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New insights into the structure of the MHC class I peptide-loading complex and mechanisms of TAP inhibition by viral immune evasion proteins

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ABSTRACT

Several hundred million years of co-evolution of vertebrates and invading pathogens have shaped the adaptive immune system to fight back the unwanted invaders through highly sophisticated defense mechanisms. Herpesviruses manage to dodge this immune response by hampering one of the central hinges of human adaptive immunity, the major histocompatibility complex (MHC) class I antigen presentation pathway. One of the bottlenecks of this pathway is the loading of pathogen-derived peptides onto MHC-I molecules in the endoplasmic reticulum (ER). This task is accomplished by the MHC class I peptide-loading complex (PLC), of which the transporter associated with antigen-processing (TAP) is a central component. In this review, we summarize recent structural and functional insights into the molecular architecture of the PLC, how TAP accomplishes the transport of peptides across the ER membrane, and how herpes- and poxviruses inhibit TAP-mediated peptide translocation and subsequent antigen presentation.

1. Introduction – MHC class I-mediated antigen presentation

Major histocompatibility complex class I (MHC-I) restricted T-cells constitute one of the main effector branches of the human adaptive immune system, protecting the organism against intracellular pathogens. MHC class I molecules occur at the surface of every nucleated cell and present peptides to patrolling, primed $CD8^+$ cytotoxic T-cells (CTLs). Upon detection of pathogen-derived peptides, the CTLs will induce cell death of the infected cell. The MHC class I-restricted antigen presentation pathway thus plays a central role in anti-viral immunity. Its importance is reflected by the observation that many viruses, especially large DNA viruses such as herpesviruses, have acquired dedicated immune evasion proteins that specifically interfere with MHC-I dependent antigen presentation. These immune evasins likely contribute to the life-long persistence of herpesviruses in their hosts.

Peptide loading of MHC class I molecules is accomplished by the ER-resident MHC class I peptide-loading complex (PLC), a multisubunit complex consisting of a central peptide transporter and a luminal modular network of co-chaperones for MHC-peptide association. The PLC also performs quality control for newly assembled MHC-I/peptide complexes (Fig. 1).

A pool of peptides representing the protein landscape within the cell is continuously generated by the cytosolic proteasome-ubiquitin system. The resulting peptides are transported into the ER lumen by the transporter associated with antigen-processing (TAP, a member of the ATP-binding cassette (ABC) transporter family). On the luminal face of the PLC, the chaperones tapasin, calreticulin, and ERp57 stably install and stabilize nascent MHC molecules in the proximity of TAP. This arrangement facilitates the proper loading of peptides with sufficient affinity into the MHC-I peptide binding groove (Antoniou et al., 2003; Hewitt, 2003; Pamer & Cresswell, 1998). Once peptides are stably associated with MHC-I molecules, the MHC I-peptide complexes are released from the PLC and shuttled to the cell surface for antigen presentation (Spiliotis et al., 2000).

Due to its central role in antigen presentation it is not surprising that TAP is a frequent target for viral inhibition, especially among viruses that develop life-long infections. This viral 'lifestyle' requires elaborate ways of molecular camouflage. Through a long period of coevolution with their hosts, DNA viruses such as herpes-, and poxviruses have independently acquired highly efficient means of blocking TAP-mediated peptide transport and/or subsequent peptide loading onto MHC-I (Schuren et al., 2016; van de Weijer et al., 2015; Verweij et al., 2015; Windheim et al., 2004). These viral TAP-inhibitors have no structural similarity and all bind TAP at different sites (van de Weijer et al., 2015). An increasing body of functional studies and recent advances in structural biology now allow a much more detailed understanding of the

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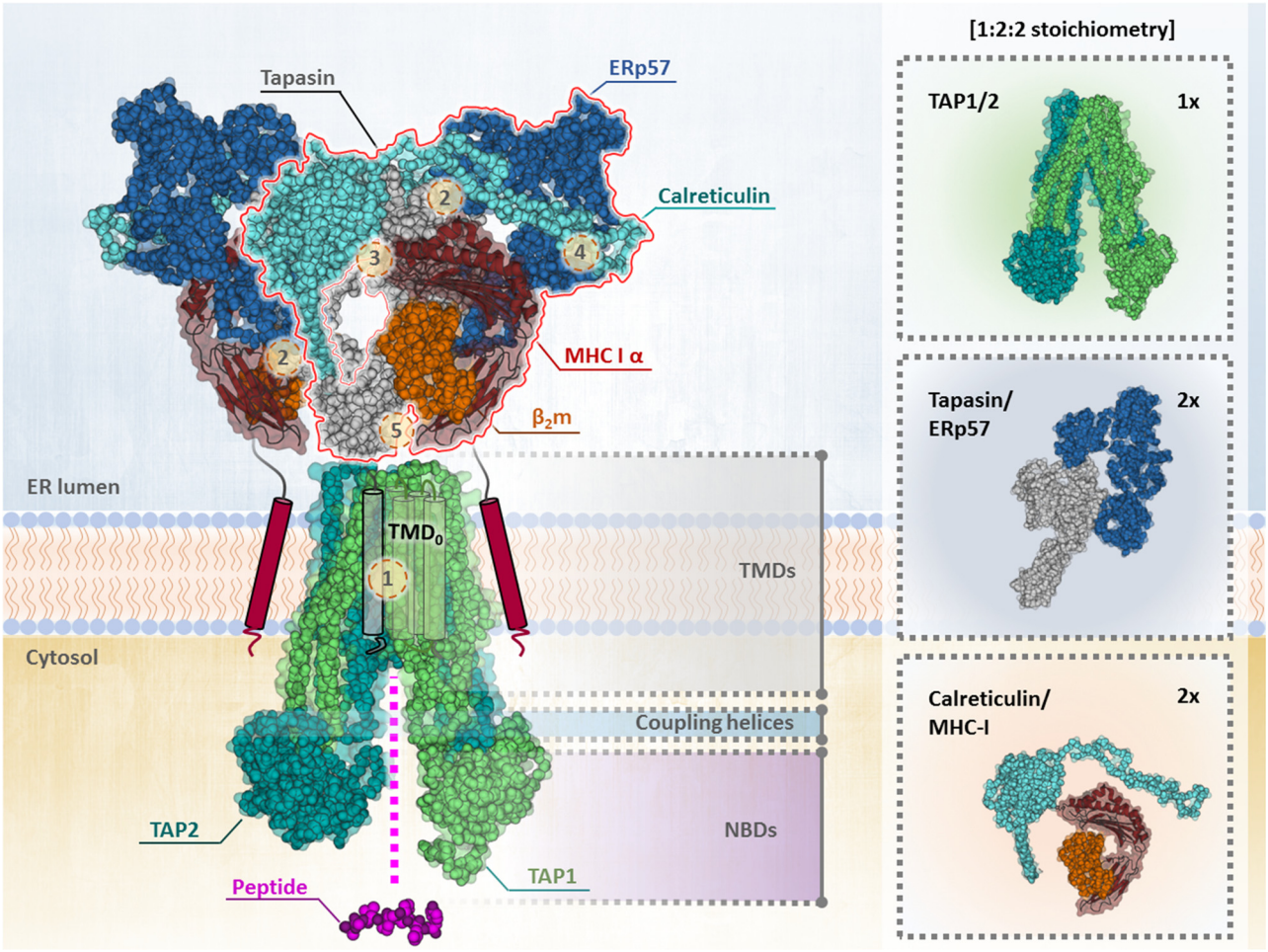

Fig. 1. Model of the MHC-I peptide loading complex (PLC). Current structural information (PDB-IDs 6ENY, 5U1D, 3F8U) was combined into a model with a 1:2:2 stoichiometry (one TAP heterodimer per two of each other compound). In this model, two sets of MHC-I and its interacting chaperones (one of the two editing modules outlined in red) can be docked independently to the two TMD_0 platforms of TAP. TAP1 is shown in green, TAP2 in teal, Tapasin in grey, ERP57 in blue, Calreticulin in cyan, and MHC-I in red/orange. Interfaces in the model that are substantiated by independent experimental evidence are marked in circles (1 TAP/Tapasin (Blees et al., 2015); 2 tapasin/ERp57 (Dong et al., 2009); 3 MHC-I/Calreticulin (Dong et al., 2009; Simone et al., 2012); 4 Calreticulin/ERp57 (Frickel et al., 2002; Russell et al., 2004; Zhang et al., 2009), 5 Tapasin/MHC-I (Blees et al., 2015; Dong et al., 2009; Simone et al., 2012)). TAP1/2 (5U1D) was docked into the electron density for the PLC (EMDB-ID 3905), but with low confidence and has to be considered purely contextual. The NBDs and different TMD segments of TAP are indicated. The proposed route of peptide transport is sketched in magenta. TAP is displayed in an 'inward' cytosol-facing orientation with separated NBDs. The right panels show the stable sub-complexes of the PLC and their relative stoichiometry (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

peptide transport cycle of TAP and the different inhibition strategies employed by the various immune evasins. This review outlines the current knowledge about the structure of the PLC and the peptide transport cycle, highlights recent findings about the differences and similarities between the various modes of TAP inhibition, and summarizes what viral immune evasion can teach us about the mechanism of antigen transport by TAP.

2. Assembly of the MHC class I peptide-loading complex

TAP, MHC-I and the chaperones tapasin, calreticulin, and ERp57 have been unambiguously identified as components of the PLC. However, our understanding about the structure and mode of action of the PLC and its stoichiometry is far from complete (Ortmann, 1997; Panter et al., 2012; Rufer et al., 2007). The functionally and structurally central constituent of the PLC is a single TAP heterodimer. Since TAP links the cytosolic peptide pool and the ER-resident MHC-I molecules, TAP is of critical importance for the MHC-I antigen presentation pathway. Its significance is reflected by the fact that cells lacking functional TAP display severe defects in MHC-I-dependent antigen presentation (de la Salle et al., 2002; Spies et al., 1992; Spies & DeMars, 1991). In these cells, MHC-I molecules are unable to leave the ER and consequently the display of antigens to the immune system is impaired.

TAP is composed of the two structurally closely related proteins TAP1 (ABCB2) and TAP2 (ABCB3) (Dean & Annilo, 2005). Like all ABC transporters, both proteins contain an N-terminal transmembrane domain (TMD) and a C-terminal nucleotide-binding domain (NBD) facing the cytosol. The core part of the TMD domains of both TAP1 and TAP2 consist of 2 × 6 transmembrane helices (numbered 1–6 according to a general convention for ABC transporters). In similarity to several other ABC transporters, the two monomers each swap two of the helices (Fig. 2) (Oldham et al., 2016b). These domains are responsible for peptide binding (van Endert et al., 1994) and form the channel that mediates the translocation of peptides. In addition to the six 'core' transmembrane helices, the TMD domains of both TAP1 and TAP2 possess a non-canonical extension at their extreme N-terminus: a four-helix transmembrane bundle called TMD_0. The two TMD_0 extensions function as an assembly platform for the remaining PLC components (explained in more detail below).

The NBDs carry out the crucial task of ATP binding and hydrolysis.

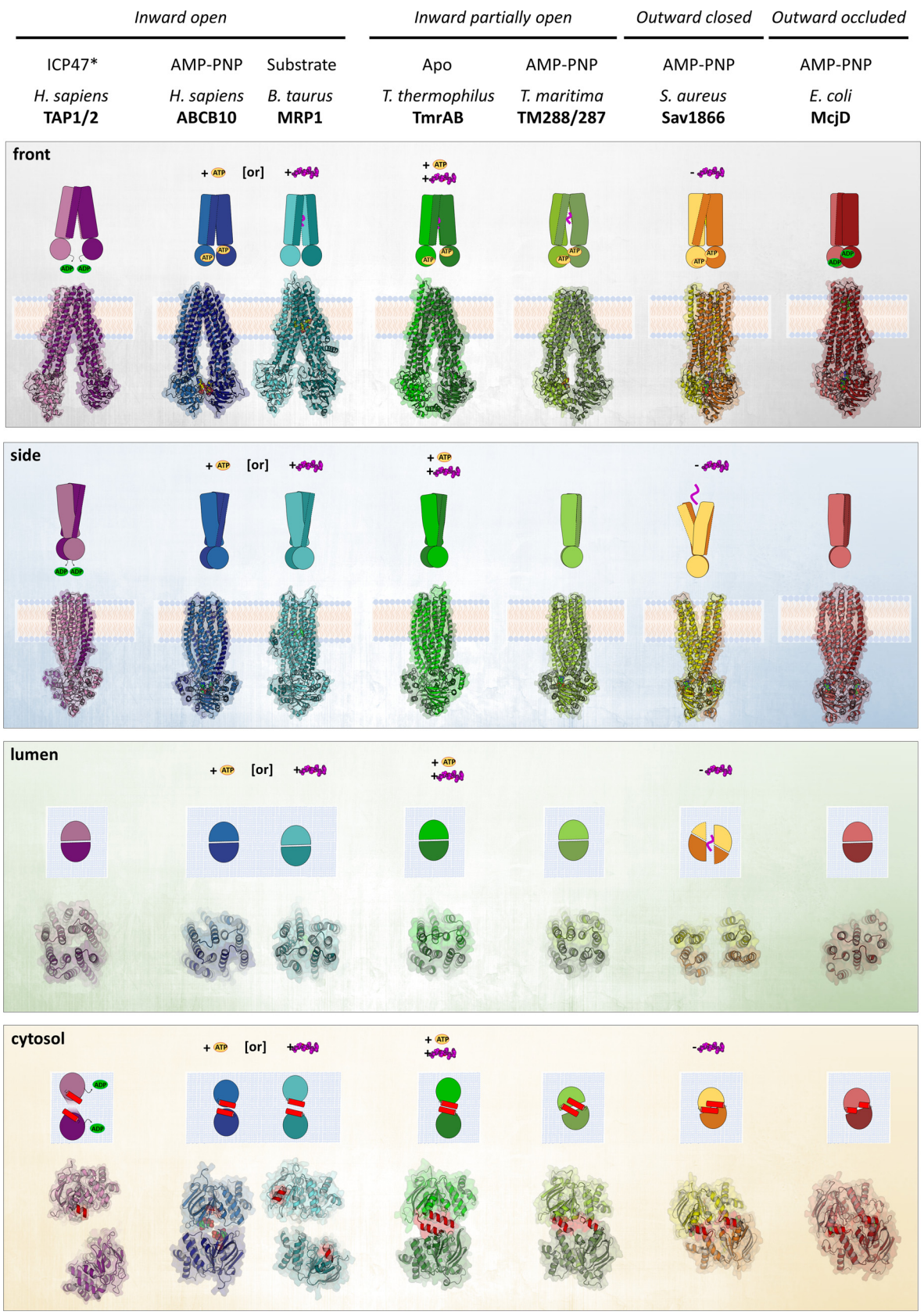

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Fig. 2. Structural information on the transport cycle of TAP extrapolated from homologous ABC transporter structures. The crystal structures of homologous type III/B-family ABC exporters allow for the reconstruction of a putative TAP transport cycle. The inward- or cytosolic-facing TAP model is based on the structural data of Oldham et al. where the NBDs are physically separated (PDB-ID 5U1D) (Oldham et al., 2016ba,b). The transporter is blocked by the HSV-1 protein ICP47 (not shown) in a peptide- and ATP-receptive state. Peptide- and substrate binding might occur independently from each other and lead to a partial closure of the transporter, similarly to the conformations of human ABCB10 (4AYT, nucleotide-bound) and bovine MRP1 (5UJA, substrate-bound, the two transporter subunits are coded on one polypeptide chain). Binding of both ATP and peptide putatively triggers the closure of the cytosol-facing NBD domains. The crystal structures of TmrAB from *Thermus thermophilus.* (5MKK) and TM287/288 from *Thermogata maritima* (4Q4A) represent putative intermediate stages of the peptide transport cycle (Hohl et al., 2014; Nöll et al., 2017). The closed ER-facing conformation is based on structural information from Dawson et al. (2ONJ, *Staphylococcus aureus* Sav1866) and shows interacting NBDs and a cavity formed by the TMDs towards the ER (Dawson & Locher, 2006). Cargo release and subsequent ATP hydrolysis take place after the transporter is opened to the ER lumen. McjD from E. coli is present in an outward-occluded state (4PL0) (Choudhury et al., 2014). The different panels show the four transporter structures from different angles (from top to bottom: front-, side-, top- and bottom-view), the grey arrows indicate the putative conformational flow. The zipper helices in the NBD domains are colored red. The zipper helix of TAP2 was left out of the construct for experimental reasons (Oldham et al., 2016b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

These processes are thought to power conformational changes of the TMDs that enable peptide transport into the lumen (Neefjes et al., 1993; Spies et al., 1990; Van Kaer et al., 1992).

The architecture of the luminal portion of the PLC has been controversially discussed for decades. It is now widely accepted that the chaperones tapasin, ERp57, and calreticulin form a stable 'editing module' that recruits, stabilizes and proof-reads MHC-I molecules (Panter et al., 2012). Several stoichiometric models have been proposed, the most popular suggesting that two such editing modules can be accommodated by TAP per PLC. Very recently, a single-particle cryo-EM structure of natively expressed human PLC in combination with crosslinking-mass spectrometry (XL-MS) data have provided a wealth of new information on the molecular organization of the PLC (Blees et al., 2017). Although the inherent flexibility of the isolated complex limits the resolution and information content concerning the relative positioning of TAP to the other PLC components, the complex structure provides unprecedented insights into the architecture of the luminal chaperone network of the complex. The structure shows that indeed up to two MHC-I editing modules can be accommodated per PLC to form a slightly skewed pseudo-C2 symmetrical structure.

The only contacts between TAP and the rest of the PLC are formed at an intra-membrane interface between TAP and tapasin. The chaperone tapasin then acts as a scaffold for assembling all the other components. Recent publications agree that TAP1 and TAP2 each recruit one tapasin molecule through a single binding site located in their respective TMD_0 transmembrane helix bundle (Hulpke et al., 2012a, b; Panter et al., 2012). Thus, the TMD_0 helices of TAP form an assembly hub for the PLC chaperone modules. The association of a single tapasin moiety to one of the TAP subunits is already sufficient for peptide translocation (Hulpke et al., 2012a).

According to the XL-MS data reported by Blees et al., two isoforms of tapasin can be incorporated into the PLC. The L-shaped tapasin protein consists of an N-terminal fusion domain (formed by a seven-stranded beta barrel adjacent to an immunoglobin fold), a second, membrane-proximal immunoglobulin domain, and a single transmembrane helix (Dong et al., 2009). A conserved intra-membrane ionic 'lock-switch'-interaction between the tapasin transmembrane helix and either TMD_0 domain of TAP has been proposed to act as one of the central PLC interfaces (point 1 in Fig. 1) (Blees et al., 2015). Unexpectedly, a third tapasin binding site has been found in the transmembrane domain segment of TAP1. However, tapasin recruitment to this site seems to be dispensable for peptide translocation, and indeed the binding site is occluded in fully assembled TAP heterodimers. Instead of being a constitutive PC subunit, the additional tapasin appears to solely function as an assembly chaperone for TAP and is lost upon assembly of the TAP1/2 heterodimer (Leonhardt et al., 2014).

The luminal portion of tapasin forms a structural and functional unit with ERp57, to which it is stably associated through a disulfide bridge (Vigneron et al., 2009). The structure of the tapasin-ERp57 complex has been solved by X-ray crystallography (Dong et al., 2009). The soluble protein disulfide isomerase ERp57 consists of four globular thioredoxin-like domains (called a, b, b', and a' from N-to C-terminus) that form a 'U'-shape around two contact points with tapasin (point 2 in Fig. 1), as well as a C-terminal region. Of the four thioredoxin-like domains, only the N/C terminal a/a' domains have retained their redox activity (Frickel et al., 2004). This redox activity is dispensable for the functionality of the PLC (Peaper & Cresswell, 2008; Zhang et al., 2009), and instead the main role of ERp57 within the PLC seems to be the maintenance of structural integrity of the individual editing modules, in conjunction with tapasin (Stepensky et al., 2007). Together, ERp57 and tapasin also ensure that MHC-I stably binds high-affinity peptides before dissociating from the PLC (reviewed extensively in Hulpke et al. (Hulpke & Tampé, 2013)). Two unexpected additional interfaces between opposing editing modules have been found in the cryo-EM structure and accompanying XL-MS studies (Blees et al., 2017). One interface is located between ERp57 and tapasin from the opposing editing module, the other one between the two tapasins, suggesting an additional stabilizing role for the PLC quarternary arrangement. As a result, the two tapasin molecules in the fully assembled PLC bend over by about 30° to form an arc with a potential outlet window for peptides emerging from TAP. As a note of caution, Blees et al. used gradient fixation (GraFix) in order to conformationally stabilize the complex for cryo-EM. GraFix is a cross-linking technique which might potentially influence the observed interface.

Within each editing module, TAP and the tapasin/ERp57 subcomplex stably associate to a static 'core' complex that transiently associates with one or two copies of MHC-I/calreticulin at two independent binding sites (Panter et al., 2012). The two tapasin/ERp57 subcomplexes in the PLC independently each recruit one MHC-I molecule (pre-associated with calreticulin) (Wearsch et al., 2011). A charged interface with a fast off-rate was observed for the interaction between calreticulin and ERp57, which might reflect a dynamic 'screening' of calreticulin/MHC-I sub-complexes by the PLC (Frickel et al., 2002; Kozlov et al., 2006). The percentage of fully occupied PLCs (associated with 2 MHC-I/calreticulin subcomplexes) varies depending on the involved MHC-I alleles and as a function of peptide supply (Neisig et al., 1996; Panter et al., 2012). In the single particle dataset of Blees et al. consisting of approximately 620,000 particles, one of the editing modules is always fully assembled, while some subpopulations miss one calreticulin and/or one MHC-I substrate in the second module, which is in line with previous reports (Panter et al., 2012). The authors conclude that due to peptide editing, the off-rate of MHC-I association is slower than the on-rate, which might lead to a relatively high occupation with MHC-I (Blees et al., 2017). However, the use of the viral inhibitor ICP47 for purification may have an additional influence on MHC-I occupation. Moreover, such variable complex composition also occurs for the 26 S proteasome, which generates the peptides in the cytosol (Asano et al., 2015; Guo et al., 2018), suggesting that variable complex stoichiometry is a general means to buffer capacity of the peptide degradation and MHC display system.

MHC-I consists of a heavy α chain and the small soluble immunoglobulin β_2 microglobulin (β_2m). The α chain consists of two domains forming the peptide binding cleft (called α1 and α2), an immunoglobulin domain (α3), and a single transmembrane helix. In

addition to the more classical HLA alleles, HLA-E, F, and G are also incorporated into the PLC (Blees et al., 2017). The conformational plasticity observed in the N-terminal β-sheet of tapasin appears to be a crucial factor for receptor promiscuity.

Nascent MHC-I heavy chains depend on the chaperone activity of the ER-resident lectin calnexin and its soluble homolog calreticulin for folding and association with β_2m. The characteristic hook shape of calreticulin is formed by three parts. A globular part formed by its N- and C-terminal domains contains the carbohydrate-binding site and is essential for chaperone activity. Besides that, calreticulin contains an unusual proline-rich hairpin protrusion in between N- and C-terminal domains called the P domain, which at its very tip contains a binding site for ERp57, and a C-terminal helical domain. Upon association with β_2m, MHC-I is passed from calnexin to calreticulin, which then facilitates its association with the PLC. Calreticulin binds the mono-glucosylated N-linked glycan chain of MHC-I, as it does with many other proteins in the ER lumen (point 3 in Fig. 1) (Blees et al., 2017). In their cryo-EM structure, the hairpin-domain of calreticulin exhibits considerable flexibility as it hovers over the peptide binding groove of MHC-I. Calreticulins extended alpha-helical C-terminal acidic domain is facing towards the membrane, potentially contacting tapasin. This observation is in line with a potential lipid-sensing function of this helix (Wijeyesakere et al., 2016).

Within the PLC, the MHC-I/calreticulin unit engages in several contacts with the ERp57/tapasin subcomplex. Experimentally verified contacts are formed between MHC-I and tapasin, as well as between calreticulin and ERp57. As determined by transverse relaxation optimized spectroscopy NMR (TROSY-NMR), the tip of the calreticulin P domain forms a contact with ERp57, thereby stabilizing interactions between the three functional PLC subunits (Frickel et al., 2002). It is assumed that this is the only interface between calreticulin and ERp57 (Frickel et al., 2004). According to a study investigating the ability of calreticulin to bind to specific point mutants of ERp57, the P domain tip of calreticulin is engaged at the b' domain of ERp57, (point 4 in Fig. 1) (Russell et al., 2004). According to this assay, the redox-active a and a' domains are dispensable for the binding, whereas a deletion of the C-terminal region reduces the binding by about 50%. A newer heteronuclear single quantum coherence (HSQC) NMR study has mapped the binding site to two residues located in close proximity at the interface of the b and b' domains (Kozlov et al., 2006), concomitant with the cryo-EM structure (Blees et al., 2017).

Co-Immunoprecipitation experiments with mutant tapasin revealed an extended MHC-I binding site in the N-terminal domain (Dong et al., 2009). Furthermore, the deletion of a loop located on the same side of tapasin, but within the C-terminal domain, abrogated the binding (point 5 in Fig. 1) (Simone et al., 2012), although a corresponding interface was not observed in the single particle structure (Blees et al., 2017). Two recently solved crystal structures of human TAPBPR (TAP binding protein, related) in complex with a murine MHC-I molecule seem to confirm this interface (Jiang et al., 2017; Thomas & Tampé, 2017). TAPBPR has a similar function and interface as tapasin, but does not associate with the PLC and instead seems to additionally act in the Golgi compartment (Boyle et al., 2013). According to a homology model based on the complex structure, tapasin could insert a loop into the MHC-I peptide binding groove. This loop could compete with the C-terminus of peptides and thus account for peptide editing. In contrast, the transmembrane domains of both MHC-I and tapasin/TAPBPR seem to be dispensable for the interaction, as soluble tapasin mutants still stably associate with MHC-I (Simone et al., 2012).

The model presented in Fig. 1 is based on the single particle structures of the human TAP and PLC, respectively. The model is in agreement with propositions from other authors (Dong et al., 2009; Fisette et al., 2017; Hulpke & Tampé, 2013). Interfaces that have been verified in independent experiments are marked in the figure. In the figure, the single particle structure of TAP was fitted into electron density obtained by Blees et al., in which TAP is only faintly resolved (and was not modelled by the authors). Thus, intra-membrane interfaces and the relative orientations of TAP and the chaperone network implied in Fig. 1 are contextual.

Additional factors that are functionally coupled to the PLC, such as the two closely related ER aminopeptidases associated with antigen processing (ERAP1/2), interact with the peptides *en route* (Chen et al., 2016; Saveanu et al., 2005), but there is no *in vivo* evidence for binding to the PLC to date (Kanaseki et al., 2013; Kanaseki et al., 2006; Serwold et al., 2002). In addition, TAPBPR appears to functionally complement MHC-I binding by tapasin (Hermann et al., 2013). How these factors interact with the PLC is not yet understood. Further, it is unknown which conformational changes TAP undergoes upon peptide translocation, and how the peptide is then delivered to the MHC-I peptide binding groove.

3. Current understanding of the TAP peptide transport cycle

The central task accomplished by the peptide-loading complex is the unidirectional transportation of peptides from the cytosol into the ER by TAP. Substantial effort has been made to understand in detail how peptides are translocated by the transporter. Over decades, a host of biochemical data have identified the structural motifs involved in nucleotide binding, roughly mapped the peptide binding region, and revealed secondary structures that are responsible for the crosstalk between ATP hydrolysis in the NBDs and conformational changes in the transmembrane helices (reviewed extensively in Seyffer and Tampé, 2015. A special feature of TAP among ABC transporters is the presence of its TMD_0 domains, whose function and importance have already been discussed. It is generally agreed that TAP and other ABC transporters undergo alternating cycles of opening towards the cytosol ('inward') or the lumen/extracellular space ('outward') powered by ATP hydrolysis of the NBDs and executed by motions of the TMDs (reviewed in Locher et al.(Locher, 2016)). However, the picture is not complete, as of yet this wealth of information has not been conclusively integrated into a robust trajectory of how TAP and its substrates move during the transport cycle. Furthermore, the precise conformational changes that are induced by the binding of either substrate or nucleotides remain uncharted.

TAP is classified as a type III/B-family exporter and shows a common fold with all structurally characterized ABC exporters (Locher, 2016; Parcej & Tampé, 2010). Human TAP1/2 exhibits remarkable structural similarity to several related peptide or multidrug exporters within this class, occurring in both eu- and prokaryotes (with root mean square deviations in the low Ångstrom range). In recent years, several new high-resolution structures of these transporters have been solved, sampling the transporters in different conformations. This has tempted many authors to devise structural models of TAP based on structures of relatives and to develop transport models of a 'general ABC transporter' (Abele & Tampé, 2011; Eggensperger & Tampé, 2015; Mayerhofer & Tampé, 2015; Oldham et al., 2016b; Parcej & Tampé, 2010; Seyffer & Tampé, 2015). The current (structural) understanding of the TAP transport cycle is largely based on such extrapolations, and for this reason we have summarized the novel insights these new structures can (and cannot) provide (Fig. 2). However, it has to be noted that an extrapolation across species and experimental methods has to be interpreted with caution, as the transporters most likely do not undergo the same structural cycles and no common mechanism has been proposed (Locher, 2016).

3.1. Resting state

A high resolution cryo-EM structure of human TAP trapped in an inward-facing state was solved in 2016 (Oldham et al., 2016a, b). In the resting state visualized by the structure, TAP is trapped by the viral immunoevasin ICP47 in a cytosol-facing V-shape conformation with two wide-open NBDs, supposedly mimicking the peptide- and ATP-

receptive resting state of the transporter (Jin et al., 2012; Oldham et al., 2016b; Oldham et al., 2016a).

Without ICP47, however, TAP appears to display a degree of flexibility that is prohibitive for structural studies (Oldham et al., 2016b), raising the question whether this broad separation would occur without the inhibitor as well. Several models exist to interpret the functional role of NBD separation. In the case of TAP, the most conclusive model is the so-called processive clamp or 'switch' model. This model implies that the NBDs dimerize upon binding of two ATP molecules and completely separate after sequential ATP hydrolysis; this model is in line with the structures mentioned above (Higgins & Linton, 2004; van der Does & Tampé, 2004). An alternative model (called the constant contact model) suggests that the NBDs stay associated at all times, involving an asymmetric opening of one of the nucleotide binding sites at a time (Locher, 2016).

However, confirming a correct model proved difficult to address experimentally. Complicating factors are the replacement of the lipid membrane environment by detergents (common to most studies), crystal packing (crystallographic studies), and the complete absence of nucleotides, all of which might force the transporters into non-physiological conformations. Given the high concentration of ATP and ADP in the cytosol (mM range), it seems likely that apo states characterized by methods such as X-Ray crystallography and diverse biophysical methods (Foerster resonance energy transfer (FRET) / luminescence resonance energy transfer (LRET), cross-linking mass spectrometry (XLMS), or double electron-electron resonance pulsed electron paramagnetic resonance (DEER-EPR)) are very short-lived, if present at all.

In the absence of substrate and nucleotide analogues, several other structures have been found to persist in inward-open conformations, including homologues of the multidrug resistance transporter P-glycoprotein (P-gp) from different organisms (Aller et al., 2009; Jin et al., 2012; Kodan et al., 2014) as well as the mitochondrial iron-sulfur cluster exporter Atm1 from *S. cerevisiae* (Srinivasan et al., 2014). All these structures display varying degrees of NBD separation, and in some cases, this variation can even be observed in different structures of the same transporter. Indeed, a recently published cryo-EM study on human P-gp shows that without substrate or peptide, P-gp can adopt several states with differing degrees of NBD closure (Frank et al., 2016). Similarly, several different structures of the LPS exporter MsbA exhibit considerable differences in NBD separation in the absence of nucleotides or substrate (Mi et al., 2017; Ward et al., 2007). However, extremely wide-spread conformations such as the one found for MsbA or the oligosaccharide flippase PglK from *C. jejuni* are most likely not physiologically relevant (Perez et al., 2015).

Further, there might be differential behavior of homo- and heterodimeric transporters. For example, while a complete separation of the NBDs has been proposed for the homodimeric MsbA based on spin labeling and EPR spectroscopy (Zou et al., 2009), mechanistic and structural studies of mammalian P-gp and BmrCD from *B. subtilis* suggest a constant contact between NBDs during transport that is only possible in heterodimers (Mishra et al., 2014; Siarheyeva et al., 2010; Tombline & Senior, 2005). Consequently, some authors suggest a model in which heterodimeric transporters constantly associate their NBDs in a way reminiscent of the constant contact model, while homodimeric transporters such as MsbA completely separate their NBDs according to the switch model (Mishra et al., 2014). The structure of TAP however shows the heterodimeric transporter in a state with wide-open NBDs. In this light, it remains to be determined to which extent the separation of the NBDs is induced by the viral inhibitor and the deletion of a C-terminal helix in TAP2, or to which extent the conformational cycles of ABC transporters can be unified into simplified models at all. Further aspects of NBD separation are discussed in George and Jones (2012).

3.2. Binding of substrate and ATP

Binding of both the substrate and ATP is thought to provide the trigger for conformational changes that ultimately lead to a complete closure of the NBD domains and a rearrangement of the channel. TAP is able to bind both peptides and ATP independently from each other (Muller et al., 1994; Russ et al., 1995; van Endert et al., 1994), but exhibits no peptide translocation without ATP (Meyer et al., 1994; Neefjes et al., 1993; Shepherd et al., 1993; van Endert et al., 1994) and no basal ATP hydrolysis without peptide (Herget et al., 2009). Thus, clearly both substrates need to be bound for this movement to happen.

It appears possible that binding of either substrate or ATP might make the transporter adopt a 'primed' conformation that shows signs of TMD closure. This is reflected by the human mitochondrial orphan transporter ABCB10, the structure of which was solved in the presence of several ATP analogues, but without the (yet unidentified) substrate (Shintre et al., 2018). The nucleotide-bound transporter is still present in the 'inward' facing open conformation with open nucleotide binding pockets, although the separation of the NBDs varies between different crystals and is not as pronounced as in the TAP structure. ATP binding introduces a slight conformational change compared to the unliganded ('apo') structure, but is not sufficient to trigger NBD occlusion.

The ABCB10 structure shows that nucleotides are capable of binding to ABC transporters before the substrate, but there are also *vice versa* examples that show substrate binding independent of nucleotides. In one such example, substrate-bound bovine P-gp (MRP1) adopts a conformation very similar to that of nucleotide-bound ABCB10 and also lacks NBD closure (Johnson & Chen, 2017). Hence, it seems plausible also for TAP that although there is no fixed order to peptide and ATP binding, slight structural rearrangements might occur upon engagement of one component that make the transporter more receptive for the missing component.

3.3. Formation of active sites for ATP hydrolysis

In order to reach the ATP-hydrolysis competent 'outward'-facing state, ABC transporters need to bring together their cytosolic part and dimerize their NBD domains. Since the active sites for ATP hydrolysis are both formed by residues from both TAP chains, NBD closure is an essential part of the catalytic mechanism. Accordingly, many transporters are inactivated when NBD closure is physically inhibited (Gerber et al., 2008; Ward et al., 2013).

The conformational flow necessary to accomplish the closing motion and formation of the catalytic centers is a topic of intense research. The conserved power stroke for the movement is generally thought to be generated by the consolidation of the cytoplasmic TMD segments (Figs. 1 and 2) (George & Jones, 2012; Oldham et al., 2008). An important role in this process is attributed to the so-called coupling helices that lie at the interface between the NBD and transmembrane domains and are thought to allosterically transmit information on ATP binding (in the form of conformational changes in the NBDs) to the TMDs (indicated in Fig. 1) (Choudhury et al., 2014).

Recently, structures of *T. thermophilus* TmrAB and *T. maritima* TM287/288 were solved in novel conformations raising questions about on-pathway intermediate states (Hohl et al., 2014; Nöll et al., 2017). Contacts between the NBD domains are formed in both structures, but the cytosolic parts of the TMD domains providing the power stroke remain separated.

TmrAB is a multidrug resistance protein with a broad substrate specificity that can functionally substitute TAP in human cells. Although it was crystallized in the presence of AMP-PNP, TmrAB is present in an unliganded state with a unique asymmetric conformation. It possesses approaching NBD domains, whose nucleotide and peptide binding pockets remain open towards the solvent. As an intriguing feature, contacts between the two NBDs are present, but largely restricted to their C-terminal helices. It is currently unclear whether this conformation represents an intermediate state, or whether the TmrAB transporter is simply not separating its NBDs as much as is observed for TAP in the 'inward-facing' resting state due to the C-terminal helices

preventing a complete separation of the NBDs. In many structures containing nucleotides mimicking 'outward-occluded' or post-hydrolysis states (such as AMP-PNP or ADP vanadate, respectively), the C-terminal helices are rearranged and swapped between NBD domains to tightly lock the interface. It appears conceivable that such a swapping movement is one of the steps leading to the firm occlusion of NBD domains. However, these helices are subject to considerable evolutionary variation, and it remains to be determined how common their role among ABC transporters turns out to be (Nöll et al., 2017; Srinivasan et al., 2014).

TM287/288 is present in a semi-closed state that is not open towards the 'outside'. The structure shows one open nucleotide pocket, but a more extensive NBD interface reminiscent of that found in the structure of Sav1688 (see below). Like TAP and TmrAB, TM287/288 contains a single consensus ATP-binding site, whereas the second site contains degenerate motifs with decreased ATP binding or hydrolysis. The TM287/288 structure is complexed with AMP-PNP bound only to the non-canonical, high ATP affinity site, not to the catalytic site. It seems that the NBDs are not fully closed yet, which might possibly represent a functional intermediate, but a definitive role of this asymmetry for substrate transport has not been proven yet. The structural aspects of NBD asymmetry are even less explored for TAP. Upon NBD closure, TAP forms a 'canonical' binding site and a 'non-canonical' nucleotide binding site, the latter of which is formed by an atypical Walker B motif and H-switch in TAP1 and an unusual C-loop in TAP2 (Chen et al., 2004; Zaitseva et al., 2004). Both of its ATP binding sites seem to have similar affinities for ATP and ADP, but mutations in the canonical and non-canonical binding site, respectively, seem to be tolerated to different degrees (Karttunen et al., 2001; Procko & Gaudet, 2008; Saveanu et al., 2001; Zaitseva et al., 2004).

3.4. Peptide release

The AMP-PNP-bound multidrug transporter Sav1688 from *S. aureus* represents the 'outward'-facing, NBD-closed state from which substrates are most likely released (Dawson & Locher, 2006). After the NBD domains have approached to adopt an occluded conformation, the transmembrane helices open up outwards and orthogonally to the movement of the NBD domains. Adapting this state is sufficient for the release of peptides (Grossmann et al., 2014). It is currently unknown whether these movements also affect the positioning of the TMD_0 domains and the other PLC constituents. In contrast to other transporters, which usually allow a certain degree of retrograde transport, TAP is a 'diode' and strictly unidirectional. The underlying structural determinants of TAP unidirectionality are unclear, but it seems likely that a strongly reduced substrate affinity in the outward-facing state plays a key role in the process (Grossmann et al., 2014).

3.5. ATP hydrolysis

After peptide release, ATP hydrolysis likely triggers the return of TAP to an inward-facing orientation. A recent structure of the antibacterial peptide transporter McjD from *E. coli* shows an outward-facing, occluded state that likely exists after peptide release, but before ATP hydrolysis (Choudhury et al., 2014). The homodimeric MsbA trapped with ADP vanadate is present in a similar conformation but with completely closed NBDs (Mi et al., 2017), similar to the recently solved structure of the peptide transporter PrtD from *A. aeolicus* (Morgan et al., 2017). As for TAP, it is possible that an asymmetric ADP-bound state might exist, as became apparent with experiments involving ADP-agarose and the viral inhibitor US6 (Kyritsis et al., 2001). To complete the cycle, ADP release brings the transporter back into the resting state. It has so far not been excluded that the two ATP hydrolysis events occur independently from each other, and they may even separately trigger different stages of the transport cycle.

3.6. General remarks

Although this mechanistic deduction allows for a general idea of how type III/B-family peptide or multidrug exporters might work, several inconsistencies and complications are subject to controversies in the field (Locher, 2016). Thus, it remains questionable whether the structures of different transporters can accurately reflect the transport cycle of TAP. In 2015, Moeller et al. presented a population-oriented negative stain EM based approach, in which sophisticated classification schemes of MsbA and P-gp in either an apo, substrate, ATP, or ADP-vanadate bound state revealed the full spectrum of conformations observed after solubilization in a bilayer-mimicking environment (Moeller et al., 2015). Upon incubation with a given combination of substrate and nucleotide, both transporters show a range of different conformational populations. Although the resolution was modest, this study showed that (i) even in a purified state with a defined amount of nucleotides and substrates, there is substantial conformational heterogeneity, and (ii) the two exporters are occupying strikingly different conformational states in different stages of their transport cycle and behave very differently upon nucleotide binding. Indeed, the differences in catalytic activity, transport function, and local concentration of substrates on both sides of the membrane might dictate differential uses of the available conformational landscapes.

For these reasons, it is relevant to structurally characterize human TAP in distinct conformations within the transport cycle. The many viral Inhibitors of TAP could be useful tools in this respect, as they trap TAP in different conformations.

4. TAP-inhibition

Among all DNA viruses, the *Herpesviridae* have acquired the most extensive arsenal of genes to mitigate antigen surface presentation. *Herpesviridae* express numerous immune evasion molecules that (i) cause degradation of MHC-I (Park et al., 2010; Wiertz et al., 1996a, Wiertz et al., 1996b), (ii) lead to retention of immature molecules in the cis-Golgi (Ziegler et al., 1997), (iii) induce enhanced endocytosis of MHC-I (Lehner et al., 2005; Jianmin Zuo et al., 2009) and (iv) block MHC-1 protein synthesis to reduce its surface expression (Fenwick & Clark, 1982; Glaunsinger et al., 2005; Zuo et al., 2008). The PLC and especially TAP appear to be prominently targeted components of the pathway.

Herpesviruses independently developed distinct methods to block TAP. TAP-inhibitors can be identified in all three herpesvirus subfamilies (Verweij et al., 2015). To date, four herpesvirus-encoded TAP-inhibitors have been identified: (i) ICP47 encoded by herpes simplex virus (HSV) 1 and 2, (ii) BNLF2a encoded by Epstein-Barr virus (EBV), (iii) US6 encoded by human and rhesus cytomegalovirus (HCMV and RhCMV), and (iv) UL49.5 encoded by a broad range of varicelloviruses. Here, we highlight novel findings mainly concerning ICP47 and the poxvirus-encoded TAP inhibitor CPXV012, for both of which substantial new findings have been published recently. For reviews on the function of the other herpesvirus inhibitors, we refer to Verweij et al (Verweij et al., 2015). and Van de Weijer et al. (van de Weijer et al., 2015).

4.1. ICP47

The first viral protein found to inhibit TAP function is the HSV-1 (and HSV-2)-encoded Infected Cell Protein 47 (ICP47) (Früh et al., 1995; Hill et al., 1995). ICP47 is an 88-amino acid cytosolic protein and the only known soluble TAP inhibitor (Ahn et al., 1996; Tomazin et al., 1996). ICP47 causes retention of MHC-I molecules in the ER by competitively blocking the binding of cytosolic peptides to TAP (Tomazin et al., 1996). A number of studies have identified the key residues within the ICP47 sequence. Using synthetically produced or recombinantly expressed ICP47 truncation mutants, the active domain of

ICP47 was mapped to the first 34 residues (Galocha et al., 1997; Neumann et al., 1997). Fragments of this length were able to efficiently block peptide binding. In addition, a recently published study showed that the highly conserved residues 50–52 (coined the 'PLL-motif' by the authors) in the central region of ICP47 are responsible for freezing TAP in the 'inward'-facing conformation (Matschulla et al., 2017). This study demonstrates that the previously described active residues of ICP47 are not sufficient for full inhibition of TAP. Only a combination of the active N-terminal region with the PLL-motif leads to complete TAP inhibition. In line with these findings, a study from Herbring et al. suggests a dual interaction mechanism of ICP47 with a destabilizing active domain of ICP47 that inhibits the function of TAP, whereas a conserved C-terminal region next to the active domain of ICP47 is essential for the complete stabilization of the TAP-ICP47 complex (Herbring et al., 2016).

The cryo-EM structure of TAP in complex with ICP47 revealed the molecular details of this dual inhibition mechanism (Oldham et al., 2016a). As mentioned above, ICP47 indeed traps the transporter in an 'inward'-facing resting state. The first 43 amino acids of ICP47 form a helix-turn-helix motif that wedges itself into the TAP pore and directly clogs its peptide binding region. Presumably, the interface generated by the first 34 amino acids is large enough to provide efficient competitive inhibition. The residues of the 'PLL' motif precisely locate to one of the two pairs of coupling helices (formed by coupling helix 2 of TAP1 and coupling helix 1 of TAP2) and presumably prevent the transmission of the power stroke from the NBDs to the TMDs, which leads to the observed freezing of the transporter.

4.2. CPXV012

For a long time, inhibition of TAP was thought to be unique for herpesviruses. Recently however, a protein from cowpox viruses (CPXVs) was identified as a powerful TAP-inhibitor. CPXVs are part of the *orthopoxvirus* family. In healthy humans, an infection with CPXVs causes local skin lesions and is self-limiting (Bourquain et al., 2013), but an infection of immune compromised patients may be lethal (Czerny et al., 1991). An enlarging animal host range and growing numbers of CPXV infections in Europe and parts of Asia recently led to an increasing worldwide awareness of this public health concern (Vorou et al., 2008).

CPXVs encode a cluster of sophisticated immune-evasion proteins, including the proteins CPXV203 and CPXV012, that evade CTL recognition by hampering the MHC-I antigen presentation pathway (Alzhanova & Früh, 2010; Seet et al., 2003). CPXV203 was found to target fully assembled MHC-I molecules and to retain them in the ER. A deletion of CPXV203 did not fully restore MHC-I surface expression, indicating that a second protein might be involved in the inhibition of this pathway (McCoy et al., 2013).

Subsequently, CPXV012 was identified as the second CPXV protein that interferes with MHC-I-mediated antigen presentation (Alzhanova et al., 2009; Byun et al., 2009). The 70 amino acid type II transmembrane (TM) protein CPXV012 consists of a short cytosolic N-terminal domain (mapped to residues 1–11), a single transmembrane helix (12-26), and a C-terminal luminal domain (27-70) (Lin et al., 2014; Luteijn et al., 2014). It impedes TAP-mediated peptide transport via its ER-luminal domain, blocking ATP binding to the NBDs of TAP (Luteijn et al., 2014). More precisely, the amino acid residues 41–65, all located in the ER-luminal domain, appear to be sufficient for inhibition, whereas the TM domain and cytosolic N-terminal tail could possibly enhance the efficiency of inhibition (Luteijn et al., 2014). In contrast, a different study showed that an isolated C-terminal 10mer CPXV012 fragment (residues 60–70) is sufficient for blocking ATPase activity of TAP, indicating that the extreme C-terminus of CPXV012 is the inhibitory fragment of the viral protein (Lin et al., 2014). Notably, the two identified active regions only overlap by six amino acids.

The CPXV012 ortholog D10L of the CPX strains GRI-90 and GER 91-3 does not inhibit TAP function (Alzhanova et al., 2009). CPXV012 and D10L have a high degree of sequence identity within their cytosolic and TM regions, but have a very different ER-luminal C-terminal region (Dabrowski et al., 2013). The finding that the C-terminal domain of CPXV012 is necessary for inhibition of TAP supports the conclusion that the lack of inhibitory capacity of D10L is related to the sequence of its C-terminal domain (Alzhanova et al., 2009).

The underlying genetic background for this abrupt decline in sequence identity is likely a deletion of 5 nucleotides that results in a frameshift of the gene segment that encodes the ER-luminal domain of the protein. The resulting alternative protein sequence is leading to a stop codon 25 residues after the gene segment encoding for the TMD, resulting in a shorter C-terminal reading frame. The domain formed by this alternative sequence was described to mimic a TAP substrate bound to the outward-facing TAP before release into the ER lumen (Lin et al., 2014).

CPXV012 blocks ATP binding to TAP, but does not interfere with peptide binding (Lin et al., 2014). Co-immunoprecipitation studies showed that CPXV012 directly associates with the TAP complex (Lin et al., 2014). This interaction seems to be restricted to TAP, as CPXV012 did not co-precipitate with TAP-like (TAPL), a homodimeric peptide translocation complex located in lysosomes, sharing 38% amino acid sequence identity with TAP1 and 40% with TAP2 (Demirel et al., 2010; Lin et al., 2014; Zhang et al., 2000).

In 2014, a model of CPXV012 was proposed by Luteijn et al. in which the C-terminal part of CPXV012 'snorkels' the ER-membrane in parallel to the lipid-water interface. The latter is likely related to the strong affinity of this domain for phospholipids (Luteijn et al., 2014). Evidence for this theory was provided by an assay that measured the surface pressure of Langmuir lipid monolayers in the presence or absence of CPXV012. A rapidly and strongly increasing surface pressure after incubation with the viral inhibitor indicated that the ER-luminal domain can penetrate lipid monolayers (Luteijn et al., 2014).

The affinity for a lipid environment was taken as an indicator to presume a direct interaction of the viral protein with the TM helices of TAP (Luteijn et al., 2014). The constant binding of the inhibitor to the low-affinity release site of outward-facing TAP is thought to simulate a high luminal peptide concentration, resulting in a negative feedback mechanism of the TAP-mediated peptide translocation machinery (Lin et al., 2014; Luteijn et al., 2014). This indicates that the inhibition mechanism of CPXV012 is unique amongst the viral TAP inhibitors identified so far, but the conformational state(s) in which CPXV012 interacts with TAP remains unknown.

4.3. Functional orthogonality of TAP inhibitors could elucidate the TAP transport cycle

The different mechanisms of inhibition employed by the individual TAP inhibitors are functionally intertwined with the transport cycle of the ABC transporter. Since all viral TAP inhibitors interact with TAP in a very specific manner, they all are likely to trap the transporter in distinct conformational stages of the transport cycle. In this sense, viral compounds may provide unique insights into specific steps of the TAP-transport cycle, but it is challenging to assign the herpesvirus inhibitors to specific states of the TAP-transportation cycle only based on the presence or absence of substrate or nucleotide binding. Here, we briefly summarize the current notion of when and where the viral inhibitors could bind during the peptide translocation cycle.

ICP47 and BNLF2a are the only known TAP-inhibitors that act on the cytosolic side of TAP; all other inhibitors most likely lead to inhibition via the ER-luminal side. The only known complex structure of human TAP is the one of ICP47 that binds in an 'inward-facing' resting state. BNLF2a is a tail-anchored protein that is targeted to the ER membrane post translationally and a substitution of the hydrophobic C-terminal transmembrane region was shown not to be essential for inhibition of TAP (Horst et al., 2011). Since BNLF2a has no functional

residues on the luminal side and the N-terminal domain was identified to be sufficient for interfering with the binding of both peptides and ATP (Horst et al., 2011), it most likely also clogs the pore of TAP, like ICP47.

In contrast to the cytosolically acting viral inhibitors ICP47 and BNLF2a, the HCMV-encoded TAP inhibitor US6 binds from the luminal side and does not interfere with peptide binding, which implies that this inhibitor locks TAP in a different state. Seyffer et al. speculate that US6 indeed binds in a post-hydrolysis state, since US6 competes with ATP, but not ADP binding (Seyffer & Tampé, 2015), suggesting that US6 interferes somewhere between an inward open and a substrate-bound state during the translocation cycle. In line with these findings, a study from Hewitt et al. demonstrated that US6 inhibits ATP binding to TAP1 and that conformational changes of TAP caused by peptide binding are inhibited. In this publication, it is assumed that US6 traps TAP in an intermediate conformational state occurring shortly after peptide binding, potentially locking it in a 'primed' state (Hewitt et al., 2001).

As already mentioned, the conformational state in which CPXV012 binds to TAP is unknown. Since the inhibitor is interfering with ATP binding but not with peptide binding, CPXV012 may bind between an outward, occluded and a substrate-bound state of TAP. An allocation for the varicellovirus-encoded inhibitor UL49.5 appears to be even more intricate. Different variants of UL49.5 are encoded by the equine herpesvirus types 1 and 4 (EHV-1 and 4), bovine herpesvirus types 1 and 5 (BoHV-1 and 5), pseudorabiesvirus (PRV), and many other varicelloviruses. These UL49.5 variants inhibit TAP in distinct ways; all mentioned variants inhibit conformational rearrangements that would follow peptide and ATP binding. In addition, UL49.5 of EHV-1 and 4 interfere with ATP binding to TAP. UL49.5 of BohV-1 strongly reduces TAP protein levels by targeting both subunits for proteasomal degradation (Koppers-Lalic et al., 2005).

A number of recent studies explores the functional orthogonality of different TAP inhibitors (Lin et al., 2014; Matschulla et al., 2017), which might be exploited to elucidate different TAP conformations and assign them to different states of the transport cycle.

A recent study demonstrates that US6 is unable to bind TAP that is already locked in a distinct conformation by ICP47, and *vice versa* (Matschulla et al., 2017). This would fit well with the current idea of US6 inhibiting TAP from the luminal side. However, further experiments are necessary to solidify this notion. A similar finding about unique conformational arrests of TAP during the peptide transportation cycle was reported by Lin et al. in 2014, who have shown that US6 or BNLF2a both can prevent the formation of TAP/CPXV012 complexes (Lin et al., 2014). Furthermore, Wycisk et al. show that BNLF2a and US6 are also mutually exclusive (Wycisk et al., 2011).

US6-inhibited TAP is peptide-receptive and therefore likely to be open to the cytosol, but in a conformation that precludes association with ICP47.

These findings, combined with further structural studies, could help to elucidate the conformational details of the TAP mediated peptide transportation cycle.

5. Concluding remarks / future perspectives

This review highlights the key function of TAP in antigen presentation and, based on recent new insights, sheds new light on TAP function and its inhibition by viral immune evasion proteins. Detailed structural studies into the PLC will be required for the elucidation of the interactions between the proteins involved in MHC-I restricted antigen presentation. Studies performed on PLCs complexed with viral TAP inhibitors might reveal the nature of the interaction between these viral inhibitors and TAP and will uncover their mode of action.

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