



MHC I chaperone complexes shaping immunity

Christoph Thomas and Robert Tampé

Major histocompatibility complex class I (MHC I) molecules present peptides on the surface of most nucleated cells and allow the immune system to detect and eliminate infected or malignantly transformed cells. The peptides are derived from endogenous proteins by proteasomal degradation or aberrant translation, and are translocated from the cytosol into the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP), a central component of the peptide-loading complex (PLC). The peptides are subsequently processed by ER-resident aminopeptidases (ERAP1/2) and loaded onto MHC I. This loading, however, does not happen indiscriminately: in a process called peptide editing or peptide proofreading, the MHC I-specific chaperones tapasin and TAPBPR (TAP-binding protein-related) catalyze the selection of high-affinity peptides and stable peptide-MHC I (pMHC I) complexes. Once correctly loaded with a high-affinity peptide, pMHC I complexes travel to the cell surface where they are recognized by T lymphocytes to control their differentiation in the thymus, their priming in the lymph node, and their final long-term surveillance of target cells in the periphery. Recent structural studies of the PLC and of TAPBPR-MHC I complexes by single-particle cryo-electron microscopy, X-ray crystallography, and NMR spectroscopy have provided fundamental insights into the mechanisms of MHC I peptide loading and proofreading, highlighting the dynamic nature of the involved complexes and the conformational plasticity of the individual proteins.

Address

Institute of Biochemistry, Biocenter, Goethe University Frankfurt, Max-von-Laue Str. 9, 60438 Frankfurt/Main, Germany

Corresponding authors:

Thomas, Christoph (c.thomas@em.uni-frankfurt.de),
Tampé, Robert (tampe@em.uni-frankfurt.de)

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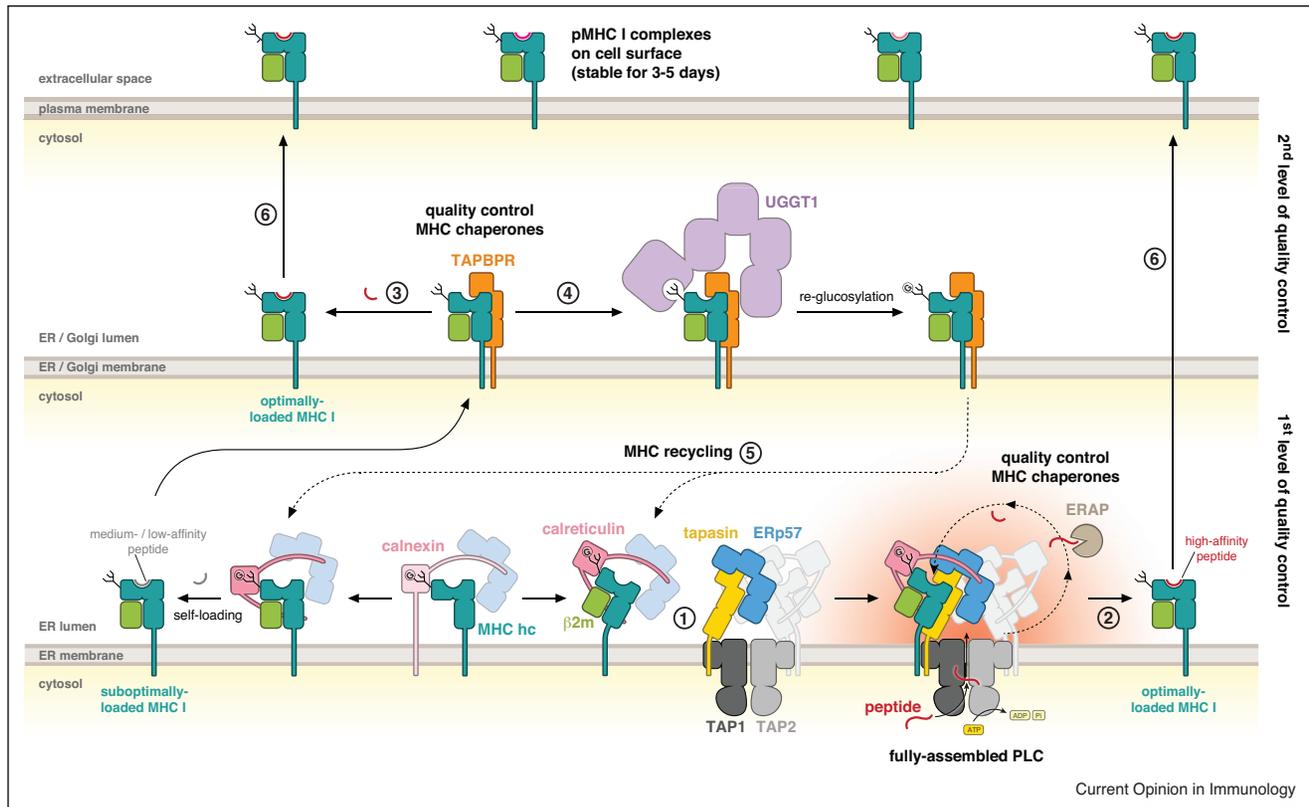
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Introduction

Most nucleated cells of jawed vertebrates provide the immune system with information about their health status

by displaying peptides at the cell surface on MHC I heterodimers, which consist of the peptide-binding, polymorphic heavy chain, and the smaller β 2-microglobulin (β 2m). By scanning the pMHC I complexes via T-cell receptors (TCRs), antigen-experienced CD8⁺ T lymphocytes of the adaptive immune system are able to recognize foreign, antigenic peptides, and destroy infected or cancerous cells [1,2]. The peptides presented by MHC I are predominantly a small subset of the protein fragments generated by proteasomal degradation in the cytosol; they are selectively transported into the ER where the loading of the MHC I with peptides takes place. Peptide translocation into the ER is carried out by the heterodimeric ABC (ATP-binding cassette) transporter TAP [3]. Inside the ER, peptides can be further trimmed by the aminopeptidases ERAAP1 and ERAAP2 to a length of 8–10 amino acids that is optimal for MHC I binding [4–7]. During *de novo* synthesis, the MHC I heavy chain is co-translationally N-glycosylated at a conserved site with the glycan $\text{Glc}_3\text{Man}_9\text{GlcNAc}_2$ [8]. After the first two glucose residues are cleaved off by glucosidases, the resulting monoglucosylated glycan is bound by the lectin-like chaperon calnexin and the disulfide isomerase ERp57 [9,10]. Following association with β 2m and dissociation of calnexin [11], the inherently unstable peptide-deficient MHC I is guarded by calreticulin, another lectin-like chaperone. MHC I allomorphs, which fall within the tapasin (Tsn) specificity spectrum, assemble with Tsn-ERp57 and TAP into the PLC [12,13]. The actual peptide loading for those allomorphs is then catalyzed by Tsn, which is conjugated to ERp57 via a disulfide bridge [14,15] (Figure 1). Most importantly, Tsn not only accelerates peptide loading, but also discriminates low-affinity peptides in favor of high-affinity ones [16,17], which are able to form kinetically stable complexes with MHC I. Tsn thus functions as an MHC I-specific peptide editor or peptide proofreader. If properly folded and stably loaded with a high-affinity peptide when the terminal glucose residue of their glycan is cleaved off, the pMHC I complexes can leave the ER on their secretory journey through the *Golgi* compartment to the cell surface. The selection of high-affinity peptides during editing is essential for an efficient hierarchical immune response as it increases the half-life of the pMHC I complexes at the cell surface and gives T lymphocytes enough time to sample the presented peptides and become differentiated, matured, or activated. Early studies of the antigen presentation pathway indicated that quality control of MHC I is not limited to Tsn-catalyzed peptide editing but extends beyond the ER into the *Golgi* compartment [18]. UDP-glucose:glycoprotein glucosyltransferase 1 (UGGT1) has been identified as an important player in this second quality control step [12,19]. UGGT1 is the

Figure 1



The cellular environments of tapasin and TAPBPR in the antigen presentation pathway. Newly assembled MHC I heterodimers can be recruited to the PLC by calreticulin (step 1) where the MHC I-specific chaperone tapasin catalyzes loading of high-affinity peptides in the peptide-rich environment of the ABC transporter TAP1/2 (step 2). The gradient of peptide concentration and peptide diversity around the PLC is depicted by a red cloud. In a second level of quality control, the tapasin homolog TAPBPR facilitates peptide exchange outside the PLC (step 3). In the absence of suitable peptides, TAPBPR promotes re-glucosylation of MHC I via the folding sensor and glucosyltransferase UGGT1 (step 4). The resulting mono-glucosylated MHC I is able to re-engage calnexin and calreticulin and to visit the PLC in order to receive high-affinity peptide cargo (step 5). Stable pMHC I complexes are licensed to travel via the *Golgi* apparatus to the cell surface where they are recognized by T lymphocytes to evoke a hierarchical immune response (step 6).

major ER/*cis-Golgi* glycoprotein folding sensor and is able to recognize hydrophobic patches of unstable and misfolded proteins that carry a $\text{Man}_9\text{GlcNAc}_2$ glycan. UGGT1 re-glucosylates the glycan of its client proteins to $\text{Glc}_1\text{Man}_9\text{GlcNAc}_2$, feeding the client proteins back into the calnexin/calreticulin cycle [20]. UGGT1 is also capable of detecting suboptimally loaded MHC I and of enabling these MHC I complexes to re-visit the PLC through reglucosylation [12,19].

Over the past few years, it has become evident that Tsn is not the only MHC I-dedicated chaperone catalyzing peptide proofreading: the Tsn-related protein TAPBPR shares ~20% sequence identity with Tsn in its luminal region and is also $\text{IFN}\gamma$ -inducible but lacks the ER retention motif, operates outside the PLC, and is independent of ERp57 [21–23]. Yet, just like Tsn, TAPBPR recognizes peptide-receptive MHC I and catalyzes

peptide proofreading, albeit with a different allomorph specificity and, apparently, a different MHC glycan preference than Tsn [23,24*,25*,26]. While Tsn is restricted to the ER and functions in the peptide-rich environment of TAP, TAPBPR operates beyond the ER in the peptide-depleted *Golgi* compartment (Figure 1). Tsn and TAPBPR appear to complement each other in optimizing the surface expression of MHC I molecules, which differ in their dependency on the two editors; for example TAPBPR depletion severely impairs HLA-B*07:02 surface expression, even in the presence of Tsn [24*]. Interestingly, TAPBPR has recently been shown to promote the interaction of UGGT1 with peptide-receptive MHC I [27*]. The contribution of TAPBPR to MHC I quality control is, therefore, twofold: in addition to its peptide selector activity, TAPBPR supports via UGGT1 the recycling of suboptimally loaded or empty MHC I to Tsn in the peptide-rich environment of TAP in the PLC.

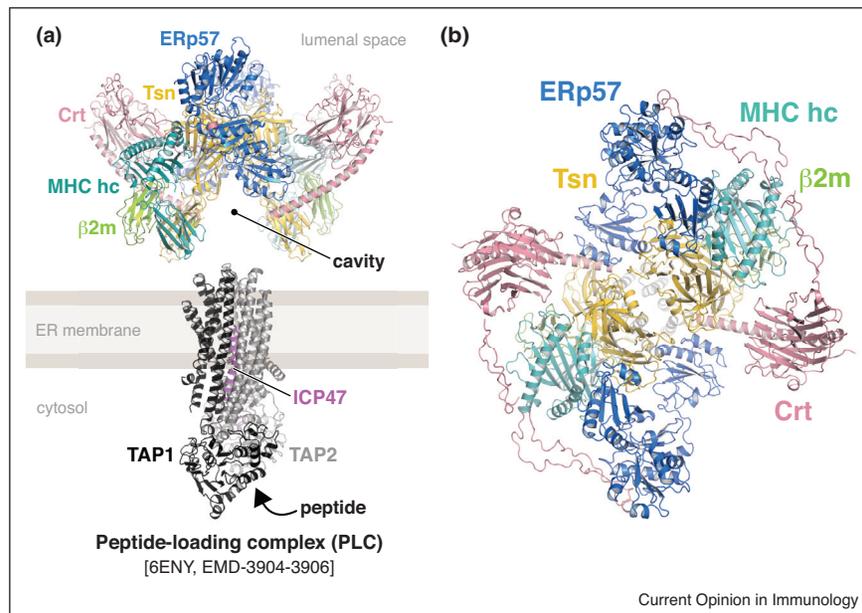
The architecture of the PLC, the interplay of its constituents, and the mechanisms of peptide editing, as catalyzed by Tsn and TAPBPR, have remained largely unknown. In this review, we discuss fresh insights into these essential aspects of antigen presentation gained from a single-particle cryo-electron microscopy (cryo-EM) study of the native PLC and X-ray crystallographic analyses of TAPBPR-MHC I complexes [28^{••},29^{••},30^{••}]. We further explain how the conformational plasticity of the involved protein components is a feature pivotal to the process of catalyzed peptide loading and proofreading, as highlighted by a recent NMR study of the TAPBPR-MHC I system [31[•]].

The architecture of the PLC—a dynamic hub in the antigen presentation pathway

The PLC is a supramolecular complex in the ER membrane that orchestrates peptide translocation with MHC I peptide loading and editing. In its fully assembled form, the PLC contains the peptide transporter TAP, Tsn-ERp57, and calreticulin-associated MHC I- β 2m. The significance of the PLC for an efficient immune surveillance is underscored by the fact that several viruses target the PLC to evade the host immune system and remain undetected. A prime example of such a viral evasion strategy is the ICP47 protein of human herpes simplex virus, which binds with high affinity in the cavity of TAP

and inhibits its activity [32–34]. While the individual subunits of the PLC have been known for a long time, their arrangement and interplay within the full PLC have remained largely elusive. The transient nature, the compositional heterogeneity, and the low abundance of the PLC at the ER membrane were major obstacles on the path to its structural elucidation. Utilizing a viral immune evasin as bait and reaping the benefits of advances in single-particle cryo-EM, it has been possible to prepare a reconstruction of native human PLC from a lymphoblastoid cell line [28^{••}]. Notably, not only the polymorphic MHC I types HLA-A, HLA-B, and HLA-C were found to be part of the purified native PLC but also the non-classical allomorphs HLA-E, HLA-F, and HLA-G. The cryo-EM analysis revealed two editing modules of Tsn-ERp57 and MHC I-calreticulin arranged in a pseudo-symmetric fashion around the heterodimeric TAP transporter (Figure 2). According to the cryo-EM reconstruction, the two Tsn molecules directly interact in the center of the PLC, and calreticulin binds with its lectin-like domain the mono-glucosylated N-linked glycan on the MHC I and contacts ERp57 with the tip of its extended P domain by reaching across the MHC I peptide-binding groove. The C-terminal tail of calreticulin is positioned close to the membrane-proximal domain of Tsn and points toward the ER-luminal membrane leaflet. Just above the luminal gate of the TAP transporter, the full

Figure 2



Supramolecular organization of the PLC. **(a)** Membrane-plane view of the PLC architecture, as obtained by cryo-EM, consisting of the ICP47-inhibited translocation module TAP1/TAP2 and two editing modules, each composed of the chaperones tapasin (Tsn) and calreticulin (Cr), the oxidoreductase ERp57, and the MHC I heterodimer of heavy chain (hc) and β 2-microglobulin (β 2m). ERp57 is linked to Tsn via a disulfide bond. The transmembrane regions of Tsn, the MHC I hc, and the TMD0s of TAP1 and TAP2 are not visible in the EM density. **(b)** View from the ER lumen onto the pseudo-symmetric assembly of the two editing modules, which are arranged around the central TAP heterodimer. PDB and EMD codes are shown in square brackets.

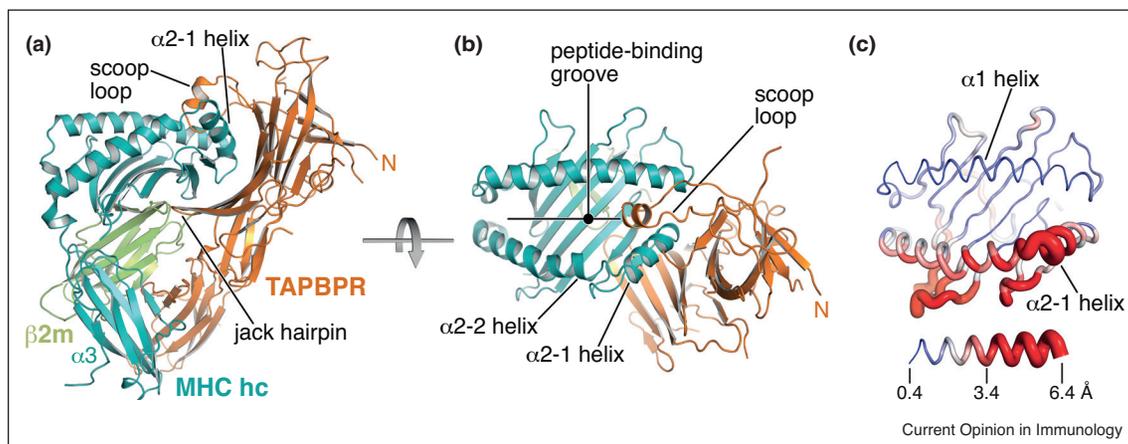
assembly of the two editing modules forms a reservoir-like cavity with two lateral openings. Peptides translocated by TAP presumably enter the ER lumen through these openings before being processed by aminopeptidases and being loaded onto MHC I. Interestingly, distinct subclasses of the cryo-EM dataset consisted of particles lacking MHC I, calreticulin, or both in one of the two editing modules, leading to an asymmetric PLC. This finding corroborates the notion that the PLC is a dynamic hub in the antigen presentation pathway, with the core PLC of TAP and Tsn-ERp57 functioning as a docking platform for MHC I-calreticulin. Subcomplexes may form spatiotemporally defined nanoclusters of antigen processing [28^{**},35,36].

Catalytic principles of the two pMHC I quality inspectors Tsn and TAPBPR

How Tsn and TAPBPR stabilize empty MHC I, accelerate peptide loading, and act as selectors of high-affinity peptide epitopes has recently been uncovered by two crystal structures of TAPBPR-MHC I complexes at 3.3 and 3.4 Å resolution, respectively [29^{**},30^{**}]. Since Tsn and TAPBPR stably associate only with suboptimally loaded or peptide-free MHC I, and as peptide-free MHC I molecules are inherently unstable, specific strategies were employed to obtain the TAPBPR-MHC I complexes: In one case, the mouse MHC I allomorph H2-D^b was refolded with a photo-cleavable peptide, and complex formation was initiated by UV irradiation. The other approach was to covalently attach a suboptimal, C-terminally truncated peptide to the MHC I (H2-D^d) that adequately stabilized the MHC I to allow refolding

but led to a sufficiently ‘frustrated’ MHC I to enable stable complex formation with TAPBPR. Both TAPBPR-MHC I structures exhibit the same overall architecture but also some notable differences: The N-terminal domain of TAPBPR, which consists of a seven-stranded β-barrel fused to an immunoglobulin (Ig)-like fold, encompasses the α2-1 helix region of the MHC I heavy chain (Figure 3), whereas the C-terminal Ig domain of TAPBPR contacts both β2m and the α3 domain of the heavy chain. At one end of the N-terminal interface, a β-hairpin, referred to as the ‘jack hairpin’, is positioned just below the floor of the peptide-binding groove of the MHC I and contacts with its tip the conserved residue Trp60 in a loop of β2m. Since Trp60 of β2m changes its conformation depending on the occupancy of the peptide-binding groove [37,38], the jack hairpin might be one structural element that enables TAPBPR to sense the loading status of the MHC I. At the other end of the N-terminal interface, the so-called ‘scoop loop’ of TAPBPR is squeezed into the MHC I F pocket region [29^{**}], which is critically involved in binding the C-terminal amino acid of peptides and crucially determines pMHC I stability [39,40]. The scoop loop is visible only in one of the two structures where it displaces and competes for crucial peptide-coordinating residues. One striking example of such a displaced MHC I residue is Tyr84, which normally coordinates the C terminus of bound peptide. In the TAPBPR complex, Tyr84 is swung out of the binding groove and stabilized in its new conformation by Glu105 of TAPBPR, which is conserved in Tsn and has been demonstrated to be important for its catalytic activity [41]. The scoop loop might be regarded as a surrogate

Figure 3



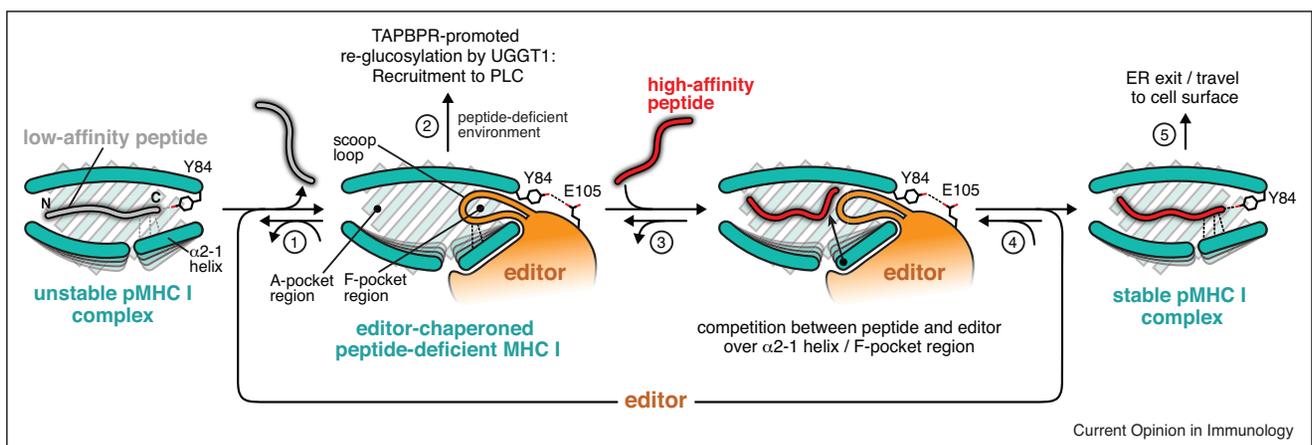
Structure of the complex between the peptide editor TAPBPR and peptide-receptive MHC I. **(a)** Overview of the TAPBPR-MHC I complex in cartoon representation, showing the concave N-terminal TAPBPR interface clamping the α2-1 helix of the MHC heavy chain (MHC hc) and the interaction of the C-terminal TAPBPR domain with β2-microglobulin (β2m) and the α3 domain of the MHC hc. **(b)** View onto the widened peptide-receptive MHC I binding groove, showing the TAPBPR scoop loop occupying the F-pocket region of the binding groove. **(c)** Putty cartoon representation of MHC I depicting the Cα atomic distances between superimposed TAPBPR-complexed H2-D^b (PDB ID: 5OPI) and uncomplexed, peptide-bound H2-D^b (PDB ID: 2F74), highlighting regions that undergo major structural rearrangements upon complex formation. The correlation between cartoon thickness and atomic distance is shown at the bottom.

of the peptide C terminus and appears to contribute to the stabilization of the empty binding groove [29^{••}]. Most importantly, in mechanistic studies with TAPBPR scoop loop mutants, we found that the scoop loop – beyond its structural role [29^{••}] – is directly involved in the exchange of peptides (unpublished data). Superimposing TAPBPR-bound MHC I onto the X-ray structure of the corresponding non-chaperoned, peptide-bound MHC I reveals in the complexed MHC I a significantly widened binding groove caused by an outward and downward shift of the $\alpha 2$ helices, relative to the $\alpha 1$ helix. These shifts are accompanied by a partial downward movement of the β strands forming the floor of the groove. Moreover, the position of $\beta 2m$ is shifted upon complex formation with TAPBPR, leading to a reorganization of its interaction network with the heavy chain. A recent NMR study of the TAPBPR-H2-D^d system confirms the TAPBPR-induced structural changes observed in the X-ray structures and delivers further insights into the MHC I dynamics during proofreading [31^{*}]. According to this study, interface regions in MHC I recognized by TAPBPR are characterized by flexibility, substantiating the concept that conformational plasticity is of central importance during catalyzed peptide optimization [42–47]. In addition, the NMR experiments by McShan *et al.* show that the chaperoned empty MHC I binding groove is still sampling conformational space, and that the discrimination of low-affinity peptides is taking place in a transient TAPBPR-pMHC I complex. The groove in the

transient TAPBPR-pMHC I complex appears to adopt a native-like conformation in the N-terminal pockets, similar to free pMHC I, whereas the C-terminal region of the groove around pockets D, E, and F is in a more open state, as observed in the X-ray structures, but the $\alpha 2-1$ helix region is still sampling multiple conformations. The NMR experiments suggest that high-affinity peptide binding subsequently induces TAPBPR dissociation through negative allosteric communication between distinct peptide-binding and TAPBPR-binding sites at both ends of the MHC I groove, the $\alpha 2-1$ helix region, and the β -sheet floor of the groove.

Taking the insights gained from the X-ray structures and the NMR study into account, one can infer the following model of TAPBPR-catalyzed peptide loading and proofreading that is most likely shared by Tsn (Figure 4): The peptide editor recognizes suboptimally loaded MHC I primarily through its interaction with the $\alpha 2-1$ helix; the interaction of its jack hairpin with the floor of the binding groove and Trp60 of $\beta 2m$ may also play a role in sensing the loading status of the MHC I. The editor is essentially sampling structural elements on the MHC I that are responsible for high-affinity peptide binding. Upon binding, the editor skews the conformational equilibrium of the MHC toward an open peptide-binding groove through the concave surface of its N-terminal domain, causing dissociation of the low-affinity peptide and stabilizing the resulting

Figure 4



Mechanism of catalyzed MHC I peptide loading and proofreading. Suboptimally loaded MHC I complexes are recognized by the editors tapasin and TAPBPR mainly through their interaction with the $\alpha 2-1$ helix region, which exhibits increased flexibility in MHC I complexes with low-affinity peptide cargo. Upon engaging suboptimally loaded MHC I, the editors stabilize a high-energy ensemble of MHC conformational states that are characterized by a widened binding groove, resulting in dissociation of the low-affinity peptide. The F-pocket region of the MHC I in the TAPBPR complex is occupied by a TAPBPR loop ('scoop loop'), and crucial peptide-coordinating residues are displaced, including Y84, which is swung out of the groove and coordinated by a conserved glutamate in the editor. In environments with a low concentration of suitable peptides, the ability of TAPBPR to promote MHC re-glucosylation by UGGT1 comes into play: the resulting mono-glucosylated MHC I can re-engage calreticulin and potentially be recruited to the Tsn-containing PLC where the peptide concentration and peptide diversity is higher. Only high-affinity peptides can eventually compete with the editor over the F-pocket region and the $\alpha 2-1$ helix of the MHC I, leading to its dissociation. The resulting stable pMHC I complex is licensed to travel to the cell surface.

peptide-deficient high-energy ensemble of MHC conformational states. This stabilization lowers the activation energy of the exchange reaction and thereby increases the rate of peptide exchange. The key peptide-coordinating MHC residue Tyr84 is swung out of the binding groove and is hydrogen-bonded in its new position by a glutamate side chain of the editor. The scoop loop might further stabilize the ensemble of open binding-groove conformations from which the peptide has been expelled, acting as a peptide surrogate in the F-pocket region [29**]. Only high-affinity peptide epitopes are subsequently able to compete with the editor over the α 2-1 helix and other structural elements crucial for peptide binding. In this step, peptide recognition by the chaperoned MHC I seems to be initiated by the A-pocket and B-pocket regions of the binding groove. The high-affinity peptide can be regarded as being able to attenuate the conformational fluctuations of the MHC I toward the state of a closed binding groove, and it can be assumed that this peptide-induced attenuation is allosterically transmitted to regions of the MHC with which the editor interacts and ultimately triggers its dissociation. The result is a stable pMHC I complex that can travel to the cell surface, and a free editor, which can scrutinize the next pMHC I client. Repeated cycles of proofreading generate an MHC I-displayed peptide repertoire enriched with high-affinity peptide epitopes.

Conclusion

Quality control of pMHC I complexes by Tsn and TAPBPR is of prime physiological importance, as it establishes a hierarchical immune response and shapes vital processes such as tumor surveillance and infectious disease defense. A precise description of the mechanistic principles governing catalysis of antigenic peptide editing is thus crucial to a thorough understanding of adaptive immune responses. The first cryo-EM structure of the PLC and the first X-ray structures of TAPBPR-MHC I complexes, in conjunction with NMR studies of the TAPBPR system, have significantly advanced our knowledge of the sophisticated cellular proofreading machinery and will possibly facilitate future therapeutic manipulations of the presented antigen repertoire, for example in cancer immunotherapies. The first steps in this direction have already been taken by employing TAPBPR-catalyzed exogenous peptide loading to tailor targeted immune responses against cells [48]. Yet, major open questions remain in the field of antigenic peptide selection: Which structural elements determine the distinct MHC I allomorph specificities of TAPBPR and Tsn? Does the shorter scoop loop in Tsn affect the spectrum of selected peptides? And how does TAPBPR mediate the action of UGGT1 on MHC I?

Conflict of interest statement

Nothing declared.

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