

Mechanisms and consequences of trimming peptides for MHC class I molecules in the endoplasmic reticulum

Nilabh Shastri, Gianna Elena Hammer, Takayuki Kanaseki, Federico Gonzalez, and Nicolas Blanchard

Division of Immunology, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720

The CD8 T cells detect abnormal intracellular events, such as viral infection or oncogenic transformation, as novel peptides presented by major histocompatibility complex class I molecules (MHC I). The MHC I molecules present a very large repertoire of different peptides that fit perfectly in their binding grooves and represent the otherwise hidden intracellular contents (pMHC I). The peptides - usually 8-10 amino acids long - are generated by proteolysis of protein precursors that begins in the cytoplasm and ends in the endoplasmic reticulum (ER). The ER aminopeptidase associated with antigen processing (ERAAP) trims peptides to their final state by removing the extra N-terminal flanking residues from peptide precursors (Serwold et al., 2002). Precision in generation of the final peptide requires synergy between ERAAP and MHC I, without which the precursors are destroyed (Kanaseki et al., 2006). In the absence of ERAAP, the normally diverse repertoire of pMHC I complexes is severely disrupted (Hammer et al., 2006). Remarkably, peptides that would normally be trimmed are presented in an "unedited" form on the surface of ERAAP-deficient cells. The unique pMHC I are highly immunogenic and elicit potent CD8 T cell and antibody responses in wild-type mice (Hammer et al., 2007). Thus, ERAAP is a quintessential editor of the pMHC I repertoire whose absence paradoxically enhances immunogenicity.

Hammer, G. E., Gonzalez, F., Champsaur, M., Cado, D., and Shastri, N. (2006). The aminopeptidase ERAAP shapes the peptide repertoire displayed by major histocompatibility complex class I molecules. *Nat Immunol* 7, 103-112.

Hammer, G. E., Gonzalez, F., James, E., Nolla, H., and Shastri, N. (2007). In the absence of ERAAP the MHC class I molecules present many unstable and highly immunogenic peptides. *Nat Immunol* 8, 101-108.

Kanaseki, T., Blanchard, N., Hammer, G. E., Gonzalez, F., and Shastri, N. (2006). ERAAP synergizes with MHC I to make the final cut in the antigenic peptide precursors in the endoplasmic reticulum. *Immunity* 25, 795-806.

Serwold, T., Gonzalez, F., Kim, J., Jacob, R., and Shastri, N. (2002). ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. *Nature* 419, 480-483.