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Abstract

The presentation of antigenic peptides by MHC class I molecules plays a vital role in generating T cell responses against infection and cancer. Over the last two decades the central role of tapasin as a peptide editor that influences the loading and optimisation of peptides onto MHC class I molecules has been extensively characterised. Recently, it has become evident that the tapasin-related protein, TAPBPR, functions as a second peptide editor which influences the peptides displayed by MHC class I molecules. Here, we review the discovery of TAPBPR and current understanding of this novel protein in relation to its closest homologue tapasin.

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Properties of the tapasin homologue TAPBPR

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Conflict of interest:

We have no conflicts of interest to declare.

Properties of the tapasin homologue TAPBPR

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Abstract

The presentation of antigenic peptides by MHC class I molecules plays a vital role in generating T cell responses against infection and cancer. Over the last two decades the central role of tapasin as a peptide editor that influences the loading and optimisation of peptides onto MHC class I molecules has been extensively characterised. Recently, it has become evident that the tapasin-related protein, TAPBPR, functions as a second peptide editor which influences the peptides displayed by MHC class I molecules. Here, we review the discovery of TAPBPR and current understanding of this novel protein in relation to its closest homologue tapasin.

Introduction

The MHC class I antigen processing and presentation pathway plays a crucial role in the selection of peptides for immune recognition, a process critical in mounting immune responses against viruses and tumours. The loading of peptide cargo onto MHC class I molecules occurs in the peptide loading complex (PLC). Within this complex is the MHC class I dedicated chaperone tapasin [1-3]. Over the past 20 years, the function of tapasin (or TAPBP which stands for Transporter associated with antigen processing (TAP) binding protein) has been extensively studied and well characterised. It is now appreciated that tapasin performs a plethora of functions in relation to peptide loading including the bridging peptide-receptive MHC class I onto the TAP transporters [1], stabilisation of TAP [4], maintaining MHC class I in a conformation receptive to peptides and peptide editing, a process which assists in the removal of low-affinity peptides and replacement with higher affinity cargo [5-8]. Precisely what happens to MHC class I molecules after peptide loading is less clear. Given that peptide-loaded MHC class I molecules are not immediately exported from the ER after dissociating from TAP [9,10], it is apparent that other regulatory checks and sorting steps occur after the PLC [11]. One such post-PLC quality control step which has recently been appreciated is that performed by UDP-glucose:glycoprotein glucosyltransferase 1 (UGT1), an ER/cis-Golgi resident enzyme that monitors glycoprotein folding [12]. UGT1 is able to reglucosylate MHC class I molecules associated with sub-optimal ligands, thereby restoring their recognition by calreticulin. This permits their re-engagement with the PLC and has been shown to influence optimal peptide selection [13,14].

The discovery of TAPBPR

In 2000, two TAPBP-like genes were discovered in the human genome in MHC paralogous regions; one on chromosome 9q34, which was suggested to be a pseudogene, and a second on chromosome 12 [15]. The *TAPBP-R* (for TAPBP-related but is also known as *TAPBP-L* for TAPBP-like) locus was identified between the *CD27* and *VAMP1* loci at 12p13.3 [16]. This locus was predicted to encode a tapasin-related protein (TAPBPR) of 468 amino acids, with 22% identity to tapasin and predicted to adopt a conformation consisting of a unique N-terminal unique domain, an IgV and IgC domain, transmembrane region and cytoplasmic tail [16]. For the following decade, the ligand for TAPBPR and its potential function(s) remained unexplored. In 2013, however, renewed interest in TAPBPR led to the discovery that MHC class I molecules were endogenous ligands of TAPBPR [17]. Thus, discovery of a second MHC class I dedicated chaperone has opened up a new avenue of MHC biology to explore, and led to renewed interest in the mechanisms controlling antigen processing and presentation. Here we provide a current review of TAPBPR biology and function in relation to its closest homologue tapasin.

Similarities between tapasin and TAPBPR

Like tapasin and other dedicated components in the antigen presentation pathway including TAP and ERAP1 [18-21], TAPBPR is IFN-γ inducible [17,22]. Furthermore, TAPBPR appears to bind to a similar conformation of MHC class I as tapasin; a heterodimer of heavy chain and β2m that is either devoid of peptide or associated with low affinity peptide [17,23,24]. Despite the significant differences in amino acid sequence between TAPBPR and tapasin, these two molecules are orientated similarly on MHC class I. Critical contacts occur between conserved amino acids within the IgC and IgV domains of the chaperones with

residues in the α3 domain and a loop under the α2 helix of MHC class I, respectively [25-28]. Given the similar orientation, we and other investigators sought to determine whether TAPBPR shared some functionality with tapasin. Recent work has confirmed this hypothesis and revealed that TAPBPR is indeed capable of functioning as a peptide editor on MHC class I molecules *in vitro* [23,24]. Therefore, it is now apparent that tapasin and TAPBPR are both intimately involved in selecting peptides for immune recognition.

Differences between tapasin and TAPBPR

Despite the similarities outlined above, the vast majority of amino acids are not conserved between tapasin and TAPBPR, resulting in several important differences between the two proteins. Clearly, improved understanding of these distinctions is essential to determine why MHC class I requires two dedicated chaperones and to establish whether they serve unique, overlapping or redundant functions in antigen processing and presentation.

Distinct effects on MHC class I peptide selection

Although *in vitro* TAPBPR shares tapasin's ability to catalyse peptide exchange on MHC class I molecules, within a cellular environment these two peptide-editors have distinct effects on the peptide repertoire [23]. The importance of tapasin in peptide loading and selection is apparent in tapasin knockout mice and cell lines in which expression of MHC class I molecules is often severely reduced due to a lack of appropriate peptide loading [1,3,29,30]. In contrast, the effect of TAPBPR on MHC class I expression and peptide selection appears comparatively more subtle. Firstly, the steady state levels of MHC class I are similar in the presence or absence of TAPBPR [17,23]. Secondly, HeLa or KBM-7 cells rendered TAPBPR deficient do not exhibit a gross impairment in peptide loading onto MHC

class I [23]. However, upon closer examination clear differences in the displayed peptide repertoire are observed. More specifically, in the absence of TAPBPR, the recovered peptide repertoire appears broader. This suggests that TAPBPR may be involved in the refinement of peptides displayed at the cell surface [23]. Interestingly, a proportion of the unique peptides displayed on MHC class I in this setting have lower affinity. Together these findings support a role for TAPBPR as a peptide editor within cells and suggest that TAPBPR may be required for quality control, rather than the initial loading of peptides in non-professional antigen-presenting cells.

Differences in cellular environment that tapasin and TAPBPR function

Given the distinct effects of tapasin and TAPBPR on peptide selection in cells, it is worth considering whether differences in the cellular environment within which these two chaperones function may account for the differences observed in their peptide-exchange activity. For example, one possible difference may be peptide concentration in the immediate environment that the proteins function in. Tapasin primarily serves its peptide editing function within the confines of the PLC, an environment rich in peptides optimal for MHC class I binding (Figure 1). Therefore, it may be speculated that upon tapasin-mediated peptide dissociation another peptide suitable for binding to MHC class I will be readily available in the proceeding peptide association step. TAPBPR, in contrast, is not an integral component of the PLC [17] (Figure 1). In fact, TAPBPR does not even appear to be restricted to the ER since the MHC class I molecules bound to TAPBPR acquire Endo-H resistance with time [17](Figure 1). Presumably, therefore, TAPBPR-mediated peptide dissociation may occur in a microenvironment relatively deficient in peptide especially as the TAPBPR:MHC I complex migrates through the secretory pathway. Consequently, upon TAPBPR-mediated

peptide dissociation, it is conceivable that there may be a lack of suitable, high-affinity replacement peptides, resulting in an empty MHC I complex (Figure 1). In this way, TAPBPR could function to fine-tune the peptide repertoire.

As pH varies significantly throughout the secretory pathway [31] the acidity of the subcellular environment may have important implications for the peptide-editing functions of tapasin and TAPBPR. As a predominately ER-resident protein, tapasin functions in a near neutral pH. In contrast, TAPBPR operates within a wider pH range as it moves through the secretory pathway (ER: pH ~7.2, cis-Golgi: pH ~6.7, trans-Golgi: pH ~6.0) (Figure 1). Peptide-editing by TAPBPR in more acidic environments may enforce more stringent criteria on the peptides selected.

It is currently unclear in which subcellular environment(s) TAPBPR functions as a peptide-editor. In contrast to tapasin, TAPBPR does not contain an obvious retention/recycling motif within its cytoplasmic tail, which initially led to the suggestion that it was not retained in the ER but was potentially expressed on the cell surface [16]. While more recent work supports the lack of ER retention of TAPBPR [17], we have been unable to detect any endogenously expressed TAPBPR (when using specific monoclonal antibodies which recognise folded human TAPBPR) at the cell surface as yet, even when TAPBPR levels are boosted in cells by IFN-γ treatment. However, when TAPBPR is over-expressed in cells, it is detectable at the cell surface [17]. Perhaps this genuinely reflects the ability of endogenous TAPBPR to traffic, albeit transiently, to the cell surface but at levels below the limits of detection. Alternatively, it may be an artefact of over-expression and, as a consequence, results in disruption of the delicate balance of proteins that regulate the subcellular distribution of TAPBPR.

Differences in co-factors that tapasin and TAPBPR associate with

As a key component of the PLC, tapasin makes a number of essential contacts with the TAP transporters [1-3,32,33], ERp57 [34,35] and of course MHC class I (Figure 1). In contrast, our current, over-simplified model of TAPBPR is one in which it performs peptide-editing on MHC class I in isolation, without any additional co-factors (Figure 1). But is this really the case? Recent work from our laboratory suggests TAPBPR works in collaboration with at least one additional co-factor, namely the ER/cis-Golgi resident enzyme UGT1 (unpublished observations). Our data suggests that TAPBPR functions as a bridge between UGT1 and MHC class I, and serves to promote the reglucosylation of MHC class I, thereby restoring their recognition by calreticulin (Figure 1). Therefore, not only does TAPBPR influence peptide selection by functioning as a peptide-editor in its own right, but it also has the capacity to improve peptide optimisation by promoting peptide-receptive MHC class I molecules to associate with tapasin/PLC.

Differences in affinities for MHC class I

In contrast to tapasin, TAPBPR can function as a peptide-editor on MHC class I molecules *in vitro* in the absence of a leucine zipper or additional association partners [23,24]. Furthermore, the luminal domains of TAPBPR appear to interact more tightly than the luminal domains of tapasin to certain MHC class I molecules, including HLA-A2 and H2-D^b, which are peptide-free or loaded with low-affinity peptides [24]. If these differences in apparent affinity are also applicable to the cellular environment, then it is unclear what prevents TAPBPR from outcompeting tapasin for MHC class I in the ER. Perhaps this is one of the reasons that basal TAPBPR expression is low in cells. It may also be possible that the

two chaperones recognise slightly different conformations of MHC class I; for example, differences in the N-linked glycan attached to the MHC class I molecule. Another possibility could be that the affinity of tapasin and TAPBPR for MHC class I is pH-dependent as has been found with the cowpox immune evasion protein CPXV203 [36]. The association of this viral protein with MHC class I, which has a footprint that overlaps with both tapasin and TAPBPR, is dependent on the local proton concentration as exemplified by the observation that CPXV203 binds weakly to MHC class I at the pH found in the ER but the strength of the association is increased by 50-fold in more acidic conditions found in the Golgi [36].

Difference in polymorphisms and alternative forms

Finally, difference in the degree of genetic variation is apparent between TAPBPR and tapasin, which may provide some clues to their roles in health and disease. Whereas tapasin is monomorphic, TAPBPR is comparatively polymorphic with a number of distinct alleles present in humans. Interestingly, a number of distinct splice forms of TAPBPR have been identified which raises the possibility of alternative functions of this protein [37].

Conclusions

With the discovery of the role of TAPBPR in peptide selection, a new picture of the MHC class I antigen processing and presentation pathway is beginning to emerge in which events occurring outside of the PLC serve as important quality control checkpoints, but are yet intertwined with the PLC (Figure 1). Untangling the functions of tapasin and TAPBPR is now needed to understand precisely how peptides are selected on MHC class I for presentation to the immune system.

Figure legend

Figure 1: Working model of the function of TAPBPR in the classical pathway.

In the peptide-rich environment of the PLC, peptide editing via tapasin helps with the initial loading of peptides onto MHC class I molecules. 2) If the resultant MHC class I molecule is loaded with a peptide of suitable affinity which induces a stable conformation, the MHC class I molecule is permitted release through the secretory pathway after glucosidase II trimming of the terminal glucose on the MHC class I glycan. 3) If the resultant MHC class I molecule is loaded with a lower affinity peptide or one which does not induce a stable conformation, then TAPBPR binds to the MHC class I molecule and performs a second peptide-editing step. If the MHC class I molecule achieves a stable conformation, loaded with a suitable peptide, then it is permitted release through the secretory pathway. 4) However if the MHC class I fails to achieve a stable conformation and/or is in a peptide-receptive state, the glycan on the MHC class I molecule is reglucosylated by UGT1 which is brought into close proximity via TAPBPR. This results in recognition of the MHC class I by calreticulin and consequently in its rebinding to the PLC. Therefore, TAPBPR influences the peptide repertoire presented on the cell surface of MHC class I molecules by functioning as a peptide editor and by promoting rebinding of peptide-receptive MHC class I molecules to the PLC

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This paper, together with **23, describes a functional role for TAPBPR as an MHC class I peptide editor. This work also determines the affinity of TAPBPR for MHC class I, revealing the luminal domain of TAPBPR interact more tightly than the luminal domains of tapasin to certain MHC class I molecules.
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Properties of the tapasin homologue TAPBPR

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Highlights

- TAPBPR is a second MHC class I-dedicated chaperone in the antigen processing and presentation pathway
- Like tapasin, TAPBPR acts as a peptide editor and influences the final peptide repertoire displayed on the surface of cells
- In contrast to tapasin, TAPBPR is not a component of the peptide-loading complex and therefore regulates novel aspects of antigen processing and presentation