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Current Opinion in Immunology

To TAP or not to TAP: alternative peptides for immunotherapy of cancer

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Intracellular processing of antigens is crucial for the generation of T cell immunity towards cancers, since cleaved protein products are the molecular targets of these adaptive lymphocytes. The majority of antigenic peptides requires the TAP transporter to gain access to the peptide loading complex in the ER lumen where they bind MHC class I (MHC-I). This pivotal role of TAP in antigen processing makes the system vulnerable for modifications in cancer cells and indeed human cancers frequently silence this gene epigenetically. Interestingly, TAP-independent processing pathways then become apparent and partly restore MHC class I presentation with alternative peptides. In this review we discuss recent insights on how TAP-independent processing of immunogenic peptides occurs, and how these antigens can be exploited for cancer immunotherapy.

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Current Opinion in Immunology 2020, **64**:15–19

This review comes from a themed issue on **Antigen processing**

Edited by **Sebastian Amigorena**

For a complete overview see the Issue and the Editorial

Available online 14th January 2020

https://doi.org/10.1016/j.coi.2019.12.004

Introduction

A sophisticated antigen-processing machinery has evolved in most nucleated cells of our body and its ultimate goal is to 'report' viral and mutated antigens to specific T lymphocytes in order to clear virus infected and transformed cells [1]. Antigen processing is a complex and continues process where small fragments of intracellular proteins are generated by a multitude of proteases, including the proteasome, and are loaded onto MHC-I molecules in the ER by the peptide loading complex (PLC). Nascent MHC-I heavy chains and β2-microglobulin (β2m) assemble as 'empty' MHC-I heterodimers, which then are recruited by calreticulin. The ERp57 (disulphide-linked with the thiol oxidoreductase) and tapasin proteins complete the macromolecular PLC and are critical for the stabilization of 'empty' MHC-I molecules and to facilitate optimal peptide loading [2,3•,4]. Before cytosolic peptides can access the chaperoned MHC-I complexes, the peptides need to travel across the ER-membrane via the transporter associated with antigen processing (TAP). Therefore, TAP is a key component of the PLC and responsible for the majority of peptides that bind MHC-I molecules.

To TAP: the gateway for efficient antigen presentation

The heterodimeric TAP1/TAP2 pump is a member of the ATP-binding cassette (ABC transporter) superfamily, which is responsible for transport of cytosolic peptide substrates across the ER-membrane. The two subunits, ABCB2 (TAP1) and ABCB3 (TAP2), have a highly conserved nucleotide-binding domain (NBD) and a multiple transmembrane (TM) spanning domain. The outer TM-helices are important for binding with the PLC component tapasin, whereas the inner helices form the transmembrane pore that is accessible from either site of the membrane for peptide transport [5]. TAP is able to bind only one peptide at the time with lengths ranging from 8 to 16 amino acids, although transport of much larger peptides is not excluded [5]. Preferred peptides for transport by human TAP contain positively charged amino acids at N-terminal position 1 and 2, aromatic residues at position 3, and hydrophobic or basic amino acids at the C-terminal position [5]. The first step of the peptide translocation cycle is initiated by binding of one peptide substrate in the cavity of the TAP-complex in its inward 'cytosolic' facing (IF) conformation. Interestingly, Cryo-electron microscopy (cryo-EM) captured two distinct IF conformations, IF^{narrow} and IF^{wide} with a cavity size of 4650 versus 5900 Å, allowing binding of larger and bulkier peptides. Notably, high peptide concentration increased the number of observed IF^{wide} conformations, suggesting that peptide binding in the cavity stabilizes this conformation [6•]. Binding of two ATPs to the NDBs allows dimerization, and allosteric conformation of the TAP-complex into an outward 'ER' facing (OF) structure where the peptide substrate can be released into the ER-lumen [7]. Interestingly, the OF^{open} conformation could not be detected in the TAP turnover experiments, suggesting that this conformation is highly transient. When the catalytic base was mutated, disabling ATP-hydrolysis, it was possible to capture two distinct OF conformations, namely OF^{open} and $OF^{occluded}$. These two OF conformations were also captured in the post ATP-hydrolysis state when ATP was bound in the non-canonical site, while ADP-vanadate was bound at the canonical site. This

suggest that ATP hydrolysis is not the driving force for the OF to IF conformation, as previously thought. The release of phosphate, possibly through channels at the canonical NBD site, results in movement of TM3 and TM4 and unlocking of the gate, which initiates the progressive return to the IF conformation allowing another round of the peptide translocation cycle [6•].

TAP inhibition in human disease

The central role of TAP for antigen processing makes it a vulnerable target for immune evasion. Indeed, dedicated proteins from herpesviruses which cause chronic infections, for example, CMV, HSV and EBV, inhibit the function of TAP during viral reactivation to escape $CD8^+$ T cell control (reviewed in Ref. [8]). Recently, cryo-EM technology revealed the structures of some of these viral evasion proteins with TAP. ICP47 from HSV forms a long helical hairpin that plugs the translocation pore of TAP from the cytoplasmic side and thereby acts as a high affinity competitor for peptide binding in TAP [9,10]. The active domain of ICP47 is located at the N-terminal site (aa 3–34) and is indispensable to arrests TAP in its open inward-facing conformation resulting in inhibition of its transport function [11]. Interestingly, recent data showed that the highly conserved C-terminal region of ICP47 is crucial to increase the stability of ICP47-TAP, thereby locking the transporter in its peptide-repellent conformation [11,12]. Similarly, UL49.5 from the bovine herpesvirus BHV-1 also arrests the TAP-complex in an open inward-facing conformation [13]. In addition, this viral protein tags TAP for proteasomal breakdown [8]. Other TAP-targeting viral proteins, like CPXV012, interfere with the nucleotide-binding domain of TAP, thereby interfering with ATP binding, resulting in conformation-arrest of the transporter [14,15]. Remarkably, patients with loss-of-function mutations in TAP1 or TAP2 do not display an increased reactivation of these herpesvirus infections, suggesting that TAP-independent presentation of viral antigens is sufficient to control viral disease [16]. For some viruses such peptide-epitopes have been characterized [17–22].

Alternative processing pathways of TAP-independent peptides

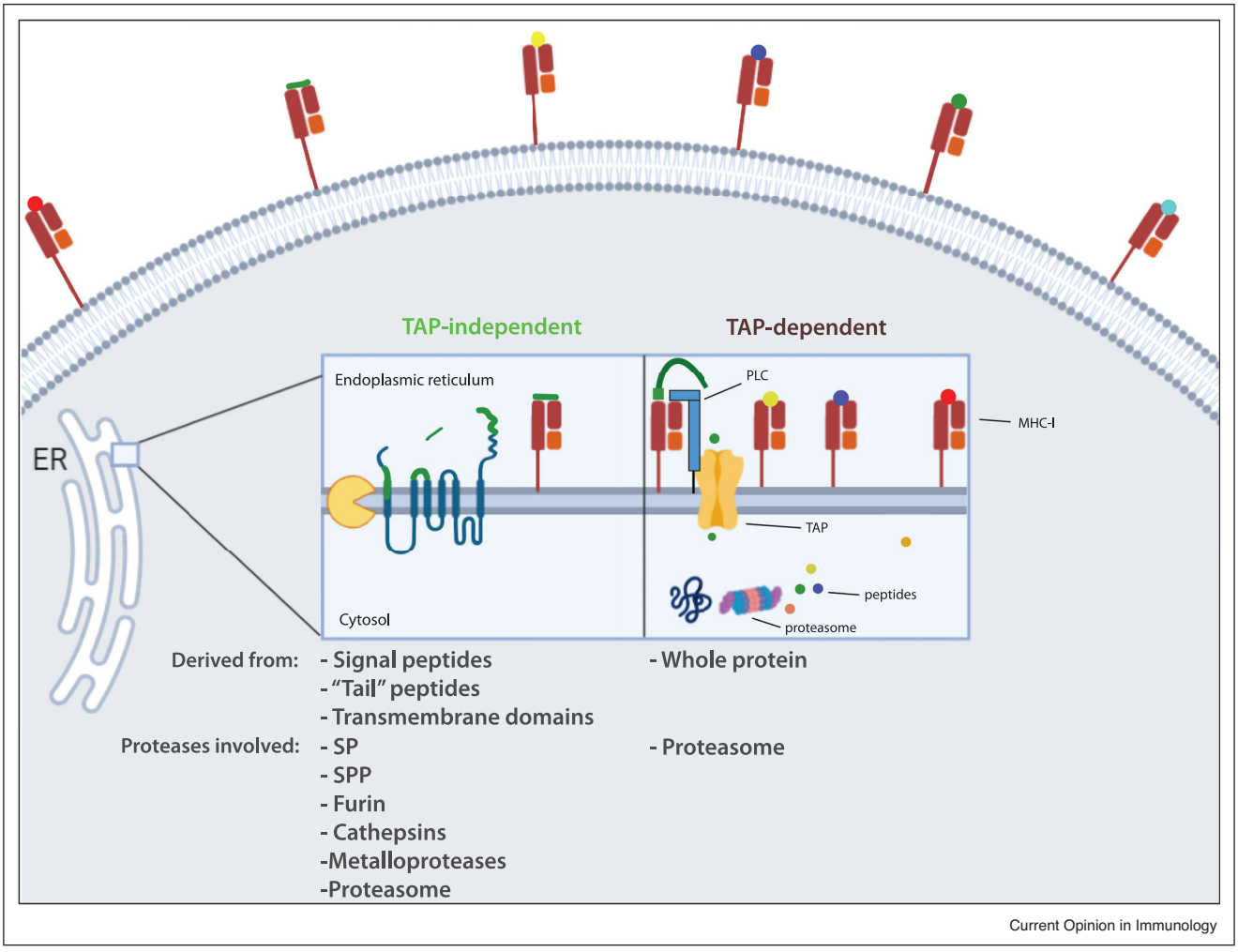
Malignant cells also frequently manipulate TAP expression, especially after increased immune pressure, resulting in immune escape and tumor progression [23]. Importantly, complete abrogation of TAP does significantly affect surface levels of MHC-I, but still sufficient peptides find their way to MHC-I molecules for detectable surface display and functional T cell recognition through alternative processing pathways (Figure 1) [24••]. Peptide-elution analysis from TAP-proficient cells showed that peptides are equally distributed in their parental proteins, whereas the positions from TAP-deficient cells are skewed towards the N-terminus and C-terminus of the parental proteins [25]. Approximately 30% of all TAP-independently processed peptides are derived from the N-terminal location of the parental protein, indicating that peptides derived from signal peptides are a vast source for this repertoire [25]. Interestingly, signal peptides often contain hydrophobic amino acids (e.g. valine and leucine) to recruit ER-docking proteins and have therefore a higher chance to bind HLA-A2 molecules, as their preferred anchor residues on position two and nine are hydrophobic amino acids. Consequently, surface expression of HLA-A2 and some other alleles are relatively insensitive to TAP abrogation, compared to other class I HLA alleles [26]. We indeed found that 80% of the predicted TAP-independent signal peptides from human cancers have strong predicted binding affinity to HLA-A2 [24••].

Many proteases and peptidases are involved in the processing of immunogenic peptides, among which the proteasome plays a pivotal role (reviewed in Ref. [27]). Interestingly, the proteasome also strongly contributes to the generation of TAP-independently processed antigens. We estimated that approximately 50% of MHC-I molecules on TAP-deficient cells were filled with proteasome cleaved peptides [28]. An example of such a peptide is the TAP-independent peptide $PMEL_{209–217}$ the processing of which was described by others [29]. Expression of a signal-peptide mutant of the PMEL protein, preventing transport to the ER membrane, still results in efficient processing of this TAP-independent, proteasome-dependent peptide. Inhibition of acidification of endolysosomes strongly augmented $PMEL_{209–217}$ presentation, suggesting that endosomal MHC-I recycling plays an important role in its presentation [29]. Another TAP-independent but proteasome-dependent peptide was described by our group, and liberation of this peptide required activity by metalloproteinases as well [28]. Importantly, presentation of this peptide was also increased when endosomal vesicle acidification was inhibited, again suggesting that endocytic recycling significantly contributes to the processing of TAP-independent peptides [28].

Other proteases have been identified that contribute to the immunopeptidome of TAP-deficient cells [27,30,31]. Signal peptidase (SP) cleaves pro-proteins destined for secretion or the cell membrane once synthesis of the protein is completed [27]. The ER-intramembrane localized residual stub of the signal peptide needs further cleavage by the aspartyl protease 'signal peptide peptidase' (SPP), releasing the peptide into the ER without the need of TAP transport. The signal peptide of insulin is an example of such an epitope, and presentation of this SPP-mediated, TAP-independent peptide stimulates autoimmune diabetes progression [32,33]. In cancer, the signal peptides of LRPAP1 and calcitonin are presented on many cancers with reduced TAP levels [24••,34••].

Interestingly, we found that the SPP enzyme can also liberate the C-terminal end of an ER transmembrane

Figure 1



TAP-dependent and TAP-independent antigen-processing characteristics.
Cytosolic peptides generated by proteasomal degradation of proteins can be transported into the peptide loading complex (PLC) by the TAP transporter. Antigen processing through this pathway results in the presentation of endogenous 'self' peptides as well as exogenous viral peptides representing the whole proteome. When TAP-function is abrogated, antigens are still loaded unto MHC class I molecules through alternative TAP-independent pathways. Most of these TAP-independently processed peptides are derived from the N-terminal signal sequence or C terminal 'tails' of proteins. Many proteases are involved in the liberation of these TAP-independent peptides.

protein so that this C-tail peptide can be TAP-independently presented [28]. Knockdown of SPP and SPPL2a in TAP-deficient cells lowered MHC-I surface expression by 23% and 35%, respectively, indicating that the SPP family seems responsible for a significant number of TAP-independent peptides. Finally, the ER-Golgi resident protease furin, was described to be responsible for C-terminal cleavage from a secretory protein [35]. However, the significance of this protease for the liberation C-terminal derived peptides in cancers is yet unknown.

TAP-independent antigens for immunotherapy

Clinical relevance of these TAP-independent processing routes became apparent when we discovered that part of this immunopeptidome was absent under normal TAP-proficient conditions. Thereby, these alternative peptides selectively emerged on TAP-deficient cells and were immunogenic for the $CD8^+$ T cell system. In the last decade we extensively studied these so-called TEIPPs ('T cell epitopes associated with impaired peptide processing', reviewed in Ref. [36]). A common trait of TEIPP peptides is that they are non-mutated 'self' peptides, derived from normal housekeeping proteins and are only MHC-I presented upon defects in the conventional antigen-processing machinery [36]. Central and peripheral tolerance mechanisms ordinarily prevent immune attack against 'self' peptides, and although TEIPPs constitute 'self' peptides they are not presented by MHC-I in the thymus or on antigen presenting cells and,

consequently, we observed efficient positive selection of cognate $CD8^+$ T cells. Our data demonstrated that the thymus produces output of naïve TEIPP-specific T cells, which are fully functional [37]. Pre-clinical mouse as well as human studies confirmed that $CD8^+$ T cells-specific for several TEIPPs remain naïve in the repertoire and are therefore exploitable for immunotherapies [24••,37].

Currently, efforts are being conducted to bring TEIPPs to the clinic. Since most TEIPP-specific $CD8^+$ T cells remain naïve, even in the presence of TAP-deficient cancers, their activation via therapeutic intervention is necessary. Our group showed in a pre-clinical mouse tumor model that vaccination strategies successfully leads to activation and tumor infiltration of TEIPP-specific $CD8^+$ T cells, resulting in tumor control [37,38]. Moreover, others showed effective tumor control in a xenograft tumor model by a peptide vaccine containing conventional and TEIPP tumor antigens [34••]. An alternative strategy for TEIPP immunotherapy is transient tumor-targeted silencing of TAP [39••]. siRNA-mediated silencing of TAP function in tumor cells *in vivo* evoked strong immune activation in the tumors, including $CD4^+$ and $CD8^+$ T cells and NK cells, the presentation of targetable TEIPP antigens and, finally, delay of tumor outgrowth. Combination therapy with these nucleolin-targeted aptamers and T cell transfer reduced tumor growth in several pre-clinical mouse models, including the metastatic breast cancer model 4T1 [39••].

Concluding remarks

While many cancers downregulate TAP expression via epigenetic silencing, loss-of-function mutations are relatively rare [40•,41,42]. Therefore, instead of a complete loss of TAP activity, reduced protein expression is often observed and evaluated at protein level by tissue slide staining. Analysis of 135 non-small cell lung carcinoma samples recently revealed low TAP expression in 53% and intermediate TAP expression in 32% of the cases [34••]. Similar levels are observed in other tumor types [43,44]. The immunopeptidomes of these intermediate expressing tumors might consist of a mixture of TAP-mediated peptides and TEIPPs. A critical threshold might exist below which TEIPPs emerge at MHC-I at the cell surface, however, this threshold of TAP expression still needs to be determined in order to select the cancers targetable for TEIPP-directed immunotherapy. We have indications that expression levels of the parental protein might compensate for relative high residual TAP levels [38], suggesting that critical TAP levels might differ per TEIPP antigen. Secondly, expression of β2 m and HLA heavy chains are indispensable for presentation of TEIPP antigens [38]. Loss of HLA alleles is observed in 40 % of early stage non-small-cell lung cancers, limiting the group of patients that can be considered for TEIPP targeted immunotherapy [40•,45]. On the contrary, TEIPP antigens are non-mutated 'self' peptides from widely expressed proteins and as such represent shared antigens, which are exploitable for many cancer types. We demonstrated that the HLA-A2 presented $LRPAP1_{21–30}$ peptide is at least presented by melanoma, lung carcinoma, lymphoma and renal cell carcinoma [24••]. Finally, the proof of the pudding is in the eating and several initiatives have recently been launched to evaluate the safety and potential of TEIPP vaccination or T cell receptor-based immunotherapy in the clinic. Hopefully, TEIPP antigens become valuable tools to treat cancers with loss of TAP function.

Declaration of interests

Nothing declared.

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