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ERAP1 shapes just part of the immunopeptidome

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ABSTRACT

ERAP1 is an aminopeptidase involved in trimming long peptides to the lengths required for presentation by MHC class I. ERAP1 substrate preference is for peptides with hydrophobic or aliphatic N-terminal amino acids, with lower efficacy with charged and small hydrophilic amino acids and almost complete inefficiency with proline. Since ERAP1 efficiently trims peptides to eight amino acids or even shorter, and many MHC-I allotypes can only bind peptides that are eight or nine amino acids or longer, ERAP1 both produces and destroys potential ligands of these alleles. The observation that ERAP1 modulates the levels of presentation for only a subset of the immunopeptidome conflicts with the common assumption that most MHC-I peptides are derived from longer peptides that are produced by the proteasome, transported into the endoplasmic reticulum (ER) by the Transporter Associated Peptide Presentation (TAP) and then trimmed by ERAP1. A more likely mechanism is that cellular protein degradation produces surplus amounts of peptides that fit perfectly and are rapidly loaded onto the MHC, with only a minority of peptides requiring trimming within the ER before loading. Alternatively, ERAP1 may not be present in all ER compartments or vesicles where peptide processing and loading take place and thus affects just a subset of the immunopeptidome.

1. Background on antigen processing and presentation

The immunopeptidome is the assortment of peptides, bound and presented on the surface of most nucleated cells of vertebrates in the context of the Major Histocompatibility Complex (MHC). In humans, the MHC is known as the Human Leukocytes Antigen (HLA) and the immunopeptidome is referred to as the MHC or HLA peptidome or the ligandome. The MHC class I (MHC-I)-bound peptides are products of cellular protein degradation, which are thought to be degraded mostly by the proteasome in the cytoplasm and the nucleus [1–7]. In addition, some of the peptides are produced by vesicular/lysosomal degradation of proteins engulfed by autophagosome or by phagocytosis, but the relative contribution of these pathways to the immunopeptidome is not fully clear [8–12]. Proteasomes produce peptides that are mostly 3–22 amino acids long [13], many of which are longer than those eventually bound to MHC class I. Therefore, many of these long proteasomal products need to be transported into the ER, and also have to be further trimmed to length of mainly 8–9 amino acids that fit their binding pockets on the MHC-I molecules. Peptide binding to the MHC is assisted by specialized chaperones within the ER that catalyze peptide binding and exchange, selecting peptides of sufficient affinity and stability [6,7]. Once assembled with high affinity peptides, the polymorphic MHC-I heavy chain, the non-polymorphic β2-microglubulin and their bound peptide cargo (three-component MHC molecules) are transported to the cells' surface, where they present the bound peptides to circulating T cells, thereby alerting them about the health state of the cells. The endoplasmic reticulum-resident aminopeptidases, ERAP1 and ERAP2, are thought to be the main proteases responsible for the peptide trimming process within the ER [14–16]. ERAP1 (ERAAP in mice) was the first aminopeptidase assigned with this role [17–20]. It was suggested that both enzymes (ERAP1 and ERAP2) function as a molecular complex that trims peptides in a concerted fashion [21,22]. Both aminopeptidases have a partial, yet clear effect on the presented MHC peptidome. Another source of peptides for MHC presentation is the leader sequences of proteins that are transported into the ER. These leader sequences are removed from the proteins after their translocation into the membrane or into the lumen of the ER [23]. There, they are further processed into shorter peptides to fit the MHC binding sites, just like any other MHC ligand. The level of contribution of signal peptides to the immunopeptidome or to the ERAP1 substrate pool is not known [24,25]. Cross-presentation, i.e., the process of phagocytosis and processing of proteins that originate from outside of the cells and their presentation by class I MHC on antigen presenting cells, was very recently suggested to also involve ERAP1 [26]. Since the trimming process affects only part of the MHC peptidome, only large-scale immunopeptidome analysis can provide a valid 'bird's eye' view regarding the specific roles of ERAP1/2 in the trimming of proteolytic peptides to fit them to their presenting MHC [14,27].

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ERAP1 is thought to be the main trimming enzyme of the ER, responsible for fitting peptides that need to be shortened to the required length, while ERAP2 seems to be responsible for shaping a smaller subset of the peptidome, trimming many ligands to lengths even shorter than are useful for binding to MHC. However, the relative contribution of ERAP1 and ERAP2 have not yet been described. Importantly, ERAP1 destroys many potential ligands, since it trims 9-amino-acid-long 'good' ligands to 8 or shorter amino acids, which are too short to bind to most HLA allotypes [19]. In addition, while ERAP1 is present in most cells, it is somewhat more polymorphic than ERAP2, with different levels of activity and potentially different specificities among its 10 most commonly present haplotypes (in humans). While ERAP2 is present in smaller amounts in most (human) cells, it is absent in some people and is completely absent in rats and mice [14,27].

The roles of ERAP1 and ERAP2 in shaping the MHC peptidome were recently reviewed in a number of excellent reviews [14,15,27–30]. Therefore, this review will only attempt to cover this subject from the 'big-data' MHC-peptidome point of view. The introduction of large-scale MHC/HLA peptidome analyses into the field of antigen processing and presentation (APP) research has clarified many issues in this field, and has enhanced our understanding of the role of the different components of the APP machinery in shaping the MHC peptidomes [1,31–36]. The most effective methodology used for such studies, in relation to the role of ERAP1/2 in shaping the MHC peptidome, involves perturbation of ERAP1/2 expression by complete knockout of the genes or by expression of specific ERAP1/2 allotypes or haplotypes. The effects of ERAP1/2 modulation are then followed by large-scale immunopeptidome analysis via immunoaffinity purification of the MHC molecules and analysis of their bound peptidomes by capillary chromatography and tandem mass spectrometry. While this review deals with ERAP1, the role of ERAP2 in shaping the immunopeptidome is reviewed elsewhere in this issue [37].

2. Some ERAP1 haplotypes are risk factors for autoimmune/auto-inflammatory diseases genetically associated with HLA alleles

Since some isoforms of ERAP1, and to a lesser extent ERAP2, are known to be genetically associated with several autoimmune/inflammatory diseases, in epistasis with some allotypes of MHC class I, there is significant interest in the role of these enzymes in modulating the relevant peptidomes [38–42] It was assumed that the genetic association between the specific HLA allotypes and these aminopeptidases involves the peptide-trimming function of ERAP1/2, and might be related to the generation of specific peptides that elicit pathologic immune responses or modulate the stability of the MHC molecules at the cell surface. The role of these enzymes in shaping the MHC/HLA peptidomes of the disease-associated HLA allomorphs has been studied and reviewed extensively [14,27,39]. However, after many years of research, not a single HLA-bound peptide was identified to be the key inducer of these diseases, much like the lack of understanding the molecular role of the two enzymes or the different associated HLA class I allotypes in promoting these pathologies [14,39,42,43].

3. The enzymatic specificity of ERAP1

Due to the restricted peptide-binding specificities of the MHCs, only a small subset of the large complexity of peptides translocated into the ER or trimmed by ERAP1, likely fits the consensus sequence motifs of the MHC allotypes. If sufficiently high-affinity peptides are not available, the MHC complexes will not be stable and will either not be transported to the cell surface or be sent there as non-functional complexes that tend to form dimers which may even elicit inflammatory conditions [44–52]. The concentrations of the different peptides present in the ER, their processing dynamics and the sequence preference of ERAP1 significantly affect the production rates of the peptides that fit the consensus sequence motifs of the MHC haplotypes, influencing the final presented MHC peptidome. ERAP1 trims peptides to lengths of no less than 8 amino acids, since its substrates (peptides) are possibly bound during catalysis along their entire length, including their C-termini, and are trimmed by the catalytic site, which is located at a fixed distance [53,54]. Binding the peptides substrates at one end (C-terminus) and trimming them at a fixed distance, from the other end (N-terminus) that reaches into the catalytic site of ERAP1, not only defines the minimal lengths of the peptides that are effectively trimmed by ERAP1, but also influences the substrate preferences and dynamics of the enzyme. Thus, ERAP1 trims with a specificity that is defined by the specificity of ERAP1 in trimming the N-terminal amino acids and the binding affinity induced by the nature of the substrate peptides' C-terminus, with some additional effect of the amino acids at positions 3–5. The C-terminal binding pocket prefers hydrophobic and aliphatic amino acids over charged (both positive and negative) amino acids. Therefore, longer peptides with positive C-termini are trimmed slower and subsequently accumulate inside the ER. Peptides of 8–9 amino acids also accumulate, since these are not efficiently trimmed by ERAP1 (a molecular ruler mechanism) [53]. Thus, a larger abundance of peptides with charged C-termini can be found among the products of trimmed long peptides, while many good potential ligands with hydrophobic C-termini are destroyed [53]. ERAP1 activities complement the preference of TAP and MHC molecules, which shows a preference for peptides with hydrophobic or basic C-termini, depending on the specific TAP and organism [55,56] and many MHC molecules prefer the binding of such peptides as well [57]. ERAP1 complements the preference of TAP for longer peptides with hydrophobic or basic C-termini, from which it efficiently produces the shorter peptide ligands. The accumulating peptides with negatively charged C-termini are of no relevance for HLA binding since none of the known HLA-I allotypes are capable of binding peptides with Asp or Glu at their C-terminus. The same holds also for the inability of the known HLA to bind peptides with Pro at their C-termini [57].

Another interesting effect of ERAP1 is the high prevalence of negatively charged amino acids in the middle (non-anchor) positions of the MHC-bound peptides. This is due to the presence of a negative patch, positioned close to the middle of the peptide binding-site of ERAP1 [15,58], causing a preference for positively charged amino acid selection for degradation and 'sparing' from destruction peptides with negatively charged amino acids at their middle. Indeed, higher numbers of HLA-B27 peptides contained Asp and Glu in their middle in the presence of ERAP1 [59].

4. 'In solution' versus 'template model' trimming

As explained above, the 'in-solution' trimming is a well-established mode of action of ERAP1. In this mode, the peptides are trimmed within the ER and after trimming, when they reach the proper lengths for binding to the MHC, they do so, thus releasing the MHC for transport to the cell surface (reviewed recently in [27]). This mode of action is supported by demonstration synthetic peptide trimming by a purified ERAP1 protein in the absence of MHC [53,60]. The other mode of action, termed the 'template model', suggests trimming of peptides that are anchored to the MHC at their C-termini and protrude at their N-termini from the binding groove of the MHC [60–62]. Trimming of MHC-anchored peptides is rather difficult to physically demonstrate since it requires following in real-time the trimming process with peptides bound to MHC, while extended out of their binding pocket at their N-termini [22,63]. Both of these models can equally explain the molecular causes for the genetic association of specific HLA allotypes with ERAP1 in the induction of autoimmune/auto-inflammatory diseases if these involve peptide presentation at all [39].

ERAP1 and MHC compete for the same substrate/ligands pools. ERAP1 is not processive, i.e., it must release the trimmed peptide products after the removal of each amino acid [53]. The released shorter peptides may bind to the 'peptide-receptive' MHC molecules

waiting within the ER, before binding ERAP1/2 for further trimming. Thus, if 'snuggly' bound, the peptides are protected from further trimming and removed from the compartment by transport to the cell surface.

We can therefore conclude that while the immunopeptidome is shaped by the activity of ERAP1, it does not represent the full breadth of peptides produced by ERAP1 if most trimming happens 'in-solution'. If ERAP1 trims peptides 'in-solution' within the ER, and only some of them bind to their cognate MHC allomorphs, then ERAP1 likely generates a pool of peptide products that is many fold more complex than the one eventually comprising the immunopeptidome. Since these products of N-termini degradation are produced at different rates, according to their lengths and sequences, and the MHC selects only a small subset of the products, the MHC peptidome is mostly shaped by the sequence preference for peptide binding of the MHCs rather than by the proteolysis process of the aminopeptidases. However, if peptide trimming is mostly happening while the peptides are already bound to the MHC (template model) than the repertoire of proteolysis products is shaped by both the trimming preference of the ERAP1 and the binding specificity of the presenting MHC allotypes. In such a case, the selectivity of the C-termini and the middle of the peptides in binding to ERAP1 are less likely to affect its selectivity, since these should be defined more by the selectivity of the MHC allotypes.

5. ERAP1 produces and destroys many MHC peptide ligands

As explained above, ERAP1 produce and destroy potential MHC peptide ligands [64]. ERAP1 both helps produce peptides for loading on to the MHC when it encounters peptides longer than the desired lengths but it also destroys some of the ligands when it over-trims peptides to 8 or shorter when the presenting MHC allotypes cannot bind peptides of shorter than 9 amino acids. In addition, since it has some preference for aliphatic/hydrophobic amino acids at the N-termini and at the C-termini, it leaves behind an abundance of products with small hydrophilic or charged amino acids at these ends that are useful ligands for only some of the HLA allotypes [14,19,27]. ERAP1 trims peptides with a preference for aliphatic sidechains; it is very inefficient at trimming peptides with proline at their N-termini or containing proline at the second position [18,65]. Thus, a higher abundance of MHC peptides with proline at their N-termini or P2 position is expected, due to inefficient cleaving of Pro-X and X-Pro [18,61,65,66]. Similarly, a lower abundances of peptides with Pro at the N(−1) to N(−3) and even at further upstream positions [67] are expected, since ERAP1 fails to trim such peptides to the preferred lengths. The MHC peptidomes are mostly comprised according to the preferences of A, B, (C in some cases) and F pockets of the MHC, which bind the P1, P2 (P3) and Pn positions of the peptides according to the preferences of the peptide-binding consensus of the individual MHC allomorphs [57]. Gly, Ser and Lys are poorer substrates of ERAP1 and therefore peptides with these amino acids, which accumulate more in the ER in the presence active ERAP1, are more abundant in the immunopeptidome of ERAP1-WT HLA-B27 rats [59]. To conclude, the substrate specificity of ERAP1 affects the final MHC peptidomes by producing or destroying ligands according to their N-termini, P2 positions, middles, C-termini, and even the abundances of better or worse amino acids upstream of the ligands that bind the MHC. Thus, ERAP1 affects the MHC peptidome not only by the products it produces, but possibly, even more importantly, by the ligands that it does not destroy [64].

6. The methodology of analyzing immunopeptidomes

MHC peptidomes are first analyzed by immunoaffinity purification of the MHC molecules with their bound peptides, under mild conditions, from cell extracts. The purified MHC molecules can be endogenous allotypes expressed by cells or recombinant allotypes, which can be transfected into cells that fully or partially lack other MHC allotypes [67,68]. In addition, any type of cultured cells can be transfected with the extra-cellular domain of the MHC. These shorter, soluble MHC molecules are released from the cells with their peptide cargo and can be collected from the cell culture media in large amounts, irrespective of the endogenous haplotypes expressed by the cells [69,70]. After immunoaffinity purification from the cell extracts or from conditioned media, the peptides are detached from the MHC molecules by acid denaturation, concentrated, and analyzed by capillary chromatography and tandem mass spectrometry (MS). The resulting large datasets and the use of powerful bioinformatics tools, enable analysis of complex MHC peptidomes and identification and quantification of tens of thousands of peptides [32,33,35,71]. The magnitude of the data and the sensitivity and reproducibility of the assays facilitates comparative immunopeptidome analyses that can detect even minor changes in the relevant peptidomes induced by specific ERAP1 allotypes [59,72–78]. The current methodology requires starting from about 10^8 cells, or their tissue equivalent, in order to reach identification and (relative) quantitation of several thousands of MHC peptides in a single experiment. Even though it can be assumed that the HLA peptidomes are composed of several tens of thousands of different peptides, conclusions pertaining to the effect of a particular enzyme, such as ERAP1, on the entire MHC peptidome can be reached rather rapidly and accurately using the MHC peptidome data of just a few thousand peptides, which represent the entire peptidome.

MHC peptidomics is very different from proteomics since the sequences of MHC peptides do not end with just the two amino acids, Arg and Lys, as commonly occurs in proteomics analysis. The enzyme of choice for proteomics analysis is trypsin, which cleaves only at the C-termini of Arg and Lys, producing a largely predictable pool of peptides from any given source protein. In contrast, MHC peptide sequences are defined mostly by their anchor positions, usually P2 and Pn. In many of the allotypes, most consensus sequences allow for different amino acids at these positions [57]. In addition, most tryptic peptides are observed as doubly charged ions during mass spectrometry, with one positive charge at the C-terminus and one at the N-terminus. In contrast, MHC peptides have less predictable sequences and many of them have only one positive charge during the mass spectrometry, rendering their fragmentation and subsequent identification by MS/MS less effective, generating datasets with larger error rates.

Immunopeptidome analysis enables following of both the levels of peptides, at the surface of or secreted from the cells, and in addition, and of the dynamics of their production and degradation [79–81]. Specifically, the use of dynamic stable isotope labelling of cultured cell (dynamic-SILAC) peptidomes allows for following both the changes in the levels of the presented peptides, as well as the changes in the rates of their synthesis and degradation, even if these do not affect their total level of presentation.

7. Why ERAP1 changes the level of presentation of only a subset of the immunopeptidome

While it is very clear that many peptides are shortened by the activities of ERAP1, it is also very clear that the majority of the immunopeptidome is left untouched by the enzyme; the presence of ERAP1 in the cells does not change the lengths of most of the HLA peptides and leaves about 70% of their levels unaltered [14,59]. In mice, the peptidomes of some MHC allomorphs did not change as significantly as those of selected MHC allotypes [20,72]. Thus, the current assumption that proteasomes produce a pool of mostly longer peptides, which are taken up into the ER by TAP and serve as the sole source of peptides for trimming and loading onto the MHC molecules, may be an over-simplification. This enigma can be explained in different ways. The first simple explanation proposes that while the proteasome indeed produces peptides that are mostly longer than those capable of binding to the MHC, there is a large surplus of available peptides for loading onto the MHC [82], including many that do fit. The peptides may be

loaded so rapidly onto peptide-receptive MHC molecules when they enter the ER, that ERAP1 activity does not significantly impact the scheme of the resulting immunopeptidome. However, there are no current publications that attempted to determine the rates of loading of ligands onto the peptide-receptive molecules (see an excellent review on the early stages of assembly and transport of MHC in [83]). Only the peptides that are better binders than others would be affected. The subset of HLA-B27 peptides affected by ERAP1 knockout in B27 transgenic rats was actually of somewhat lower calculated affinity to the HLA [59], as determined by NetMHC calculation meaning that these peptides are likely not-yet-fully processed peptides that need further processing to fit the cognate HLA [84]. In human cells expressing allomorphs, such as HLA-B27, ERAP1 knockout had a larger effect [73] than the effect noticed in the transgenic rats [59]. Similarly, the MHC peptidome presented by mouse spleen cells after ERAP1 (ERAAP) knockdown had lower affinity to their cognate MHCs [20,72]. Alternatively, it is possible that ERAP1 is not uniformly present in the ER, where peptide loading onto the MHC takes place; it may encounter only some of the peptide substrates. This hypothesis is supported by the observed non-uniform presentation of MHC peptides [85,86]. Whether ERAP1 is present in only some of the vesicles in which the MHC molecules are loaded, is not known, to the best of my knowledge.

8. If ERAP1 is located within a small and confined vesicle, just a few ERAP1 molecules should be sufficient to trim enough peptides for loading

MHC peptide processing and presentation includes proteolysis, transport, trimming and chaperoned uploading of peptides onto the MHC molecules. The proteasomes (or the autophagosome) degrade surplus cellular proteins, possibly thousands-fold more than are needed for loading onto the peptide-receptive MHC molecules [82,87]. Thus, each of these proteolytic pathways alone is more than sufficient to produce peptides for MHC presentation. The possibility that ERAP1 is not a rate-limiting factor was suggested by the observation that heterozygote expression of ERAP1, which produces about half the amount of ERAP1 molecules, had practically no impact on the MHC peptidome of the cells. Only complete ERAP1 knockout modulated the immunopeptidome significantly [59]. On the other hand, if excess amounts of peptides would be available for loading within the ER, one would expect that only a subset of the best, high affinity peptides would be loaded and sent to the cell surface. Such a phenomenon is clearly not in the 'best interest' of the cells and organism, which would need to sample the full repertoire of peptides to 'faithfully' represent the protein production and degradation scheme of the cells. This is needed so that pathogen-derived peptides will be presented effectively with the onset of infection [88,89]. Such a feat would be feasible if peptide production, trimming, loading and release to the cell surface were all optimized to represent the entire proteome, including the 'unexpectedly' newly expressed viral 'non-self' sequences. Such cellular 'goals' can be achieved if peptide uploading to the MHC is rapid and trimming is sufficiently slow. This way, the majority of the peptides would be loaded before they have a chance to be trimmed and most peptides would be loaded and sent to the cell surface before they have a chance to be replaced by just a few selected higher-affinity peptides. Thus, the 'source' of substrates is the pool of peptides in the ER, while the 'sink' is the MHC molecules that shuttle the peptides out of the ER, as well as the peptidases that degrade the leftover (majority) peptides that do not fit.

9. So, why is ERAP1 needed at all?

It is clear that ERAP1 is not essential for life, since both mice and rats that were knocked out for ERAP1 survived in non-sterile environments. At the same time, it is also clear that ERAP1 modulates the MHC peptidome to some extent, with a more significant effect on some allomorphs of MHC. Its association with autoimmune/auto-inflammatory diseases certainly places it in a position of significance in human wellbeing and health [38–42] as detailed above. In addition, ERAP1 (and ERAP2) are associated with providing some resistance to infectious diseases, mostly in associations with some HLA allotypes [42,90–93], (see also [94] with opposing data) and with immune reaction to cancer [95,96]. In addition, since ERAP1 (ERAAP) are evolutionary conserved aminopeptidases, it is very unlikely that this enzyme is not significant for the wellbeing and immune protection of the organisms. However, it also quite possible that the main role of ERAP1 may be in other cellular function, such as degrading the surplus peptides that accumulate in the ER, as needed to avoid cellular stress, and not only to provide a more complete representation of the peptides diversity within the immunopeptidome of specific selected MHC allomorphs. Such a roles would not require ERAP1 to be 'super-fast', but rather to act at about the same rate as peptide accumulation within the compartment. More research is clearly needed to characterize further its role and mode of action.

10. Conclusion

ERAP1 is an important aminopeptidase endowed, among other roles, with the function to trim peptides to fit the binding site on the MHC. While ERAP1 clearly modulates the immunopeptidome, it affects only a subset of the peptide repertoire and does so in a somewhat unpredictable manner since it both produces and destroys potential ligands capable of binding their cognate MHCs. In addition, the effects of ERAP1 differ between the HLA allotypes and, so far, the molecular basis for its genetic association with certain diseases remains elusive.

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Appendix A. Supplementary data

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