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INVITED REVIEW

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Intracellular peptide transporters in human – compartmentalization of the "peptidome"

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Abstract In the human genome, the five adenosine triphosphate (ATP)-binding cassette (*ABC*) half transporters ABCB2 (TAP1), ABCB3 (TAP2), ABCB9 (TAP-like), and in part, also ABCB8 and ABCB10 are closely related with regard to their structural and functional properties. Although targeted to different cellular compartments such as the endoplasmic reticulum (ER), lysosomes, and mitochondria, they are involved in intracellular peptide trafficking across membranes. The transporter associated with antigen processing (TAP1 and TAP2) constitute a key machinery in the major histocompatibility complex (MHC) class I-mediated cellular immune defense against infected or malignantly transformed cells. TAP translocates the cellular "peptidome" derived primarily from cytosolic proteasomal degradation into the ER lumen for presentation by MHC class I molecules. The homodimeric ABCB9 (TAP-like) complex located in lysosomal compartments shares structural and functional similarities to TAP; however, its biological role seems to be different from the MHC I antigen processing. ABCB8 and ABCB10 are targeted to the inner mitochondrial membrane. MDL1, the yeast homologue of ABCB10, is involved in the export of peptides derived from proteolysis of inner-membrane proteins into the intermembrane space. As such peptides are presented as minor histocompatibility antigens on the surface of mammalian cells, a physiological role of ABCB10 in the antigen processing can be accounted.

Keywords ABC transporter · Antigen presentation · Membrane transport · Peptide-loading complex · Transporter associated with antigen processing

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Abbreviations ABC: ATP-binding cassette · BHV-1: Bovine herpesvirus type 1 · CTL: Cytotoxic T-lymphocyte · DHFR: Dihydrofolate reductase · DRiPs: Defective ribosome products · GFP: Green fluorescent protein · ER: Endoplasmic reticulum · EHV-1: Equine herpesvirus type 1 · i-AAA: Intermembrane space-oriented ATPase associated with a variety of cellular activities · ICP47: Infected cell protein 47 · IFN-γ: Interferon-γ · LAMP-1/2: Lysosome associated membrane protein-1/2 · MDL: Multidrug resistance like · MHC: Major histocompatibility complex · m-AAA: Matrix-oriented ATPase associated with a variety of cellular activities · NBD: Nucleotide-binding domain · PLC: Peptide-loading complex · TAP: Transporter associated with antigen processing · TAPL: Transporter associated with antigen processing-like · TMD: Transmembrane domain · UL49.5: Unique long region protein 49.5 · US6: Unique short region protein 6

The adenosine triphosphate (ATP)-binding cassette (*ABC*) genes display one of the largest families of transmembrane proteins. Based on their sequence similarities, the 48 *ABC* genes in the human genome are divided into seven subfamilies, ABCA to ABCG [17]. Noteworthy, transport proteins of the ABCB subfamily are very heterogeneous with regard to their function, their structural organization as full and half transporters, and N-terminal extensions that are responsible for recruitment of interaction partners or specific membrane targeting [43]. Based on structural and functional similarities, the five ABC half transporters, ABCB2, ABCB3, ABCB9, representing the TAP family and ABCB8 and ABCB10, are closely related; they are all involved in intracellular trafficking and compartmentalization of peptides (Fig. 1).

Gene organization of TAP, TAPL, and ABCB10

The genes coding for the human transporter associated with antigen processing (TAP)1 and TAP2 (ABCB2 and ABCB3), are located on chromosome 6p21 comprising 10 kb each [6, 60]. Each subunit is encoded by 11 exons,

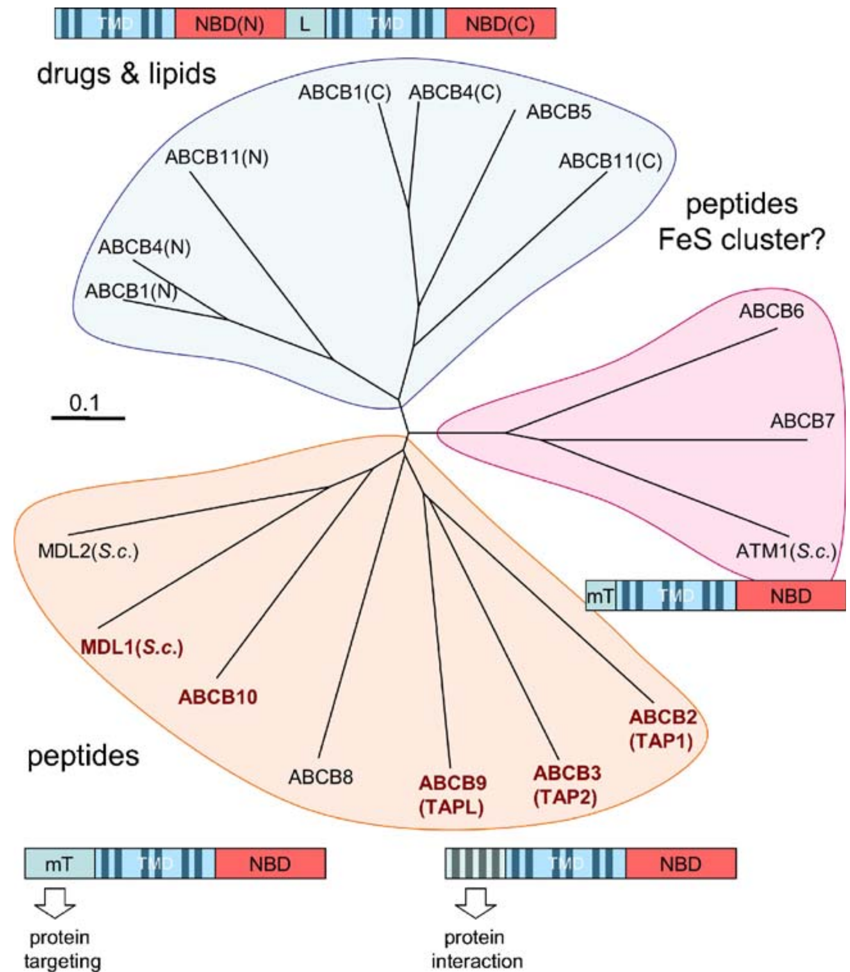

Fig. 1 Phylogenetic relationship and domain organization of the subfamily B of human *ABC* transporters. The phylogenetic tree of human *ABCB* transporters and homologues from *S. cerevisiae* (*MDL1*, *MDL2*, and *ATM1*) is derived from amino acid sequence alignments of the core *TMDs* (*blue*) and the *NBDs* (*red*). Putative transmembrane helices are indicated by *black bars*. The unique N-terminal domains (*grey*), which are essential for specific targeting or recruitment of specific interaction partners, are not used in the alignment. Sequences were aligned using ClustalW (http://www.ebi.ac.uk/clustalw/)

whereas, eight of these are of the same size. The exon–intron boundaries are identical [85]. The tap genes are arranged in a head to head orientation within the MHC class II locus in close proximity of two immunoproteasomal subunits, *lmp2* and *lmp7* [8, 29, 59]. The transcription of the four genes (*tap1*, *lmp2*, *tap2*, and *lmp7*) is responsive to interferon-gamma (IFN-γ) indicating a common regulation and concerted function of these genes in antigen processing. Comparing TAP sequences of different species from human to fish, phylogenetic differences can be detected. However 98.8% homology of human TAP1 with gorilla TAP1 is found, 69.2% homology with hamster and only 40% with salmon TAP1. Although TAP genes of all species (jawed vertebrates) are polymorphic, only rat and most likely also fish TAP alleles show a functional polymorphism reflected by different substrate specificities [74].

The closest homologue of the TAP1 and TAP2 genes is ABCB9, which is assigned to chromosome 12q24 [17]. ABCB9 shows an exon–intron organization which is similar to that of the mammalian TAP genes [89]. Together with the overall amino acid sequence identity of 38% for TAP1 and 40% for TAP2, ABCB9 is called TAP-like (TAPL) [96]. Very similar to TAP1 and TAP2, TAPL is composed of 12 exons including the first noncoding exon. An alternative splicing of exon 12 generates three different human TAPL isoforms (12A, 12B, and 12C). Isoform 12A (2,298 bp coding for 766 amino acid residues) was cloned from the T-lymphoblast CEM cell line [103]. The isoforms 12B and 12C, both containing truncated C-termini (683 and 681 amino acid residues, respectively) were isolated from HEK-293 and HeLa cells, respectively [41]. Four different rat TAPL isoforms were identified, two of them also show truncated C-termini (708 and 693 amino acid residues) [95]. In contrast to TAP1 and TAP2, the transcription of ABCB9 is not responsive to IFN-γ.

Another closely related member of the TAP subfamily is encoded by the *ABCB10* (*M-ABC2*, *ABC-me*) gene found on chromosome 1q42 [17]. The longest transcript isolated from mouse, ABC-mitochondrial erythroid (ABC-me), comprises 4,080 bp and codes for 716 amino acids [80].

TAP is the key component of the MHC class I peptide-loading complex (PLC)

TAP represents a strategic point in the pathway of antigen presentation via MHC class I molecules. This pathway can be dissected into three major steps. First, peptides are generated in the cytosol upon proteasomal degradation of unwanted, misfolded proteins or defective ribosome products (DRiPs) [40, 97]. A small fraction of these degradation products is translocated into the ER lumen by

TAP and loaded onto MHC class I molecules. Finally, after assistance of the peptide-loading complex and trimming by specialized aminopeptidases, stable peptide-MHC complexes can leave the ER via the constitutive secretion pathway to the cell surface, where MHC I molecules put the cellular "peptidome" on view for inspection by cytotoxic T-lymphocytes (Fig. 2).

Within a macromolecular peptide-loading complex (~1 MDa) composed of various auxiliary factors such as the ER resident chaperones tapasin, calreticulin, and the oxidoreductase ERp57, peptides are efficiently transferred from TAP to MHC class I molecules [18, 45, 94]. Tapasin, a type I membrane glycoprotein consisting of two immunoglobulin folds and of an N-terminal domain, bears several important functions in the peptide-loading complex. First, it stabilizes TAP as TAP expression is drastically decreased in tapasin-deficient cells [5, 25, 51, 75]. Second, by MHC class I binding and recruitment of ERp57 [19, 71], tapasin coordinates and facilitates peptide loading of MHC class I molecules [50, 62, 83, 92, 102]. Tapasin-deficient mice show an impaired immune response and an altered peptide repertoire presented on MHC class I molecules [24]. Tapasin is disulfide-linked to the thiol-dependent oxidoreductase ERp57, which originally was proposed to be involved in correct disulfide-bond formation in the α_2 domain of MHC class I molecules [19, 53, 54], but recently it was shown to be more a structural component of the MHC class I peptide-loading complex [72]. Calreticulin seems to be important for the stabilization of the PLC and for optimizing the peptide loading of MHC class I [23, 86].

TAPL—a functional homologue to TAP in lysosomes

TAPL was recently identified as an ATP-dependent peptide transporter [93]. The subcellular localization of TAPL is still under discussion. In transiently transfected COS-1 cells, TAPL–GFP fusion constructs were found in ER membranes [42]. However, when peptides harboring an N-core glycosylation targeting site were applied to TAPL-containing membranes, only a minor fraction of the transported peptides became N-core glycosylated after ATP-dependent uptake [93]. This indicates that TAPL translocates peptides into a post-ER compartment for accumulation. In contrast, TAP transports peptides into the ER lumen, where they are retro-translocated via the SEC complex [46], if not trapped by N-core glycosylation [61, 65]. In stably transfected SKOV3 cells, TAPL was found to be co-localized with the lysosome-associated membrane

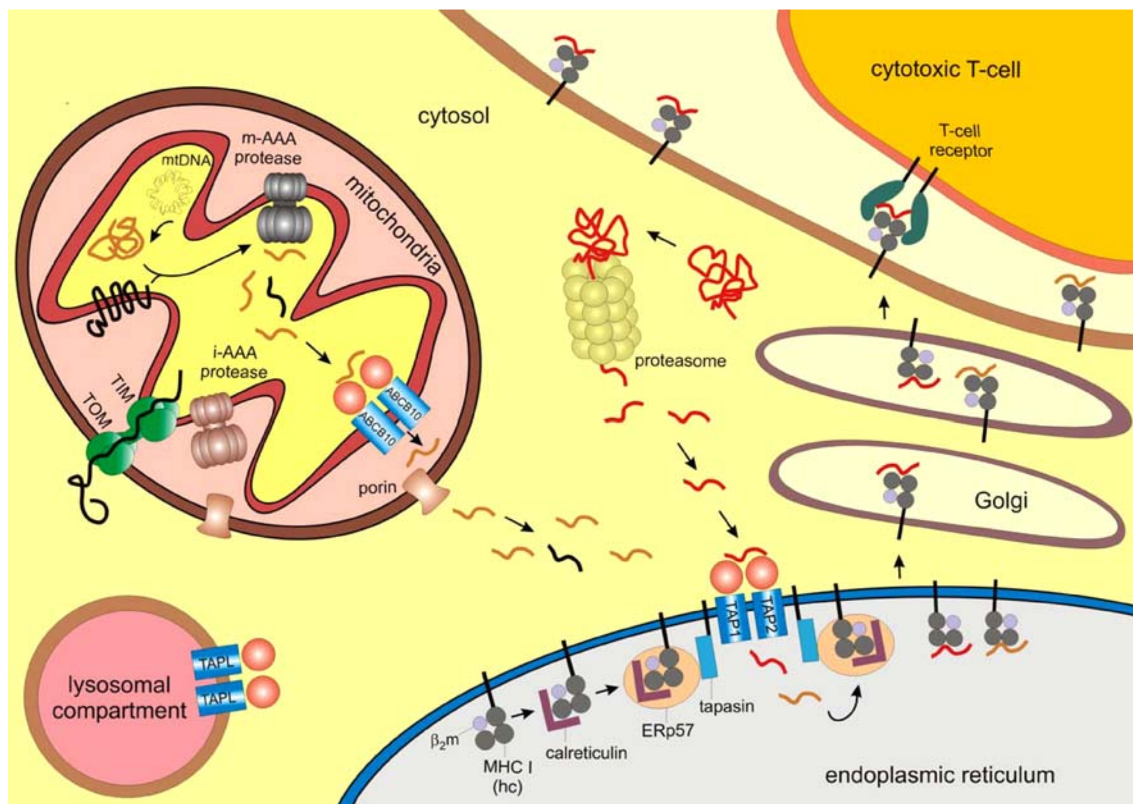

Fig. 2 Overview of intracellular peptide transporters. The peptide transporters (*TAP*, *TAPL*, and *ABCB10*) are located in different cell compartments like the *ER*, lysosome, and mitochondria. TAP transports antigenic peptides generated by the proteasome in the cytosol into the *ER* lumen for loading onto *MHC* class I molecules. Stable *MHC*–peptide complexes leave the *ER* via the Golgi network to the cell surface for recognition by cytotoxic T cells. The physiological function of *TAPL* localized in the lysosomal compartment appears to be different from the pathway of antigen processing via *MHC* class I. *MDL1*, the yeast homologue of *ABCB10*, is thought to be involved in the export of peptides derived from proteolysis of inner-membrane proteins by *m-AAA* proteases into the intermembrane space. It is speculated that these peptides finally cross the road of the antigen-processing pathway

protein, LAMP-1. This lysosomal localization was confirmed by subcellular fractionation [103]. These data are supported by immunofluorescence analysis of HeLa cells, where TAPL is co-localized with LAMP-2 (Özlem Demirel, Rupert Abele, R.T., submitted for publication).

Little is known about the physiological role of TAPL. Although TAPL belongs to the same subfamily of ABC transporters as P-glycoprotein (ABCB1), speculations about a role in multidrug resistance could not be confirmed [103]. Remarkably, TAPL homologues were also identified in jawless vertebrates such as sea lamprey (*Petromyzonmarinus)* [89], lacking an adaptive immune system, in nematodes (*Caenorhabditis elegans*) and in plants (*Arabidopsis thaliana*). Although TAPL shares structural and functional similarities with the TAP complex, several indications suggest its own, specialized biological role, different from the MHC class I antigen processing: (1) TAPL is expressed in species lacking an adaptive immune system, (2) TAPL is not able to restore antigen presentation via MHC class I molecules in TAP1- or TAP2-deficient cells, and (3) TAPL is localized in the lysosomal compartment (Özlem Demirel, Rupert Abele, R.T., manuscript in preparation). Strikingly, TAPL expression is drastically up-regulated in monocytes during maturation into immature and mature dendritic cells. As there are indications that MHC class II molecules are loaded with peptides from endogenous proteins in a TAP-independent manner [14], we suggest that TAPL transports endogenous peptides from proteasomal degradation into the MHC class II compartment for cross-presentation in dendritic cells. Apart form this putative function in antigen processing, TAPL is also expressed in Sertoli cells [103], which however do not express MHC class II molecules. Questions regarding the physiological role of TAPL pave the way for further investigations.

Mitochondrial peptide transporter with fuzzy physiological roles

Like TAPL, the physiological role of human ABCB10 (ABC-me, M-ABC2) is still an open question. ABC-me (ABC-mitochondrial erythroid), located in the inner mitochondrial membrane, was suggested to play a role in erythroid differentiation [80]. ABC-me is induced during erythroid maturation in cell lines and primary hematopoietic cells, and its over-expression enhances hemoglobin synthesis in erythroleukemia cells. ABC-me may mediate critical mitochondrial transport functions related to hem biosynthesis [80]. In contrast to enzymes involved in hem biosynthesis, our knowledge is quite limited about how biosynthetic intermediates are transferred across mitochondrial membranes. Hem biosynthesis occurs predominantly in erythroid cells. The first and the three last steps take place in the matrix of the mitochondria, whereas steps in-between take place in the cytosol. It is, therefore, presumed that ABC-me may be involved in one of these transport processes. Langer and coworkers have identified MDL1 (multi-drug resistance like), the ABCB10 homologue, from *Saccharomyces cerevisiae*, as a putative peptide transporter in the mitochondria [99]. By analyzing the fate of the degradation products of the mitochondrial inner-membrane proteins, it was shown that MDL1 is involved in the mitochondrial export of peptides of 600 to 2,100 Da. These peptides are generated by the matrix-oriented ATPase associated with a variety of cellular activities (m-AAA) protease in the mitochondrial matrix and exported via MDL1 across the inner mitochondrial membrane [99]. Along with peptides generated by the intermembrane space-oriented ATPase associated with a variety of cellular activities (i-AAA) protease, they are finally released from the mitochondria either by passive diffusion through porins or the preprotein translocase of the outer mitochondrial membrane (TOM) [35, 58] (Fig. 2). Deletion of *mdl1* reduces peptide export. The physiological role of the released peptides is currently not known. It is tempting to speculate that their physiological role might be in the communication between the mitochondria and the cellular environment. However, as peptides derived from mitochondrially encoded gene products are presented on the cell surface by maternally transmitted minor histocompatibility antigens (MHC) class I molecules [20], a physiological role of ABCB10 or its close homologue ABCB8 (M-ABC1) in antigen processing in mammals appear also likely.

MDL1 has also recently been identified as a high-copy suppressor of the mitochondrial ABC transporter ATM1 (ABCB7), which is decisive for the assembly of cytosolic Fe–S clusters [12]. It was shown that over-expression of MDL1 reduces the mitochondrial iron content and decreases the sensitivity to H_2O_2 and transition metal toxicity in Δ*atm1* cells [12]. How ABCB10 indeed adopts such diverse physiological functions, or whether these eventually fall in place like in a puzzle, will require future investigation.

Structural organization of the TAP complex

TAP is expressed in almost all nucleated cells. Human TAP1 and TAP2 are composed of 748 and 686 amino acids, respectively. For transport activity, the two half transporters form a heterodimeric TAP complex [38], which is located in the ER and *cis*-Golgi [39]. However, neither an ER-targeting sequence nor an ER-retention signal has been identified.

The heterodimeric TAP complex couples the binding and hydrolysis of ATP to the translocation of substrates across membranes [1]. Two transmembrane domains (TMD) build up the translocation pathway, whereas, the two cytosolic nucleotide-binding domains (NBD) energize the peptide translocation. According to hydrophobicity analysis, sequence alignments, and experimental data, TAP1 and TAP2 have ten and nine transmembrane helices, respectively [78]. The transmembrane domains can be further subdivided into unique N-terminal extensions (N-domains) and a 2×6 transmembrane helix core region (Figs. 1 and 3) [43]. Remarkably, transport complex lacking the extra N-terminal domains shows wild-type

activity in peptide binding and transport, demonstrating that the 2×6 TM core region is essential and sufficient for ER targeting, assembly of the heterodimeric complex, and translocation pathway. It has been further demonstrated that the N-terminal domains bind tapasin and are, therefore, essential for the formation of the peptide-loading complex [43, 44]. The transmembrane domain harbors also the peptide-binding site, which was localized to the last cytosolic loop and a region of 15 amino acids after the last transmembrane helix of each TAP subunit [69]. Notably, both TAP subunits are required for peptide binding [90].

Functional nonequivalence of the two motor domains of TAP

The NBDs convert the chemical energy of ATP into mechanical movement of peptides across membranes. The mechanism of the ATP-driven transport is highly complex and still controversially discussed. In recent years, high-resolution crystal structures of several NBDs have provided insights into possible mechanisms. The overall structures of the NBDs are very similar [77]. Like others, the NBD of TAP1 forms an L-shaped molecule comprised of two lobes (arm I and II). The catalytic domain (arm I) is composed of a Rec-like α/β structure and contains the nucleotide-binding site composed of the Walker A and Walker B motifs. In addition, arm I comprises the highly conserved D-loop and the H-loop that functions as switch region. The second lobe (arm II) forms an α-helical structure containing the C-loop and the Q-loop motif [28]. It was shown that in the presence of MgATP, the NBDs dimerize [9, 36, 57, 63, 82]. In this state, two ATP molecules are bound at the interface of two monomers and sandwiched between the Walker A and B motifs of one NBD and the C-loop of the opposite NBD. The glutamate residue following the Walker B motif may act as a catalytic base in ATP hydrolysis, presumably by coordinating the water that attacks the γ-phosphate [63, 91, 100]. However, the recent crystal structure of the HlyB-NBD provided evidence that the conserved histidine in the H-loop (H662 in HlyB) displays a "Linchpin" for ATP hydrolysis forming a catalytic dyad with the highly conserved glutamate [101]. Mutation of this conserved histidine abolished transport and ATPase activity in the histidine and maltose importers, respectively [16, 70, 81].

By functional reconstitution of TAP, it has been demonstrated that peptide binding is tightly coupled to ATP hydrolysis [30]. The contribution of both subunits in ATP hydrolysis was shown by nucleotide trapping and photo-crosslinking experiments [11]. Strikingly, chimeric TAP complexes with two identical NBDs showed a drastically reduced transport activity, whereas, TAP with exchanged NBDs was fully active [4, 15]. Furthermore, loss of transport was observed after mutation of the conserved lysine in the Walker A motif of TAP2, whereas, the same exchange in TAP1 resulted in a basal transport activity [37, 49, 76]. Notably, the highly conserved glutamate ("catalytic base") and histidine of the H-loop ("catalytic dyad") are replaced in TAP1 by aspartate and glutamine, respectively. The nonequivalence of both NBDs is also reflected in sequence differences of the C-loops. The C-loop in TAP2 is degenerated to LAAGQ compared to the canonical signature motif LSGGQ. TAP chimeras with two canonical C-loops showed the highest transport rate compared to chimeras with two degenerate C-loops showing the lowest transport rate, demonstrating that the ABC signature motifs control peptide transport efficiency [10]. Markedly, mutation of leucine or glycine in TAP1 (*L*SG*G*Q) fully abolished peptide transport; whereas, equivalent mutations in TAP2 still showed residual transport activity [10]. In summary, the functional asymmetry of both TAP subunits suggests that one NBD hydrolyzes ATP to provide energy for the transport process, whereas, the other site presumably acts as a regulatory unit for the ATPase activity.

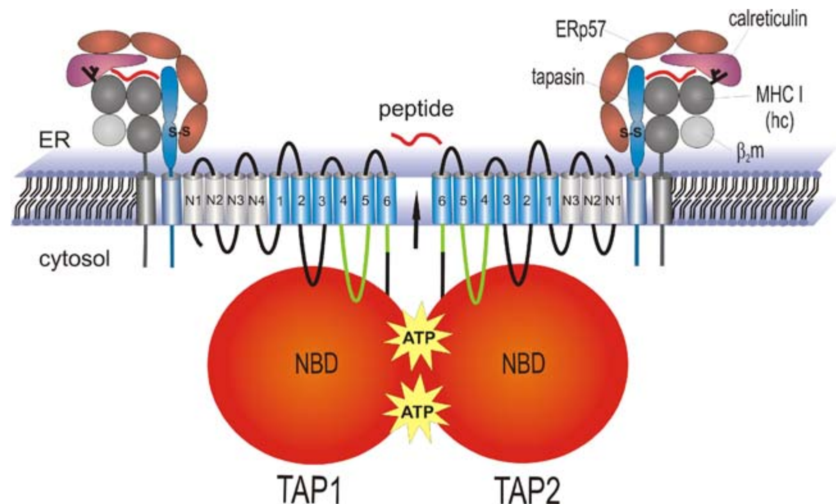

Fig. 3 Structural organization of the peptide-loading complex (*PLC*). The multi-subunit *PLC* consists of *TAP* (*TAP1* and *TAP2*), tapasin, the *MHC* class I heavy chain, $\beta_2 m$, calreticulin, and *ERp57*. The transmembrane domain of *TAP* is composed of a 2×6 transmembrane helix core region (*blue*) extended by additional four (N1–N4) and three (N1–N3) N-terminal helices (*grey*). *Green lines* illustrate peptide-binding regions. The nucleotide-binding domains (*NBDs*) energize peptide translocation by ATP binding and hydrolysis

Structural organization of the homodimeric TAPL complex

TAPL is a new member of the ABCB family, which was recently identified as peptide transporter [93]. Interestingly, the sequence identity in the putative peptide-binding regions of TAP and TAPL ranges from 30 to 55%. The homo- or heterodimerization of two half transporters is crucial for function. By dihydrofolate reductase (DHFR) fragment complementation or by pull down assays with differently tagged TAPL, recent studies confirmed the homo-dimerization of TAPL [52, 93].

On the mRNA level, TAPL is expressed in the brain, the spinal cord, and the thyroid, with the highest mRNA levels in the testis [103]. Other groups report TAPL expression also in the kidneys, the intestines, the lungs, and the stomach of rats [96]. On the protein level, TAPL was only detected in Sertoli cells [103] and dendritic cells (Özlem Demirel, Rupert Abele, R.T, submitted for publication).

The NBD of TAPL has all canonic motifs such as the Walker A and B sequences, the canonical C-loop, the putative catalytic glutamate upstream of Walker B and the H-loop. Similar to TAP1, the transmembrane domain of TAPL is composed of ten putative transmembrane helices (Rupert Abele, R.T, unpublished data). As the core transmembrane helices show a higher homology to TAP, the N-terminal domain is presumably responsible for the interaction with other proteins.

Structure–function analysis of ABCB10

MDL1, the yeast homologue of ABCB10, is involved in peptide export out of mitochondria [99]. It has been shown that both ABCB10 or MDL1, form a homodimeric complex [22, 31]. ABCB10 of mouse (ABC-me) is targeted to the inner mitochondrial membrane by an unusually long mitochondrial targeting sequence of 105 amino acid residues. Deletion of this mitochondrial leader sequence targets the protein to the ER, where it can assemble into a homodimeric complex [31]. According to the prediction algorithms for membrane topology, ABCB10 contains six putative transmembrane helices (see Fig. 1). The NBD of ABCB10 has all conserved motifs including Walker A, Walker B motifs, the C-loop, the catalytic glutamate, and histidine (H-loop) residues involved in ATP hydrolysis. Notably, within the putative substrate-binding region, ABCB10 shares 24% sequence identity with TAP2 (ABCB3).

To elucidate the ATP hydrolysis cycle of MDL1, the NBD was over-expressed in and purified from *Escherichia coli* [36]. When and how many nucleotides are hydrolyzed in one transport cycle was investigated performing beryllium fluoride-trapping experiments. It was shown that ATP binding to the NBD induces dimerization. Strikingly, in all isolated dimeric states, two nucleotides are present. As both bound ATPs are hydrolyzed and inorganic phosphate is able to dissociate from the dimer, a "processive clamp" model for the catalytic cycle was proposed [36]. Based on this model, two ATPs are hydrolyzed in the dimer, followed by the disassembly of the NBDs and reloading with new ATP. However, this model contrasts the "alternating site" model, which suggests initiation of the transport cycle by ATP binding to one of the randomly chosen NBD, preventing the other one from doing so. The second ATP binding and hydrolysis event can occur after hydrolysis of the first bound ATP. Taken together, two ATP hydrolysis events occur alternatively at each domain, which are functionally equivalent.

Chemo-mechanical coupling of ATP hydrolysis and peptide translocation in TAP

Combining biochemical and structural studies, a multistep model for the transport mechanism of TAP was proposed. Peptide binding is ATP-independent [88, 90], whereas, peptide translocation requires ATP hydrolysis [3, 61, 65, 79]. Peptide binding is composed of a fast association step followed by a slow structural reorganization of the TAP complex [68]. This structural reorganization, accompanied by high activation energies [66, 68], may disrupt the interaction between the L- and the Q-loop. The L-loop as part of the TMD is thought to be involved in the crucial crosstalk between TMD and NBD [13, 56, 64]. Subsequently, the NBDs loaded with ATP under physiological conditions dimerize, which drives the peptide across the ER membrane. ATP hydrolysis in the NBDs and the release of inorganic phosphate weakens the dimer interface. After dimer dissociation and adenosine diphosphate (ADP)–ATP exchange, the ground state for a next cycle is restored.

Overlapping substrate specificity of the intracellular peptide transporters

The best-characterized half transporters of the ABCB subfamily are represented by TAP1 and TAP2. To resolve the recognition principle and the substrate-binding motif in a systematic approach, complex peptide libraries were applied [87]. Besides free N- and C-termini, the first three N-terminal amino acid residues and the C-terminal amino acid are important for TAP recognition. Regarding the free termini, similar findings, using radiolabeled octamer peptide libraries (X_8) with modified termini, were achieved for TAPL [93]. Human TAP favors peptides with hydrophobic or basic amino acids at the C terminus. Strikingly, these are also preferred anchor residues for MHC class I binding. Notably, upon stimulation by INF-γ, immunoproteasomes preferentially generate peptides with hydrophobic and basic C-terminal residues. Thus, the proteasome, TAP, and MHC class I molecules coevolved a similar substrate specificity to optimize antigen processing. Strikingly, the T-cell receptors mainly contact the residues of antigenic peptides apart from the anchor residues where TAP shows the lowest specificity [26, 27]. Peptides with a length of eight to 16 amino acids are bound with equal affinity, but peptides of eight to 12 amino acids are most efficiently transported by TAP. Strikingly, even peptides of up to 40

amino acids in length and peptides with bulky side chains are bound and transported [32, 68, 88]. How this vast variety of substrates can share the same peptide-binding pocket remains a fascinating question.

Overlapping length specificity is observed for TAP and TAPL. The homodimeric TAPL complex has a strong preference for peptides with six to 20 residues, whereas, optimal transport efficiency is restricted to peptides of approximately 23 amino acid residues in length [93]. Remarkably, peptides up to 60 amino acid residues show almost the same transport efficiency as hexameric peptides, demonstrating a very broad length specificity of TAPL, which differs from that of TAP. Further investigations revealed that TAPL and TAP are stereo-specific and that D-isomeric and retro inverse peptides, whose peptide backbone is inverted, are not transported [93].

Currently, little or only indirect information exists about the substrate specificity of the yeast peptide transporter MDL1. The "real" substrate has not been identified yet. MDL1 was found to be involved in the mitochondrial export of peptides with six to 20 amino acid residues [99]. This length specificity of MDL1 appears to be similar to TAP and TAPL, although the function of MDL1 in direct peptide transport has to be demonstrated by in vitro experiments.

TAP as target for viral inhibitors

Viruses have evolved sophisticated strategies to life-long persistence evading cytotoxic T-lymphocytes (CTL)-mediated immune responses [55]. In particular, herpes viruses with a large DNA genome and slow replication rates are monitored by the adaptive immune system. The best-characterized viruses that interfere with TAP function are herpes simplex virus (HSV) type 1 and 2, and the human cytomegalovirus (HCMV). HSV-1 encodes the immediate-early protein ICP47 (IE12, 9 kDa), which blocks the peptide binding site of TAP from the cytosol with high affinity, and therefore, prevents peptide loading of MHC class I molecules [2, 21, 34, 84, 98]. The active domain of ICP47 has been identified from residue 3 to 34 [67]. In aqueous solution, the active domain of ICP47 appears to be mainly unstructured, whereas, it adopts an ordered helix–loop–helix conformation in the presence of negatively charged lipid membranes [7, 73].

In contrast to ICP47, the early gene product US6 from the HCMV blocks TAP from the ER lumen. The type I membrane glycoprotein (21 kDa) is composed of an ER luminal domain, a transmembrane helix and a short cytoplasmic tail. The ER-luminal domain of US6 is responsible for its ER retention and inhibition of TAP activity probably by inducing a conformational change that inhibits ATP but not ADP binding to TAP [33, 48].

Very recently, a new viral inhibitor was identified that uses a double strategy to knockout TAP function. The unique long viral protein UL49.5 from bovine and equine herpesvirus 1 (BHV-1 and EHV-1), also called glycoprotein gN, arrests TAP in a non-functional conformation and induces the proteasomal degradation of the TAP complex via its cytosolic C-terminal tail [47].

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