ T cells in response to the PDI-deficient HeLa cells, indicating that PDI does have a physiological role in the function of MHC class I molecules.

MHC class I molecules contain a disulphide bond in each of their α2 and α3 domains. PDI (specifically the catalytic and peptide-chaperone domains) was shown to regulate the oxidation and reduction of the α2 disulphide bond in the MHC class I peptide-binding groove. Importantly, depletion of PDI resulted in poor peptide loading and the accumulation of suboptimal MHC class I molecules. Both the availability and nature of the peptides were also shown to be important for PDI-mediated oxidation of MHC class I molecules (with high-affinity peptides preferentially binding to oxidized MHC class I molecules).

Finally, Park *et al.* verified the functional relevance of PDI-catalysed peptide editing in controlling viral pathogens. Having previously shown that the US3 protein of human cytomegalovirus interferes with the peptide-repertoire editing of particular MHC class I alleles, the authors show here that US3 in fact evades $CD8^+$ T-cell recognition by mediating the degradation of PDI.

This study, therefore, provides a link between antigen processing and redox regulation. The authors propose that editing the MHC class I peptide repertoire involves both a rapid thiol disulphide exchange between PDI and the α2 disulphide of MHC class I molecules, and competition for MHC class I binding among peptides of different affinities. So, the redox status of the MHC class I molecule might be a 'checkpoint' for quality control of the assembly of MHC class I molecules.

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ORIGINAL RESEARCH PAPER Park, B. *et al.* Redox regulation facilitates optimal peptide selection by MHC class I during antigen processing. *Cell* **127**, 369–382 (2006)