Title: The Ins and Outs of TAPBPR

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Abstract

Peptide presentation on MHC class I molecules (MHC-I) is central to mounting effective antiviral and antitumoral immune responses. The tapasin-related protein TAPBPR is an MHC-I peptide editor which shapes the final peptide repertoire displayed on the cell surface. Here, we review recent findings which further elucidate the mechanisms by which TAPBPR performs peptide editing on a molecular level, and how glycosylation on MHC-I influences the interaction with TAPBPR and the peptide loading complex. We also explore how the function of TAPBPR can be utilized to promote exogenous peptide loading directly onto plasma-membrane expressed MHC-I. This has led to the development of new assays to investigate TAPBPR-mediated peptide editing and uncovered translational opportunities of utilizing TAPBPR to treat human disease.

Introduction

MHC class I molecules (MHC-I) present fragments of the cellular proteome at the surface of cells for inspection by $CD8^+$ T cells, thereby playing a crucial role in the immunosurveillance of intracellular infections and tumours. Peptide loading on MHC-I is modulated in the endoplasmic reticulum (ER) by the peptide loading complex (PLC). Within the PLC, tapasin bridges peptide-receptive MHC-I to the transporter associated with antigen processing (TAP), ensuring their proximity to the point of peptide influx in the ER [1-3], while also performing peptide editing to help select optimum peptide cargo [4-7] (**Figure 1**). In 2002, a tapasin-related protein termed TAPBPR was initially described [8]. The function and properties of TAPBPR remained undefined until its ability to interact with MHC-I was discovered [9]. Since then, the role of TAPBPR in the antigen presentation pathway has been extensively investigated, unveiling further complexities regarding how peptides are selected on MHC-I.

The *Ins* of TAPBPR: Its natural role within an intracellular environment

It is now apparent that TAPBPR is an intracellular chaperone for MHC-I and a component of the antigen processing and presentation pathway [9-11]. Below, we discuss some of the functions which TAPBPR performs and recent insights into the interaction between TAPBPR and MHC-I.

Peptide Editing on MHC-I

Structural predictions and site-directed mutagenesis experiments suggested that TAPBPR adopts a similar orientation on MHC-I to the one of tapasin, raising the intriguing possibility that it may be capable of performing peptide editing on MHC-I [12]. This hypothesis was

supported a few years later following demonstration using in vitro assay that TAPBPR does indeed function as a peptide editor [13,14]. In contrast to tapasin, which requires artificial tethering to MHC-I or additional cofactors to facilitate peptide exchange [6,7], the luminal domain of TAPBPR alone is capable of modulating peptide editing on MHC-I [13,14]. Furthermore, alteration of TAPBPR expression in cells changes the peptide repertoire presented on MHC-I [13]. These discoveries established TAPBPR as a second peptide editor in the MHC-I antigen presentation pathway (**Figure 1**). While tapasin appears somewhat crucial for stable peptide:MHC-I presentation on the plasma membrane [5,15,16], TAPBPR depletion results in a more subtle phenotype on MHC-I surface expression, implicating TAPBPR in a fine-tuning or refining role of TAPBPR in the pathway [9,13]. The distinct environments within which the two peptide editors function represents one likely factor responsible for their differential effects on MHC-I. For example, tapasin performs peptide editing in a peptide-rich environment, which enables efficient peptide loading onto MHC-I. In contrast, peptide editing by human TAPBPR occurs more distally from the TAP transporters, presumably in an environment more devoid of optimal MHC-I binding peptides. Thus, peptide editing in the absence of incoming peptide would presumably result in a refining effect on the MHC-I immunopeptidome.

Insights into the mechanisms of MHC-I peptide editing

The discovery of TAPBPR provided a platform for the laboratories of David Margulies and Robert Tampe to independently solve the first crystal structures of MHC-I bound to a molecular chaperone [17,18]. Here, we only briefly touch on this insightful work as it is covered in depth in a complementary article by David Margulies in this issue of *Current Opinion in Immunology* [19]. Both published TAPBPR:MHC-I structures suggest that

TAPBPR mediates peptide dissociation by sequestering the α2-1 region of MHC-I away from the peptide, consequently 'flipping' away residue Y84 of MHC-I which is involved in hydrogen bond formation with the C-terminus of the peptide [17,18]. This is similar to the mechanism previously proposed for tapasin [20]. However, one key difference in the reported structures was the localization of a loop of TAPBPR, composed of residues 22–36, which was modelled in the structure by Thomas and Tampe near the peptide binding groove of MHC-I, consequently suggesting its involvement in mediating peptide exchange [17].

Our own recent biochemical exploration of the involvement of this loop region in peptide selection revealed that upon mutation of the K22-D35 loop, TAPBPR retained its capacity to bind to MHC-I, however lost its ability to facilitate efficient peptide exchange on HLA-A*02:01, HLA-A*68:02 and H-2K^{b} molecules [21]. A leucine residue within the loop appears to be essential for promoting peptide dissociation from MHC-I that accommodate hydrophobic amino acids in their F pocket [21]. This work suggests that the loop region is crucial for TAPBPR-mediated peptide editing and peptide selection, at least for certain MHC-I variants. A similar, albeit shorter, loop is also present in tapasin and peptides comprising this sequence have recently been crystalized with MHC-I [22]. Using an NMR-based approach, Skourgakis and colleagues have shown that TAPBPR senses peptide/MHC-I interactions along the entire length of the groove and proposed an allosterically driven release of the peptide in the presence of TAPBPR [23]. Together, these recent findings have revealed mechanistic insight into the processes involved in chaperone-mediated peptide editing. Since MHC-I are extremely polymorphic, it is important to consider that one rule might not fit all MHC-I, and multiple distinct mechanisms of peptide editing may be required to accommodate the high degree of variation in both the peptide and the MHC-I itself.

The glycan attached to MHC-I impacts its association with TAPBPR

Given that TAPBPR apparently has a higher affinity for MHC-I than tapasin [14], and that both chaperones seem to reside in the ER [9], we have previously attempted to understand the reason for which TAPBPR does not outcompete tapasin for binding to MHC-I in a cellular environment [11]. There are several possible explanations for this phenomenon and subsequent findings from our laboratory suggest that the glycan attached to MHC-I is one important factor that influences the order in which MHC-I interacts with the two peptide editors [24]. While tapasin binds to mono-glucosylated MHC-I by virtue of its interaction with calreticulin and ERp57 [25-29] (**Figure 1**), the interaction of MHC-I with TAPBPR appears to occur in a glycan-independent manner [24]. This would permit TAPBPR to bind to MHC-I molecules containing a broad diversity of oligosaccharides attachments and may be responsible for TAPBPR interacting with MHC-I further along the secretory pathway, as compared to tapasin (**Figure 1**). That being said, tapasin appears to have "first dibs" at glycosylated MHC-I. Thus, when the $Glc_1Man_9GlcNAc_2$ moiety is attached to MHC-I, the tapasin/calreticulin/ERp57 complex has greater accessibility to MHC-I than TAPBPR. These findings are consistent with the notion that MHC-I initially load peptides in the PLC, which subsequently undergo TAPBPR-mediated peptide selection (**Figure 1**).

TAPBPR influences MHC-I recycling

In 2011, UDP-glucose:glycoprotein glucosyltransferase (UGT1) was shown to be involved in MHC-I quantity control and optimal peptide selection [30,31]. By reconstituting the $Glc_1Man_9GlcNAc_2$ moiety on MHC-I loaded with suboptimal peptides, UGT1 promotes recognition of these molecules by calreticulin, consequently causing their re-engagement by the PLC. Subsequent experiments demonstrated that TAPBPR can act as a bridge between

UGT1 and MHC-I molecules, which are potentially peptide receptive [32] (**Figure 1**). Thus, in addition to directly functioning as a peptide editor [13,14], TAPBPR plays an additional role in shaping the MHC-I immunopeptidome, by recycling sub-optimally loaded MHC-I molecules back to the PLC [32](**Figure 1**). As the TAPBPR:UGT1 complex is involved in modifying the glycan attached to MHC-I, this may explain why the interaction of TAPBPR with MHC-I occurs in a glycan-independent manner.

What else is TAPBPR capable of doing?

Through its interaction with UGT1, TAPBPR is able to facilitate the re-glucosylation of MHC-I [32]. This raises the question of whether TAPBPR could adopt alternative functions through interactions with additional co-factors. Furthermore, despite current research having predominately focused on the effect of TAPBPR on classical MHC-I, could TAPBPR serve as a chaperone for other ligands as well, for example non-classical MHC-I or MHC-I-related molecules? Naturally, there is also speculation regarding whether TAPBPR could be involved in MHC-I cross-presentation.

The *Outs* of TAPBPR: TAPBPR is capable of functioning on plasma membrane expressed MHC-I

Although TAPBPR usually resides intracellularly, we recently discovered that it can promote peptide exchange on cell surface-expressed MHC-I molecules [33]. By either over-expressing TAPBPR in cells (which results in a low proportion of TAPBPR leaking to the plasma membrane) or by adding recombinant TAPBPR exogenously onto cells, we revealed that TAPBPR could efficiently promote exogenous peptide loading directly onto surface expressed MHC-I [33](**Figure 2**). The ability of TAPBPR to function on surface-expressed

MHC-I is consistent with other previously discovered properties of TAPBPR, including its binding to MHC-I in a glycan independent manner [24] and its ability to mediate peptide editing in the absence of other cofactors [13,14]. This discovery has led to a number of interesting developments and opportunities.

New assays to explore TAPBPR function

The ability of TAPBPR promote peptide exchange on plasma membrane expressed MHC-I has permitted the development of new assays to explore TAPBPR-mediated peptide editing. Prior to this, the only other available assay relied on assessing the effect of the luminal domain of TAPBPR on recombinant MHC-I refolds, using fluorescence polarization measurements [13,14]. This system was based on the pre-existing assay designed by Chen & Bouvier for tapasin [6]. From a biological perspective, the new experimental systems offer several advantages, as the MHC-I are in their naturally occurring transmembrane conformations, thus presenting a wide repertoire of peptides (albeit those which have passed through quality control mechanisms), containing a glycan (although a more mature oligosaccharide than would be found in the ER/Golgi) and abiding by the natural restrictions imposed by a cellular membrane. From a practical point of view, these assays represent high-throughput tools for measuring TAPBPR-mediated peptide editing. They rely on the cellular machinery to express, fold and load membrane bound MHC-I molecules and thus circumvent the need to perform laborious refolding reactions with recombinant MHC-I expressed in bacteria.

These newly established assays enabled us to explore whether the K22-D35 loop of TAPBPR was involved in mediating peptide exchange [21] as well as to determine which MHC-I

allotypes are subjected to TAPBPR-mediated peptide editing [34]. Our findings suggest that TAPBPR displays a clear functional preference for HLA-A molecules, particularly for members of the A2 and A24 superfamilies, over HLA-B and -C molecules. Furthermore, this work revealed that molecular features of the HLA-A F pocket, specifically residues H114 and Y116, drive the propensity of MHC-I to undergo TAPBPR-mediated peptide exchange. The development of new systems to explore peptide selection on MHC-I widens our scope of experimentation which will ultimately lead to a better understanding of the processes involved.

Potential use in Immunotherapy

Intriguingly, recombinant TAPBPR can be used to decorate cells with antigenic peptides, including viral peptides and neo-epitopes [33] (**Figure 2**). Once loaded onto MHC-I, these peptides also appear to be available for recognition by antigen-specific CD8+ T cells [33], providing promising translational opportunities for using TAPBPR to increase the immunogenicity of tumours. A key issue currently faced regarding the efficiency of immunotherapies is the low immunogenicity of tumours [35]. Recent discoveries suggest that even tumours displaying highly immunogenic peptides can avoid immune detection provided that only a small fraction of the tumour cells present the antigen [36]. Therefore, it will be interesting to explore whether the function of TAPBPR can be utilized in vivo to load immunogenic peptides of choice specifically onto tumours to increase the percentage of cells within a tumour that CTLs can detect and destroy, therefore turning immunologically ‘cold’ tumours into ‘hot’ tumours.

Concluding remarks

The discovery that TAPBPR can facilitate peptide exchange on cell surface expressed MHC-I, if given access to the plasma membrane, raises queries regarding in which cellular localization TAPBPR naturally assists in peptide selection. While TAPBPR is present in the ER and Golgi, its fate post medial-Golgi remains largely enigmatic. While it does not appear to be present on the plasma membrane when expressed at physiological levels, it remains undetermined whether it localizes into the endosomal system. With its ability to dissociate high-affinity peptides from mature MHC-I, representative of MHC-I found in recycling endosomes, there is speculation whether TAPBPR may help facilitate MHC-I cross-presentation by increasing the efficiency of peptide exchange, as occurs on MHC class II molecules via HLA-DM [37].

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Figure legends

Figure 1 – The *Ins* of TAPBPR: Its natural role within an intracellular environment.

Within the PLC, tapasin assists in loading peptides onto MHC-I. These MHC-I may then either be transported through the Golgi for presentation on the cell surface or undergo TAPBPR-mediated peptide editing. If peptide editing occurs in the absence of a suitable incoming peptide, the MHC-I may become peptide-receptive. UGT1 associated with TAPBPR can reglucosylate MHC-I, a modification which restores their recognition with calreticulin and recycling to the peptide loading complex.

Figure 2 - The *Outs* of TAPBPR: TAPBPR is capable of functioning on plasma membrane expressed MHC-I.

(**A**) When TAPBPR is over-expressed in mammalian cells by transduction or transfection, a small proportion of TAPBPR traffics to the plasma membrane. Due to its ability to interact with MHC-I in a glycan-independent manner, TAPBPR is capable of binding to, and performing peptide editing on, cell surface expressed MHC-I. In the presence of high affinity peptides, including those derived from viruses or tumour-antigens, TAPBPR can efficiently promote exogenous peptide loading directly into plasma membrane expressed MHC-I. (**B**) Treatment of mammalian cells with recombinant TAPBPR can also be used to promote exogenous peptide loading directly on plasma membrane expressed MHC-I.

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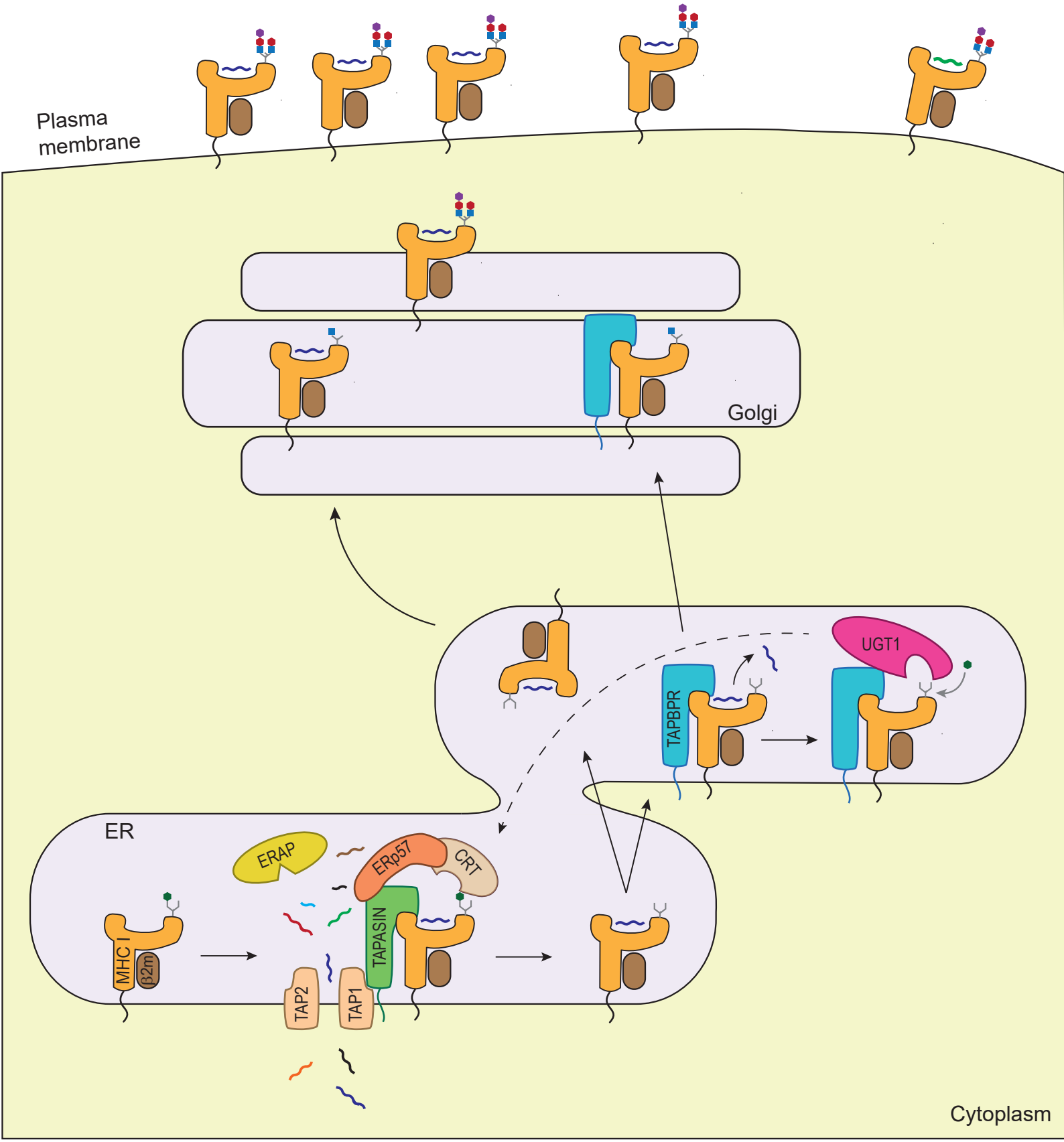
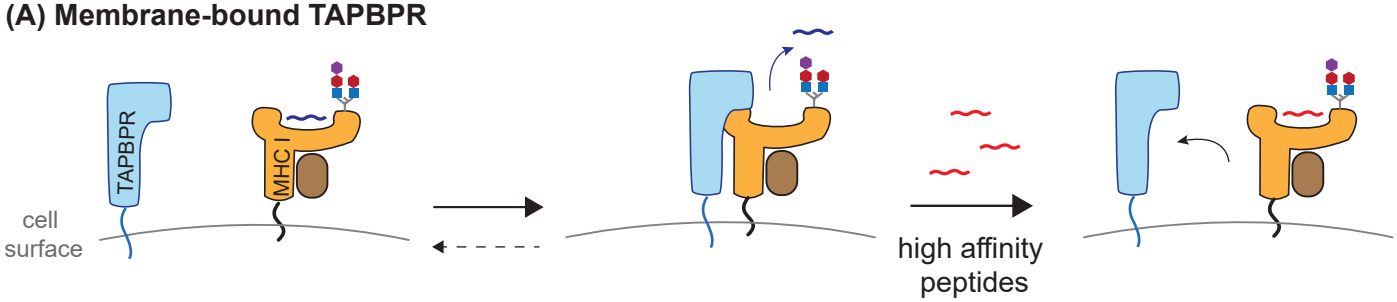

Plasma membrane
Golgi
UGT1
TAPBPR
ER
ERAP
ERp57
CRT
TAPASIN
MHC I
β2m
TAP2
TAP1
Cytoplasm
= glucose
= other monosaccharides

(A) Membrane-bound TAPBPR



(B) Soluble TAPBPR