Response to Comment on "Characterizing the N-Terminal Processing Motif of MHC Class I Ligands"

Stefan Tenzer and Hansjörg Schild

*J Immunol* 2008; 181:3731-3732; doi: 10.4049/jimmunol.181.6.3731-a

http://www.jimmunol.org/content/181/6/3731.2

References

This article cites 7 articles, 1 of which you can access for free at:

http://www.jimmunol.org/content/181/6/3731.2.full#ref-list-1

Why *The JI*? Submit online.

- **Rapid Reviews!** 30 days* from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Fast Publication!** 4 weeks from acceptance to publication

*average

Subscription

Information about subscribing to *The Journal of Immunology* is online at:

http://jimmunol.org/subscription

Permissions

Submit copyright permission requests at:

http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts

Receive free email-alerts when new articles cite this article. Sign up at:

http://jimmunol.org/alerts
Comment on “Characterizing the N-Terminal Processing Motif of MHC Class I Ligands”

In a recent article, Schatz et al. (1) characterized the N-terminal processing motif of MHC class I ligands. They demonstrated that this motif comprised approximately seven residues that matched the known preferences of proteasome and TAP, consistent with the view that these peptide ligands are the product of an intracellular pathway comprising protein breakdown in the cytosol and transport into the endoplasmic reticulum (ER). Furthermore, they also found that this was not true for residues immediately preceding the N terminus of MHC class I ligands and suggested, based on experimentally determined aminopeptidase activities, that trimming next to the final N terminus takes place predominantly in the ER. This is consistent with the proposed role of the ER-resident aminopeptidase ERAAP in the trimming to the canonical nonamer ligand length and whose role in immunity has been clearly shown in the ERAAP knockout mouse model (2). While this presents an almost complete picture of MHC class I loading, there remain a couple of unanswered questions: 1) the paucity of signal/leader sequences among MHC class I ligands, even though these should be the predominant peptide species; and 2) the lack of ligands longer than nonamers in the mature MHC class I molecules in the ERAAP knockout mouse. An intriguing possibility that is consistent with the findings of the Schatz et al. article and would answer both of these questions is that the cellular function of ERAAP is actually the degradation of signal/leader peptides generated in the ER during the synthesis of secreted and membrane proteins. The immunological consequence of this cellular function of ERAAP would be the tipping of the balance of loaded peptides away from cellular proteins to peptides that are more likely to be derived from endogenously synthesized pathogen antigens, a balance that would be inverted in the ERAAP knockout mice. The proposed cellular role for ERAAP would explain the paucity of host protein signal sequences in the population of bound peptides isolated from mature MHC class I molecules and untrimmed peptides larger than nonamers bound to class I even in ERAAP knockout cells, as well as suggest a possible identity for some minor histocompatibility antigens.

Camilo A. L. S. Colaco

ImmunoBiologics Limited
Cambridge, United Kingdom

References

Response to Comment on “Characterizing the N-Terminal Processing Motif of MHC Class I Ligands”

The possibility that ERAAP plays a role in limiting the presentation of peptides derived from signal peptides may be tempting from an immunologist’s view. In eukaryotic cells, signal peptides have a mean length of 22 amino acids and are removed by signal peptide peptidases from the N terminus of their source proteins. As most membrane and secreted proteins harbor signal peptides, the removed signal peptides could theoretically compete with peptides processed by the classical MHC class I pathway and transported by TAP into the ER. Ribosomes synthesize ~66,666 proteins s⁻¹ per cell (1); if ~15–60% are cotranslationally translocated into the ER, this leads to the generation of 10,000–40,000 signal peptides per second. This is comparable to the number of TAP-transported peptides (in a normal cell, there are ~10,000 TAP1/2 complexes that transport a total of 20,000–50,000 peptides per second (2)). However, TAP is part of the peptide loading complex, which facilitates direct loading of the transported peptides onto newly synthesized MHC class I molecules, while signal peptides are attacked by ER-resident peptidases. Additionally, especially in the mouse system, presentation of signal peptides should be extremely limited due to a simple mismatch of the specificities of signal peptidases, which cleave preferentially after the amino acids Ala, Gly, Ser, Cys, Thr, and Pro (as derived from the SignalP 3.0 Server and the training sets used for SignalP 2.0) (3), and MHC class I molecules, which preferentially bind peptides with hydrophobic or basic residues at the C terminus (4). An exception may be the human HLA-A*02 molecule, which can bind peptides with an alanine at the C terminus, and, indeed, we have recently contributed to the description of signal sequence-derived peptides on MHC class I ligands in TAP-deficient cells (5). Most of these ligands contain an alanine at their C terminus, and the major part of them is preferentially presented on the cell surface in the absence of TAP. Theoretically, signal peptides could also be cleaved by endopeptidases or carboxypeptidases in the ER that would generate peptides with different C termini; however, no such activity has yet been described.

Concerning the “lack of ligands longer than nonamers in the mature MHC class I molecules in the ERAAP knockout mouse” mentioned by Dr. Colaco, we prefer the interpretation of the data (6) by Blanchard and Shastri (7), who propose that many of the unstable and structurally unique peptide-MHC
complexes presented by ERAAP-deficient cells are most likely N-terminally extended peptides (7).

Stefan Tenzer and Hansjörg Schild

Institut für Immunologie
Johannes-Gutenberg-Universität Mainz
Mainz, Germany

References


