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TAP and TAP-like — brothers in arms?

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Abstract The transporter associated with antigen processing like (TAPL, ABCB9) is a member of the ATP-binding cassette (ABC) transporter family. Moreover, TAPL belongs to the TAP family due to its high sequence homology to TAP1 and TAP2. TAPL forms a homodimer which is localized in lysosomes with a minor fraction in the ER. It functions as an ATP-dependent peptide transporter which shows a broad peptide specificity ranging from 6-mer up to 59-mer peptides. In contrast to TAP, TAPL transports peptides with low affinity but high efficiency. This review will briefly summarize current knowledge about the structural organization and possible physiological function of TAPL in antigen processing and presentation.

Keywords ABC transporter · ABCB9 · Adaptive immunity · Antigen processing · Lysosome · Peptide transporter · TAP family · Transport assay

Abbreviations ABC: ATP-binding cassette · ER: endoplasmic reticulum · MHC: major histocompatibility complex · NBD: nucleotide binding domain · TAP: transporter associated with antigen processing · TAPL: transporter associated with antigen processing like · TMD: transmembrane domain

ABC Transporters

The ATP-binding cassette (ABC) transporters form a family of membrane proteins, which couple the energy of ATP hydrolysis with solute translocation (Higgins 1992). The ABC transporter superfamily represents the largest class of active transporters in prokaryotes, and the second

largest class (after the major facilitator superfamily) in eukaryotes. They are involved in many cellular processes, and transport a wide variety of substrates, ranging from sugars and amino acids, hydrophilic drugs and lipids to large proteins (Higgins 1992; Schmitt and Tampé 2002). ABC transporters can be found in the plasma membrane as well as in membranes of various organelles. In eukaryotes, ABC transporters exclusively function as exporters, whereas in archaea and eubacteria, they can mediate solute uptake by the help of high-affinity solute-binding proteins in the periplasm (Davidson and Chen 2004). ABC transporters contain a conserved core structure of two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) facing the cytosol (Schmitt and Tampé 2000).

The TMDs normally comprise 2×6 membrane-spanning helices (Dean et al. 2001). However, there are also examples of 2×4 and 2×10 membrane helices as in the case of the macrolide transporter MacB (Kobayashi et al. 2003b) and the vitamin B₁₂ uptake system BtuCD (Locher et al. 2002), respectively. The TMDs form the translocation pathway and, in the case of exporters, the substrate-binding site. The NBDs contain the highly conserved Walker A and Walker B motifs, as well as the C-loop (ABC signature motif), which is the hallmark of ABC-transporters. The NBDs bind and hydrolyze ATP via the conserved motifs and energize the solute transport.

The eukaryotic ABC transporters are encoded either as full transporters consisting of a polypeptide with two TMDs and two NBDs, or as half-transporters comprising only one TMD and one NBD. The latter must form either homo- or heterodimers to act as transporter (Jones and George 2004). There are 48 ABC genes in the human genome, which are divided into seven subfamilies (A-G) based on homology of the NBD (Dean et al. 2001). The function of only 16 human ABC transporters is deciphered (Borst and Elferink 2002). Notably, 17 members of this family are associated with defined human diseases (Dean and Annilo 2005). The transporter associated with antigen processing like (TAPL, ABCB9) is a half-transporter of the ABCB subfamily.

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The TAP Family

The best characterized ABC half-transporter is the transporter associated with antigen processing (TAP). TAP translocates peptides from the cytosol into the lumen of the endoplasmic reticulum (ER), where these peptides are loaded onto major histocompatibility complex (MHC) class I molecules. Assembled MHC-peptide complexes leave the ER and display their antigenic cargo on the cell surface to cytotoxic T cells (Abele and Tampé 2004). This heterodimeric transport complex consists of TAP1 (ABCB2) and TAP2 (ABCB3) (Kleijmeer et al. 1992; Lacaille and Androlewicz 1998). Both subunits are essential and sufficient for antigen processing (Powis et al. 1991; Spies and DeMars 1991; Meyer et al. 1994).

Phylogenetic analysis of human ABCB9 with ABC transporters showed that it appeared to be closely related to TAP1 and TAP2, which shares 38% and 40% amino acid sequence identity with TAP1 and TAP2, respectively, while the identity between TAP1 and TAP2 is 39% (Zhang et al. 2000) (Fig. 1). Due to the significant homology with TAP1 and TAP2, ABCB9 is also called TAP-like (TAPL) and categorized together with TAP1 and TAP2 into the TAP family. On the basis of hydrophobicity analysis and sequence alignment with TAP subunits, we propose a topology model of TAPL with 10 transmembrane helices (Fig. 1). The sequence comparison with TAP subunits shows that the transmembrane domain can be subdivided into two regions. The core domain comprising the six C-terminal transmembrane helices shows a high sequence identity to TAP, whereas the N-terminal helices are distinct.

Fig. 1 Topology model of TAPL. TAPL forms a half-transporter composed of an N-terminal TMD and a C-terminal, hydrophilic NBD localized in the cytosol. Based on hydrophobicity analysis and sequence alignments of TAPL with human TAP1 and TAP2, 10 membrane helices are predicted. The numbers resemble the N- and C-terminal residues of the membrane helices. To show the sequence

identity between the transmembrane region of human TAPL and human TAP, residues—identical in the sequence alignment between TAPL and TAP1, TAP2 or both TAP subunits—are coloured in orange, red or blue, respectively. The topology model was created with the program Textopo (Beitz 2000)

In homology to TAP (Koch et al. 2004), the N-terminal domain could be involved in recruiting accessory factors, while the core unit of six helices may assemble a functional transport complex similar to TAP1 and TAP2. The N- and C-termini as well as the putative peptide binding site are located in the cytosol.

The cDNA of TAPL was originally amplified by RT-PCR, using mRNA from rat kidney (Yamaguchi et al. 1999). Comparing the deduced primary structures of rat TAPL with the human and mouse counterparts, the mammalian TAPLs (rat, mouse, and human) are highly conserved, since about 99% of the amino acid residues are identical between rat and mouse, and 95% of the residues are identical between rodents and man in pairwise comparison. In contrast, only 75% of the residues from TAP1 or TAP2 are identical between rodents and human in spite of 90% identity between rat and mouse (Kobayashi et al. 2000). Therefore, the evolutionary rate of TAPL is much slower than those of TAP1 and TAP2 as deduced from sequence alignment analysis (Fig. 2). Moreover, a sequence closely related to mammalian TAPL but not to TAP was found in the genome of the jawless vertebrate sea lamprey (*Petromyzon marinus*) (Uinuk-ool et al. 2003). TAPL seems to be the phylogenetic progenitor of TAP with a different physiological role, as lamprey does not possess an adaptive immune system.

Gene organization of human TAPL

The human TAPL gene is localized on human chromosome 12 (12q24), which does not contain genes related to the adaptive immunity (Kobayashi et al. 2000). As shown in Fig. 3, the human TAPL gene consists of 12 exons, including the first non-coding exon (Kobayashi et al. 2003a; Uinuk-ool et al. 2003). The translation starts at position 87 of exon 2. The gene organization of hTAPL is closely related to hTAP2 gene, since both genes have a first non-coding exon, and similar splicing pattern of exon 12 (Kobayashi et al. 2003a; Penfornis et al. 2003). Exons 2 to 11 of hTAPL and hTAP2 have the same length. However, the intron length in the TAPL gene is much longer than in the TAP2 gene. The promoter of the hTAPL gene lacks canonical TATA-box and CCAAT-box but contains several GC-box elements. Four splicing isoforms of hTAPL have been identified. Three of them named 12A, 12B and 12C, respectively, are generated by alternative splicing of exon 12 (Kobayashi et al. 2003a). The full length hTAPL cDNA (12A), containing an open reading frame of 2298 bp and coding for 766 amino acids, was cloned from human T-lymphoblast CEM cell line (Zhang et al. 2000). The splicing isoforms 12B (683 amino acids) and 12C (681 amino acids), which were much shorter at the C-terminal, were cloned from HEK-293 cells, while only the 12C type

Fig. 2 Phylogenetic relationship of TAPL to other ABC transporters. Predicted amino acid sequences from members of the human ABCB subfamily and its homologues from other organisms were aligned using ClustalX. A neighbour-joining tree was generated with Phylodendron <http://www.iubio.bio.indiana.edu/treeapp/treeprint-form.html>. Full transporters were subdivided into an N- (n) and C-terminal (c) half for analysis. The horizontal bar indicates the genetic distance. Transporters without any given species name are human

ABC transporters. The species of the ABC transporters used for generation of the phylogenetic tree are: *Homo sapiens*; dog, *Canis familiaris*; mouse, *Mus musculus*; rat, *Rattus norvegicus*; bovine, *Bos taurus*; rainbow trout, *Oncorhynchus mykiss*; zebrafish, *Brachydanio rerio*; nurse shark, *Ginglymostoma cirratum*; horn shark, *Heterodontus francisci*; sea lamprey, *Petromyzon marinus*; the nematode, *Caenorhabditis elegans*; *Xenopus laevis*; and thale cress, *Arabidopsis thaliana*.

Fig. 3 Comparison of the exon-intron organization of human TAPL, TAP1 and TAP2 genes. Boxes indicate exons, in which filled boxes represent coding sequences and open boxes untranslated sequences. Introns are shown by horizontal lines. Exons are drawn

in proportion to real length. The exon and intron size (bp) is given by the numbers below and above the exons and introns, respectively. The position of the translation initiation codon is indicated with ATG and those of termination codons by TGA and TAA

was cloned from HeLa cells (Kobayashi et al. 2003a). The fourth splicing isoform of hTAPL had an internal deletion of 129 bp, which codes for 43 amino acids, encompassing the last hydrophobic region (predicted TM9 and TM10) and contains exon 7 (Zhang et al. 2000). This splice variant of hTAPL was speculated to have different substrate specificity than the full length hABCB9, since this region corresponds partially to the putative peptide-binding region. Interestingly, at least 4 different C-terminal splicing isoforms were found for rat TAPL, with a length of 693, 708, 762 and 766 amino acids (Yamaguchi et al. 2004).

bone, including the free N- and C-termini, and by side chain interactions (Uebel et al. 1997; Wolters et al. 2005). However, the peptide specificity of TAPL is very broad, ranging from 6-mer up to at least 59-mer peptides with a slight preference for 23-mers. In contrast, TAP most efficiently transports peptides from 8 to 12 amino acids in length optimized for peptide loading of MHC class I molecules (Koopmann et al. 1996). TAPL seems to work as a vacuum cleaner transporting a large variety of peptides with low affinity but high efficiency.

TAPL functions as peptide transporter

The function of TAPL as a specific and ATP-dependent peptide transporter was first demonstrated by heterologous expression in *Sf9* insect cells (Wolters et al. 2005). The transport activity of TAPL strictly requires ATP hydrolysis, since non-hydrolyzable ATP analogues, such as AMP-PNP and ATP γ S, do not energize peptide translocation. Peptide transport follows Michaelis-Menten kinetics with a $K_{m(\text{pep})}$ in the micromolar range [$6.8 \pm 2.8 \mu\text{M}$ for the peptide RRYQNSTC(Φ)L, where Φ resembles the covalently labeled fluorescein]. The turnover number of TAPL was calculated to 30 peptides/min, which is comparable to the transport activity of other ABC transporters (Eytan et al. 1996; Ambudkar et al. 1997; Patzlaff et al. 2003). Moreover, TAPL is an active transporter accumulating the peptide more than 60 fold in the vesicle lumen.

In contrast to TAP, which is a high-affinity transporter (van Endert et al. 1994; Uebel et al. 1997; Neumann and Tampé 1999), no peptide-binding activity was detected for TAPL by rapid filter assays, suggesting a low-affinity transporter (Wolters et al. 2005). Accordingly, TAPL seems to bind peptides in a different manner as TAP, although TAPL and TAP share a sequence identity of more than 49% with respect to the putative peptide-binding region.

The recognition principle of TAPL and TAP is similar, since both transporters recognize peptides via their back-

Nucleotide-dependent peptide transport

The peptide transport is energized by ATP hydrolysis. The transport follows Michaelis-Menten kinetics with a $K_{m(\text{ATP})}$ of $17.6 \pm 2.4 \mu\text{M}$ for ATP (Wolters et al. 2005), which is 4–20 fold lower than for TAP, P-glycoprotein, cystic fibrosis transmembrane conductance regulator, and maltose permease from *E. coli* (Sarkadi et al. 1992; Li et al. 1996; Landmesser et al. 2002; Chen et al. 2003). Based on the physiological ATP concentration, this $K_{m(\text{ATP})}$ value ensures that TAPL is always fully active. In order to determine the binding constant of ATP for TAPL, 8-azido [α - ^{32}P]-ATP photocross-linking assays were performed, in which 8-azido [α - ^{32}P]-ATP is a competitive substrate for ATP with a similar specificity constant ($k_{\text{cat}}/K_{\text{m}}$) as ATP. The apparent dissociation constant of $\text{Mg} \cdot \text{ATP}$ of $90 \pm 12 \mu\text{M}$ for TAPL was derived. This value is in the same range as that of other ABC transporters (Horn et al. 2003; Lapinski et al. 2003; Qu et al. 2003). A lower $K_{m(\text{ATP})}$ value than the K_{D} for TAP indicates that the ATP-binding step is followed by intermediates before final hydrolysis occurs (Fersht 1997). For such a multi-domain machinery, a multi-step process is conceivable, where peptide and ATP binding, ATP hydrolysis, and peptide transport occur in an ordered manner. As known from biochemical studies on isolated NBDs, ATP-binding induces a conformational change of the NBD enabling the dimerization of the catalytic domain, which is the prerequisite for ATP hy-

drololysis and substrate transport (Moody et al. 2002; Janas et al. 2003; van der Does and Tampé 2004; Zaitseva et al. 2005).

In competition assays with 8-azido[α - 32 P]-ATP, and by transport studies, the nucleotide specificity of TAPL was disclosed and ranked into three categories (Wolters et al. 2005): ATP as the substrate with the highest affinity for TAPL; GTP, AMP-PNP, ADP, and UTP with an intermediate affinity; and CTP as well as AMP with a very low affinity. Furthermore, this nucleotide-binding preference is also reflected in the transport activity, where GTP shows 40%, UTP 20%, and CTP 10% of the ATP-driven transport activity. Therefore, TAPL can be energized by different nucleoside triphosphates with a slight predilection for purine based nucleotides. This broad specificity is also found with other ABC transporters (Alshawi and Senior 1993; Meyer et al. 1994; Müller et al. 1994) and results from only a π - π interaction between the base of the nucleotide with the NBD (Hung et al. 1998).

Tissue distribution and cellular localization of TAPL

Based on its mRNA level, TAPL is highly expressed in testis and moderately expressed in brain, spinal cord, and thyroid (Zhang et al. 2000). However, it was also found in other tissues such as intestine, kidney, lung and stomach (Yamaguchi et al. 1999; Mutch et al. 2004). In silico analysis did not detect a signal sequence for ER insertion and subcellular targeting. Controversial results exist about the subcellular localization of TAPL. TAPL tagged with green fluorescent protein (GFP) was colocalized with PDI, a marker protein for endoplasmic reticulum (Kobayashi et al. 2000). The same group reported that the two putative N-terminal transmembrane helices are sufficient for membrane insertion (Kobayashi et al. 2004). In contrast, in double immunofluorescence staining of SKOV3 (human ovarian carcinoma cell line) using anti-TAPL antibody and a panel of organelle markers, anti-TAPL-specific staining showed a pattern overlapping with the lysosomal markers LAMP-1 and LAMP-2, and partially overlapping with the staining pattern of a marker for endosomes (Zhang et al. 2000). The lysosome localization of TAPL was further confirmed by subcellular fractionation. More recently, the subcellular distribution of TAPL was addressed by quantitative immunofluorescence confocal laser scanning microscopy in HeLa cells, which transiently expressed TAPL C-terminal tagged with a myc-epitope or GFP. Both TAPL variants colocalized with LAMP-2 but not with calnexin as an ER marker or EEA1 as an early endosome marker (Özlem Demirel, R.A., R.T., unpublished data). Furthermore, indirect evidence for the localization of TAPL in a post-ER compartment results from peptide transport studies on crude membrane preparations derived from TAPL expressed in Sf9 cells. Only a minor fraction of the transported peptide was found N-glycosylated and therefore transferred into the ER-lumen (Wolters et al. 2005).

TAPL assembles into a functional homodimeric complex

The members of the TAP family are half-transporters. Therefore, the formation of dimers is essential for a functional transporter. TAP1, together with TAP2, forms an active transport complex (Powis et al. 1991; Spies and DeMars 1991). TAP1 or TAP2 alone are not active in peptide binding and transport (Meyer et al. 1994). Since TAPL shows the same sequence identity to TAP as the TAP subunits do to one another, the dimerization of TAPL was studied. In dihydrofolate reductase protein-fragment complementation assays in SKOV3 cells (Leveson-Gower et al. 2004) and in pull-down assays with different tagged TAPL (Wolters et al. 2005), the homodimerization of TAPL was demonstrated. However, there are controversial results concerning the heterodimerization of TAPL and TAP1 or TAP2. C-terminally truncated DsRed-tagged TAPL, which contained only the first two putative transmembrane helices, showed an association with TAPL as well as with TAP1 and TAP2 (Kobayashi et al. 2004). This interaction is very surprising, since the N-terminal region of TAP1 and TAP2 comprising the N-terminal four and three transmembrane helices, respectively, are not required for dimerization, peptide binding and transport (Koch et al. 2004; Procko et al. 2005). In contrast, no interaction of TAPL with TAP1 or TAP2 was observed in dihydrofolate reductase protein-fragment complementation assays (Leveson-Gower et al. 2004). Moreover, in TAP1 or TAP2 deficient fibroblast cells exhibiting a decreased MHC class I cell surface expression, TAPL could not restore TAP function in peptide transport and antigen processing pathway via MHC class I (Ö.D., R.A., R.T., unpublished data).

Physiological function of TAPL

Although some controversy exists about the intracellular localization and interaction partners of TAPL, we propose, supported by our as well as other data, that TAPL is a peptide transporter localized lysosomal compartment. However, the physiological function is still an open issue. It has been confirmed that TAPL shows no multidrug resistance in transfected human ovarian carcinoma cells (Zhang et al. 2000). In contrast to TAP1 and TAP2, the transcription of TAPL is not affected by interferon- γ , indicating a gene regulation that is distinct from TAP1 and TAP2 (Kobayashi et al. 2000). Moreover, TAPL is not part of the classical MHC class I antigen presentation pathway, since it does not restore antigen presentation via MHC class I molecules in TAP1- or TAP2-deficient cells (Ö.D., R.A., R.T., unpublished data). Notably, TAPL expression is strongly upregulated during the maturation of monocytes to dendritic cells (Ö.D., Peter Brossart, Silke Appel, Frank Grünebach, R.A., R.T., unpublished data). Dendritic cells are the most potent antigen processing cells, expressing MHC class II beside MHC class I on their cell surface. For a long time, the paradigm existed that MHC class II

molecules expose exclusively exogenous antigens. However, it is reported that peptides from proteins of cytoplasmic or nuclear origin are also found on MHC class II molecules (Jacobson et al. 1989; Rudensky et al. 1991). This cross-presentation seems to be important for self-tolerance and anergy (Oehen et al. 1996), and could also be involved in long lasting protective immunity (Jacobson et al. 1989; Armstrong et al. 1998). The pathway of endogenous peptides to the MHC class II loading compartment is still a mystery and the focus of intensive studies. Autophagy is one possible route of peptide supply. Autophagy is a cellular process mainly induced by starvation of the cell to sustain survival, in which cellular components are enclosed into membranes and are subsequently degraded in lysosomes (reviewed in Cuervo 2004). There are different autophagy pathways, such as macroautophagy, microautophagy and chaperone-mediated autophagy. In macroautophagy, one of the discussed pathways of peptide supply to the MHC class II loading compartment, cytosolic regions and whole organelles are engulfed by membranes forming autophagosomes. These de novo synthesized vesicles fuse with lysosomes for degradation (Klionsky and Emr 2000). Subsequently, the protein fragments are loaded onto MHC class II (Dorfel et al. 2005; Paludan et al. 2005). However, an alternative route for peptide supply to lysosomes has been reported, called chaperone-mediated autophagy (reviewed in Majeski and Dice 2004). In this process, proteins are unfolded and transported directly into the lumen of lysosomes for degradation in an hsc70- and LAMP-2A-dependent manner. It was shown that this alternative MHC peptide-loading route is proteasome-dependent but TAP-independent (Malnati et al. 1992; Malnati et al. 1993; Dani et al. 2004). It is hard to imagine how LAMP-2A as a single membrane spanner protein can mediate translocation of such a diverse and complex substrate mixture. Therefore, we speculate that TAPL functions as peptide transporter in cross-presentation of endogenous antigens in the MHC class II pathway. However, a more general function should be considered, since TAPL is also found in MHC class II deficient Sertoli cells (Zhang et al. 1993) and still in lampreys. Thus, TAPL could function as a garbage collector, removing proteasomal degradation products from the cytosol for further degradation.

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