J Bioenerg Biomembr (2007) 39:489–497
DOI 10.1007/s10863-007-9120-z

Targeted degradation of ABC transporters in health and disease

Daphne Nikles · Robert Tampé

Published online: 31 October 2007

Abstract ATP binding cassette (ABC) transporters comprise an extended protein family involved in the transport of a broad spectrum of solutes across membranes. They consist of a common architecture including two ATP-binding domains converting chemical energy into conformational changes and two transmembrane domains facilitating transport via alternating access. This review focuses on the biogenesis, and more precisely, on the degradation of mammalian ABC transporters in the endoplasmic reticulum (ER). We enlighten the ER-associated degradation pathway in the context of misfolded, misassembled or tightly regulated ABC transporters with a closer view on the cystic fibrosis transmembrane conductance regulator (CFTR) and the transporter associated with antigen processing (TAP), which plays an essential role in the adaptive immunity. Three rather different scenarios affecting the stability and degradation of ABC transporters are discussed: (1) misfolded domains caused by a lack of proper intra- and intermolecular contacts within the ABC transporters, (2) deficient assembly with auxiliary factors, and (3) arrest and accumulation of an intermediate or 'dead-end' state in the transport cycle, which is prone to be recognized by the ER-associated degradation machinery.

Keywords ABC transporter · ER-associated degradation · Membrane protein · Misassembly · Misfolding · Ubiquitin proteasome pathway

D. Nikles · R. Tampé (✉)
Institute of Biochemistry, Biocenter,
Johann Wolfgang Goethe-University,
Max-von-Laue-Str. 9,
60348 Frankfurt am Main, Germany
e-mail: tampe@em.uni-frankfurt.de
URL: http://www.biochem.uni-frankfurt.de

D. Nikles
e-mail: nikles@biochem.uni-frankfurt.de

Abbreviations

ABC	ATP-binding cassette
ER	endoplasmic reticulum
NBD	nucleotide-binding domain
TMD	transmembrane domain
ERAD	ER-associated degradation
CFTR	cystic fibrosis conductance regulator
BLS	bare lymphocyte syndrome
BHV1	bovine herpesvirus 1

Architecture of ABC transporters

ATP-binding cassette (ABC) transporters build up a family of membrane proteins that translocate a wide range of solutes across extra- and intracellular membranes. The ABC superfamily is represented in almost all known organisms from bacteria to human. ABC transporters came into focus especially through the first description of the so-called P-glycoprotein (P-gp), which conferred a multidrug resistance phenotype to mammalian cells (Debenham et al. 1982; Kartner et al. 1983). Further medically important members have been identified among which e.g. homologues of P-glycoprotein in pathogenic microorganisms, the cystic fibrosis transmembrane conductance regulator (CFTR), the transporter associated with antigen processing (TAP), and a lot more (Dean and Annilo 2005). In bacteria and archaea, the ABC transporters are involved in the import of essential compounds, e.g. sugars, amino acids, vitamins or metal ions as well as in the extrusion of e.g. toxic compounds, antibiotics, or cell wall components, whereas in eukarya, ABC genes function exclusively as exporters pumping solutes to the outside of the cell or into an intracellular compartment.

The general architecture of ABC transporters emphasizes four domains, two nucleotide-binding domains (NBD) catalyzing the hydrolysis of ATP and two transmembrane domains (TMD) involved in solute binding and passageway across the membrane. Highly conserved motifs are found in the NBDs (Walker A and B, ABC signature, D, H, and Q loops), which are important for function (for review see (Schmitt and Tampé 2002)). The ATP hydrolysis cycle includes four basic steps of (1) ATP binding to each NBD monomer, (2) NBD dimer formation, (3) sequential hydrolysis of the two sandwiched ATPs, and finally (4) dissociation of the dimer (Janas et al. 2003; Smith et al. 2002).

ABC transporters are classified according to their NBD sequence. Eukaryotic members of this superfamily are organized either as full transporters harboring all four domains in one gene product, or as half transporters forming homo- or heterodimers. ABC genes are highly conserved between species reflecting their essential physiological functions. In mammalia, the genes can be divided into seven subfamilies (A to G) based on sequence homology, domain combination, and genomic organization (exon-intron structure) (Dean et al. 2001). The human ABCA subfamily comprises 12 full transporters including members of importance for the transport of cholesterol or retinol derivatives. The ABCB subfamily contains four full and seven half transporters. ABCB1 (MDR1/P-gp) confers multidrug resistance as described above. ABCB4 and ABCB11, both located in the liver, are involved in the secretion of lipids and bile acids. The half transporters *ABCB2/3* (TAP1/2) form a heterodimeric peptide transport complex essential for adaptive immunity (see below). The homodimeric peptide half transporter ABCB9 (TAP-like) is found in the lysosomal compartment, whereas the four other members ABCB6, ABCB7, ABCB8, and ABCB10 are located in mitochondria involved in iron metabolism and maturation of cytosolic Fe–S cluster protein. The ABCC subfamily contains 12 full transporters with high impact in human physiology (e.g. ion homeostasis or insulin secretion). The cystic fibrosis transmembrane conductance regulator (CFTR) protein represents an ATP-regulated chloride channel in the plasma membrane. Mutations in CFTR cause cystic fibrosis, a frequent disease that mainly affects the lungs and digestive system causing early death. The four members of the ABCD subfamily are involved in peroxisome biogenesis and long chain fatty acid oxidation. The ABCE and ABCF subfamily lacking the TMD, participate in translation initiation and ribosome biogenesis. The ABCG subfamily is composed of six "reverse" half transporters (NBD–TMD). The first member of this subfamily was identified in *Drosophila melanogaster* as modulator of eye pigmentation (white locus). Mammalian ABCG1 play a role in cholesterol transport, while ABCG2 confers drug resistance to cancer cells and is highly expressed in a subpopulation of hematopoetic stem cells.

High-resolution structures of four different ABC transporters (one exporter and three importers) have been published: Sav1866 (Dawson and Locher 2006), $BtuC_2D_2$ (Locher et al. 2002), HI1470/71 (Pinkett et al. 2007) and $ModB_2C_2$ in complex with its binding protein ModA (Hollenstein et al. 2007), all of them of bacterial origin. The x-ray structure (3.0 Å) of Sav1866 from *Staphylococcus aureus* shows an outward-facing conformation reflecting the ATP-bound state, with the two NBDs in tight contact and the two TMDs forming a central cavity closed towards the cytoplasm and exposed to the extracellular space (Dawson and Locher 2006). The crystal structure of the *Escherichia coli* $BtuC_2D_2$ (3.2 Å), translocating vitamin B12 from the periplasmic binding protein BtuF into the cytoplasm, revealed a tight contact of both, the two ATP-binding cassettes (BtuD) and the two membrane-spanning subunits (BtuC) with a translocation pathway that is blocked to the cytoplasm (Locher et al. 2002). More recently, the 2.6-Å crystal structure of the complex BtuCD-F revealed a putative post-translocation intermediate state, in which the translocation pathway is closed to both sides of the membrane (Hvorup et al. 2007). The 2.4-Å crystal structure of a putative metal-chelate-type ABC transporter encoded by the genes HI1470/71 of *Haemophilus influenzae* in nucleotide-free states exhibits an inward-facing conformation and involves relatively modest rearrangements compared to $ButC_2D_2$ structure (Pinkett et al. 2007). The 3.1-Å crystal structure of a putative molybdate transporter $ModB_2C_2$ from *Archaeoglobus fulgidus* has been solved in complex with its binding protein ModA. Here, the TMDs show an inward-facing conformation, whereas the NBDs are in an open, nucleotide-free conformation and the attached binding protein aligns the solute-binding cleft with the entrance to the presumed translocation pathway. Structural comparison with Sav1866 suggests a common alternating access and release mechanism, with binding of ATP promoting an outward-facing conformation and dissociation of the hydrolysis products supporting an inward-facing conformation (Hollenstein et al. 2007; Parcej and Tampé 2007). Although there are differences as to the various transporters, the summary of the structural data reveal an ATP-switch model for function, in which the paired NBDs switch between an ATP-dependent closed conformation and a nucleotide-free, open conformation to drive the translocation of the ligand (Abele and Tampé 2004; Higgins and Linton 2004).

Beside the structural analysis, there are a variety of functional studies towards understanding ABC transporters on a molecular level. Very recently, certain residues were for example identified downstream of the Walker B motif, the so-called H-loop, which interferes with ATP hydrolysis but not with binding (Hofacker et al. 2007; Zaitseva et al. 2006). Another approach pointed out essential residues for

the coupling of peptide binding and transport, reasoning that the transmission interface of the subunits of the eukaryotic peptide transporter TAP is restructured during ATP hydrolysis (Herget et al. 2007). Moreover, cysteine-scanning mutagenesis and subsequent cross-linking analysis have been widely used to determine certain solute binding characteristics for P-glycoprotein (Loo et al. 2006a, b), organization of the intracellular loops of BmrA (Dalmas et al. 2005), solute specificity of organic anion transporter MRP1 (Conseil et al. 2006), domain arrangement of MDR transporters (Zolnerciks et al. 2007), and several more [reviewed in (Linton 2007)]. Taken together, the extended knowledge on distribution, function and structure of ABC transporters lays the basis for molecular understanding of solute transport in a variety of biochemical processes within both prokaryotic and eukaryotic cells. The next chapter focuses on cellular interplay of these molecules and provides a closer insight into ABC transporter biogenesis and degradation.

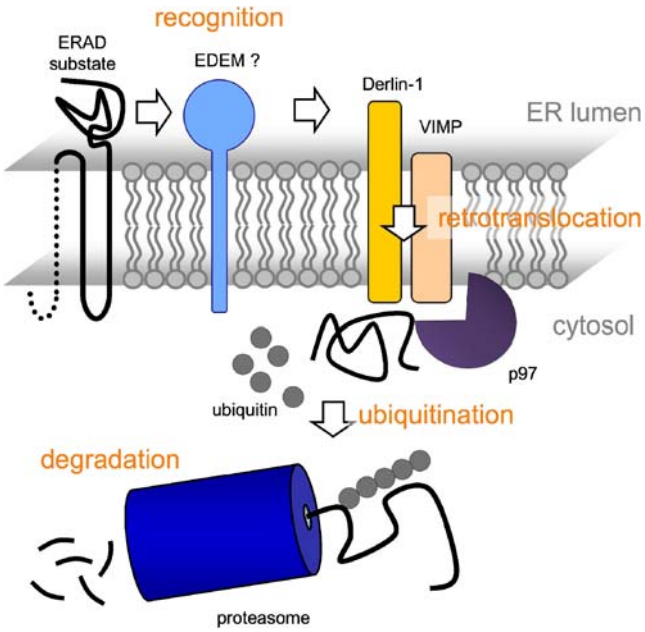

Fig. 1 The ER-associated degradation pathway. Un- or misfolded proteins are recognized by the EDEM membrane protein that hands the proteins over to the retrotranslocation proteins Derlin-1 and VIMP. The VIMP-interacting AAA-ATPase p97 operates as unfolding motor promoting ubiquitination and ultimate degradation by the proteasome

ER-associated proteasomal degradation of ABC transporters

Unfolded and misfolded proteins in the endoplasmic reticulum (ER) are recognized by the ER-associated proteasomal degradation (ERAD) machinery and transported to the cytoplasm, where they are ultimately degraded [for review see (Bar-Nun 2005; McCracken and Brodsky 2005; Meusser et al. 2005)]. In mammalian cells, the process of ERAD can be divided into four steps: recognition, retrotranslocation, ubiquitination, and degradation (Fig. 1). The recognition of un- or misfolded proteins is controlled by ER degradation-enhancing α-mannosidase-like protein (EDEM), which discriminates unfolded proteins from folded proteins (Hosokawa et al. 2001; Molinari et al. 2003) or by Osteosarcoma 9 (OS9) and the XTP3-transactivated gene product B (XTP3B) (Buschhorn et al. 2004; Cruciat et al. 2006). After the recognition process, cleavage of disulfide bonds and unfolding of the ERAD substrates takes place before they are subsequently handed over to the retrotranslocation machinery, which consists of p97, Derlin-1 and valosin-containing protein (VCP)-interacting membrane protein (VIMP) (Ye et al. 2004). Similar to Der1p in yeast (Knop et al. 1996), Derlin-1 may form a retrotranslocation channel in the ER membrane; it thus links the recognition of misfolded ER proteins to the ubiquitin-mediated proteasomal degradation in the cytosol (Lilley and Ploegh 2004; Ye et al. 2004). Derlin-1 is found to be associated with p97 adapted by VIMP. Derlin-2 and Derlin-3 are other Der1 homologs also involved in ERAD, although the exact underlying mechanism remains unclear. However it is known that p97 (also called cdc48 or VCP) is a cytosolic AAA-ATPase (ATPase associated with various cellular activities) and recruits unfolded ER proteins to the cytosol (Rabinovich et al. 2002; Ye et al. 2001). Retrotranslocated proteins are subsequently ubiquitinated by the E1–E2–E3 ubiquitin system. The corresponding ubiquitin conjugase (E2) and ligase (E3) have been shown to be specific for luminal (ERAD-L) (recruiting Hrd1 as E3) and cytosolic (ERAD-C) misfolded domains (consisting of Doa10 instead) (Carvalho et al. 2006). Once a substrate is ubiquitinated and deglycosylated, the proteasomal degradation takes place in the cytosol.

The first mammalian ER protein shown to be a substrate for ERAD has been the ABC transporter CFTR (Jensen et al. 1995; Ward et al. 1995). The proteasomal degradation of both, the wild-type CFTR and the disease-associated ΔPhe508 mutant were found to take place in an ubiquitin-dependent manner. The mutation of Phe508, which is located in the cytosolic NBD, causes CFTR misfolding and decreased abundance at the cell surface. Although independent from the ER-resident chaperone calnexin (Farinha and Amaral 2005), the degradation process of CFTR was shown to be influenced by small heat shock proteins maintaining its solubility (Ahner et al. 2007). The implication of Derlin-1 and p97 in CFTR degradation was confirmed by physical interaction with both proteins (Sun et al. 2006). Consistent with observations in yeast, p97-bound CFTR was ubiquitinated, whilst Derlin-1-associated CFTR was not, which confirmed a cytosolic localization of p97 and Derlin-1 activity in the ER-lumen. Ectopic overexpression as well as knock down approaches of Derlin-1, resulting in the increase

and decrease of CFTR levels, respectively, underlined the key role of Derlin-1 in CFTR degradation and biogenesis. In addition, the mode of action of p97 in CFTR degradation has recently been investigated in detail (Carlson et al. 2006). The protein was reconstituted in a cell-free system to define the precise contribution of p97. Complete absence of p97, however only resulted in a 50% decrease of degradation. Hence, p97 was found to function as a non-essential but important auxiliary component that facilitates extraction of transmembrane helices in ERAD.

Complementary to extended studies on CFTR, there are a number of other ABC transporters, which appear to be ERAD substrates (summarized in Table 1). The next three chapters concentrate on TAP, its structure, function and degradation and in particular the circumstances under which TAP is destabilized and may be degraded by ERAD.

Structure and function of the TAP complex

Over the last decade, TAP has been intensively studied, which resolved its important function in immune defense mechanisms in vertebrates [for review see (Abele and Tampé 2006)]. There have been certain hallmarks since the relevance of TAP in MHC class I presentation pathway was discovered in 1991 (Spies and DeMars 1991). The details about peptide recognition and transport (Heemels et al. 1993; Neefjes et al. 1993; Shepherd et al. 1993; Uebel et al. 1997; van Endert et al. 1994) were accompanied by research on the assembly of the peptide loading complex (Lindquist et al. 1998; Ortmann et al. 1994, 1997). More recently, anti-TAP viral immune evasion strategies were detected [for review see (Loch and Tampé 2005; Ploegh 1998; Wiertz et al. 1997). The finding that the 6+6 transmembrane segment core of the TAP transporter was sufficient to assemble the TAP heterodimer, peptide binding and translocation contributed to the molecular architecture of the TAP complex (Koch et al. 2004). Moreover, the membrane topology of TAP has been elucidated by cysteine-scanning approaches using thiol-specific fluorophors in semi-permeabilized cells (Schrodt et al. 2006). Direct evidence for a tight allosteric coupling between peptide binding, conformational change, translocation and ATP hydrolysis has been provided (Chen et al. 2003; Gorbulev et al. 2001; Herget et al. 2007; Neumann et al. 2002).

To sum it up, it is now known that TAP is a heterodimer consisting of TAP1 and TAP2 subunits and translocates the "peptidome" representing the degraded protein content of the cell (proteome) from the cytosol into the ER lumen [for review see (Koch and Tampé 2006)]. The macromolecular MHC class I peptide-loading complex (PLC), comprising TAP1 and TAP2, tapasin, ERp57, calreticulin, MHC class I heavy chain and β_2m, transfers the peptides on MHC class I for antigen presentation at the cell surface (Fig. 2a). This process is highly regulated within the cell and is stimulated by interferon γ. But what do we know about TAP degradation and biogenesis? So far, there are no data on Derlin-1/p97 ERAD interplay as observed in CFTR biogenesis (see above). Thus, it remains an open issue whether ERAD plays a role in the ER-resident TAP complex. However, there are some hints supporting the idea for a tight regulation of TAP by targeted proteasomal degradation.

Table 1 Degradation of ABC transporters

ABC transporter	Organism	Initiation of degradation	Ref.
CFTR/ABCC7 (wt and ΔF508)	Human	Misfolding	Jensen et al. (1995), Ward et al. (1995)
SUR1/ABCC8 (wt and mutants)	Human	Lack of K(ATP) channel misfolding	Crane and Aguilar-Bryan (2004); Yan et al. (2005)
ABCG2 (C592G or C608G)	Human	Lack of intramolecular disulfide bond	Wakabayashi et al. (2007)
ALDP/ABCD1 (several mutants)	Human	Mutations in the NBD	Takahashi et al. (2007)
TAP2/ABCB3	Human	Lack of TAP1	de la Salle et al. (1999), Heintke et al. (2003), Karttunen et al. (2001)
TAP1/2/ABCB2/3	Human	Lack of tapasin	Garbi et al. (2003), Lehner et al. (1998), Papadopoulos and Momburg (2007)
TAP1/2/ABCB2/3	Human	Viral inhibitors UL49.5 and mK3	Boname et al. (2004), Koppers-Lalic et al. (2005), Lybarger et al. (2003), Wang et al. (2007)
Pdr5 (ΔC-term and L183P)	Yeast	Misfolded NBD	de Thozee et al. (2007)
Yor1p (ΔF670)	Yeast	Space change in NBD	Pagant et al. (2007)

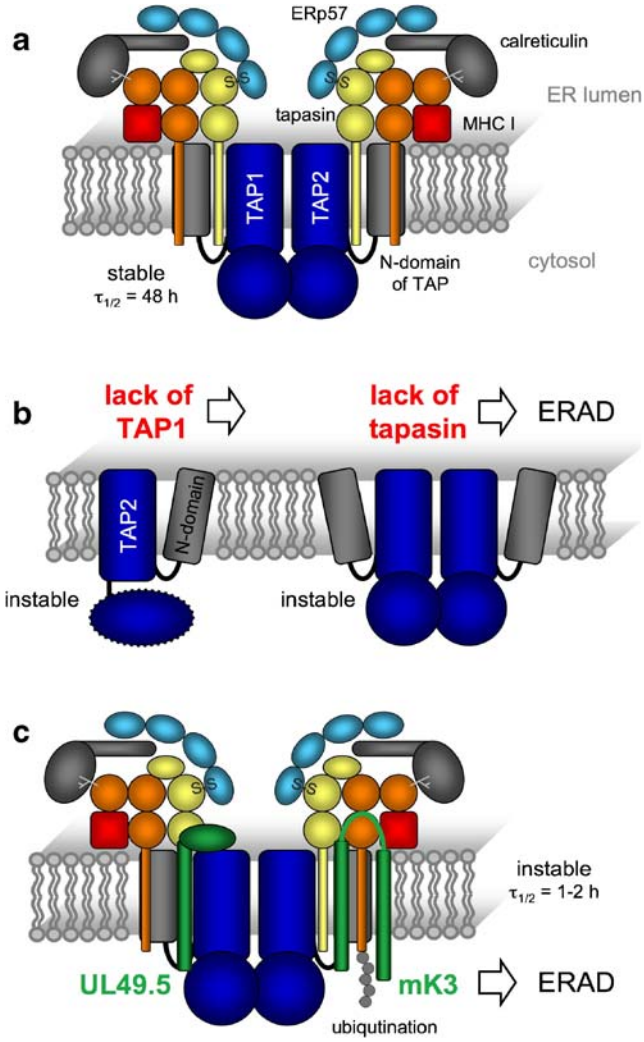

Fig. 2 Proteasomal degradation of TAP. **a** The TAP1/2 heterodimer forms the platform for the assembly of the macromolecular MHC class I peptide-loading complex consisting of tapasin, MHC class I heavy chain (*hc*), β_2m, ERp57 and calreticulin. The core TAP complex is shown in *dark blue*, the N-domain is colored in *grey*. **b** TAP2 is instable in cells lacking TAP1 (*left panel*). In the absence of tapasin, TAP is slightly instable (*right panel*). **c** TAP1 and TAP2 are targeted for proteasomal degradation in the presence of the viral factors UL49.5 (BHV-1, left panel) and mK3 (murine γ-herpesvirus-68, *right panel*), respectively

Instability and degradation of TAP2 in TAP1 deficiency (Bare Lymphocyte Syndrome, BLS)

Molecules and disease-associated states that interfere with the stability of TAP are reconciled in this and the next chapter to reveal an overall understanding of TAP biogenesis. Hence, it is known that the TAP2 subunit is instable upon absence of TAP1 since de la Salle et al. analyzed cells isolated from Bare Lymphocyte Syndrome (BLS) type I patients lacking TAP1 expression (de la Salle et al. 1999), which also exhibited no detectable levels of TAP2 (Seliger et al. 2001). This finding was confirmed in various cell lines (Heintke et al. 2003; Karttunen et al. 2001). In a melanoma cell line, which has a TAP1 frame shift resulting in an early stop, neither TAP1 nor TAP2 were detected, but expression of TAP2 was restored upon reintroduction of TAP1 arguing for a specific stabilizing effect of TAP1 on TAP2 expression (Seliger et al. 2001). Accordingly, restoring TAP1 expression in the antigen presentation pathway-deficient mouse lung carcinoma cell line also leads to recovery of antigen presentation in these cells (Lou et al. 2005). Furthermore, there are recent hints that stable, preexisting TAP1 in the ER awaits synthesis of TAP2 to form the functional TAP complex protecting newly synthesized TAP2 from rapid degradation and controlling the number of active transporter molecules (Keusekotten et al. 2006). Thus, the interaction of both half transporters plays a critical role in TAP2 stabilization, most likely by influencing TAP2-targeting for degradation, and may contribute to a tight regulation of the number of functional TAP molecules in the cell (Fig. 2b).

TAP stability mediated by tapasin

Tapasin was found to critically interfere with the assembly of the peptide-loading complex (Ortmann et al. 1997) and with stability of TAP (Lehner et al. 1998). In human B lymphoblastoid cells, TAP expression is reduced three- to tenfold in the absence of tapasin and its expression significantly stabilizes the TAP complex (Lehner et al. 1998; Tan et al. 2002). Tapasin interacts independently with TAP1 and TAP2, and the first N-terminal transmembrane helices of TAP1 and TAP2 are required for tapasin binding (Koch et al. 2004, 2006). Very recently, the well conserved connecting peptide residues ED (localized in the ER lumen close to the putative transmembrane domain) and the sequence motif (F)xxxFxxxGxxKxxxW in the transmembrane helix of tapasin were found to be responsible for the stabilization of TAP2 (Papadopoulos and Momburg 2007). Interestingly, a reduced expression of TAP2 was monitored in certain mutants of the connecting peptide, in which especially residue 414 of murine tapasin played a key role. In addition, combined and not single mutations in the putative transmembrane domain of tapasin influenced TAP2 expression. The stabilizing effect was contributed to a sequence motif (four to five residues) located on the same flank of the predicted transmembrane helix of tapasin, to which all of the relevant mutations were directed. Overall, certain residues within the putative tapasin TMD and close to the ER-luminal membrane are essential for stable expression of TAP2 (Fig. 2b).

Degradation of TAP upon viral infection

Among a variety of viral immune evasion strategies targeting the peptide-loading complex, there are to date two known viral factors, which affect the half-life of components of the peptide-loading complex (Fig. 2c). The murine γ-herpesviral protein mK3 encoding an E3 ligase, specifically targets the major histocompatibility complex I heavy chain (HC) for ER-associated degradation (ERAD) (Boname et al. 2004; Boname and Stevenson 2001; Lybarger et al. 2003; Wang et al. 2006, 2007). The other example is the varicellovirus encoded gene product UL49.5 blocking TAP function by a two-tired mechanism: it first arrests the transporter in a transport-incompetent conformation and secondly mediates degradation of the TAP complex via the proteasome pathway accompanied by a drastically reduced half-life of TAP (1–2 vs 24–48 h in the absence of UL49.5) (Koppers-Lalic et al. 2005). UL49.5 is a non-glycosylated type I transmembrane protein of approximately 8 kDa with an N-terminal signal peptide followed by an ER-luminal domain (32 aa), a transmembrane helix, and a cytoplasmic tail (17 aa), which exists both as a monomer and a dimer. The latter either consists of a disulfide linked homodimer or a heterodimer based on the conserved interaction with the viral membrane glycoprotein M (gM) that interferes with UL49.5-mediated TAP inhibition (Lipinska et al. 2006). The ORF encoding for UL49.5 is well conserved in herpesviruses and TAP inhibition has been identified for homologs from the bovine herpesvirus 1 (BHV1), the pseudorhabiesvirus (PSV) and the equine herpesvirus 1 (EHV1). It is worth noting that the viral factor is degraded itself upon the UL49.5-mediated degradation of TAP1 and TAP2. Contrary to mK3, UL49.5 does not affect the degradation of MHC class I. Furthermore, UL49.5 does not contain a RING finger motif and is thus not believed to act as an E3 ligase on its target TAP. In summary, either the degradation of TAP or the degradation of the peptide-loading complex (which then results in degradation of TAP) are observed in the presence of specialized viral proteins representing their specific immune evasion strategy; they might prove to examine an (otherwise rare) event in the cell that will accommodate further knowledge on TAP ‘fine tuning’.

Conclusions

The ERAD quality control is an established mechanism to remove misassembled or misfolded proteins and protein complexes from the ER. However, our knowledge regarding the targeted degradation of membrane proteins is not yet broad enough. Within the ABC superfamily, the ER-associated degradation of CFTR (and its misfolded mutant ΔF508) has been studied in detail. The interaction partners Derlin-1 and p97 were identified and subsequent ubiquitination followed by proteasomal degradation was observed. However, the signals required for ERAD initiation have not been identified. In particular, the folding and maturation of ABC transporters in the ER remain unsolved. As summarized in Table 1, structural alterations are often observed in multi-domain membrane proteins. Subsequent degradation of ‘folding mutants’ is typical for disease-associated loss-of-function (CF, BLS). At least for TAP, there also seems to be a tight regulation involving different factors: the lack of a transporter subunit or the auxiliary factor tapasin, as well as the effect of viral modulators (presented in Fig. 2). In the context of viral immune evasion, mK3 of γ-herpesvirus, harboring an ubiquitin E3-ligase activity, transfers ubiquitin onto MHC class I heavy chain and subsequently induces degradation of the entire peptide-loading complex including TAP. UL49.5 from bovine herpesvirus arrests TAP in a transport-incompetent conformation, and in addition induces its degradation. We propose that, within the transport cycle, UL49.5 traps an intermediate or ‘dead-end’ state of the ABC transporter, which is prone to be recognized by the ER quality control machinery. Taken together, our summary reveals certain similarities on the targeted degradation of mammalian ABC transporters. Thus, we hypothesize a common model of how ER-targeted ABC transporters are degraded in the cell by the quality control ERAD, reasoning that certain conformations may even mimic ‘misfolded’ states.

Acknowledgements We apologize to the investigators whose important contributions could not be included in this review because of space restrictions. We thank Dr. Joachim Koch for the critical reading of the manuscript. This work was supported by the Deutsche Foschungsgemeinschaft (DFG)–SFB 628 “Functional Membrane Proteomics”.

References

Abele R, Tampé R (2004) The ABCs of immunology: structure and function of TAP, the transporter associated with antigen processing. Physiology (Bethesda) 19:216–224

Abele R, Tampé R (2006) Modulation of the antigen transport machinery TAP by friends and enemies. FEBS Lett 580:1156–1163

Ahner A, Nakatsukasa K, Zhang H, Frizzell RA, Brodsky JL (2007) Small heat-shock proteins select deltaF508-CFTR for endoplasmic reticulum-associated degradation. Mol Biol Cell 18:806–814

Bar-Nun S (2005) The role of p97/Cdc48p in endoplasmic reticulum-associated degradation: from the immune system to yeast. Curr Top Microbiol Immunol 300:95–125

Boname JM, Stevenson PG (2001) MHC class I ubiquitination by a viral PHD/LAP finger protein. Immunity 15:627–636

Boname JM, de Lima BD, Lehner PJ, Stevenson PG (2004) Viral degradation of the MHC class I peptide loading complex. Immunity 20:305–317

Buschhorn BA, Kostova Z, Medicherla B, Wolf DH (2004) A genome-wide screen identifies Yos9p as essential for ER-associated degradation of glycoproteins. FEBS Lett 577:422–426

Carlson EJ, Pitonzo D, Skach WR (2006) p97 functions as an auxiliary factor to facilitate TM domain extraction during CFTR ER-associated degradation. EMBO J 25:4557–4566

Carvalho P, Goder V, Rapoport TA (2006) Distinct ubiquitin-ligase complexes define convergent pathways for the degradation of ER proteins. Cell 126:361–373

Chen M, Abele R, Tampé R (2003) Peptides induce ATP hydrolysis at both subunits of the transporter associated with antigen processing. J Biol Chem 278:29686–29692

Conseil G, Deeley RG, Cole SP (2006) Functional importance of three basic residues clustered at the cytosolic interface of transmembrane helix 15 in the multidrug and organic anion transporter MRP1 (ABCC1). J Biol Chem 281:43–50

Crane A, Aguilar-Bryan L (2004) Assembly, maturation, and turnover of K(ATP) channel subunits. J Biol Chem 279:9080–9090

Cruciat CM, Hassler C, Niehrs C (2006) The MRH protein Erlectin is a member of the endoplasmic reticulum synexpression group and functions in N-glycan recognition. J Biol Chem 281:12986–12993

Dalmas O, Orelle C, Foucher AE, Geourjon C, Crouzy S, Di Pietro A, Jault JM (2005) The Q-loop disengages from the first intracellular loop during the catalytic cycle of the multidrug ABC transporter BmrA. J Biol Chem 280:36857–36864

Dawson RJ, Locher KP (2006) Structure of a bacterial multidrug ABC transporter. Nature 443:180–185

de la Salle H, Zimmer J, Fricker D, Angenieux C, Cazenave JP, Okubo M, Maeda H, Plebani A, Tongio MM, Dormoy A et al (1999) HLA class I deficiencies due to mutations in subunit 1 of the peptide transporter TAP1. J Clin Invest 103:R9–R13

de Thozee CP, Cronin S, Goj A, Golin J, Ghislain M (2007) Subcellular trafficking of the yeast plasma membrane ABC transporter, Pdr5, is impaired by a mutation in the N-terminal nucleotide-binding fold. Mol Microbiol 63:811–825

Dean M, Annilo T (2005) Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates. Annu Rev Genomics Hum Genet 6:123–142

Dean M, Rzhetsky A, Allikmets R (2001) The human ATP-binding cassette (ABC) transporter superfamily. Genome Res 11:1156–1166

Debenham PG, Kartner N, Siminovitch L, Riordan JR, Ling V (1982) DNA-mediated transfer of multiple drug resistance and plasma membrane glycoprotein expression. Mol Cell Biol 2:881–889

Farinha CM, Amaral MD (2005) Most F508del-CFTR is targeted to degradation at an early folding checkpoint and independently of calnexin. Mol Cell Biol 25:5242–5252

Garbi N, Tiwari N, Momburg F, Hammerling GJ (2003) A major role for tapasin as a stabilizer of the TAP peptide transporter and consequences for MHC class I expression. Eur J Immunol 33:264–273

Gorbulev S, Abele R, Tampé R (2001) Allosteric crosstalk between peptide-binding, transport, and ATP hydrolysis of the ABC transporter TAP. Proc Natl Acad Sci U S A 98:3732–3737

Heemels MT, Schumacher TN, Wonigeit K, Ploegh HL (1993) Peptide translocation by variants of the transporter associated with antigen processing. Science 262:2059–2063

Heintke S, Chen M, Ritz U, Lankat-Buttgereit B, Koch J, Abele R, Seliger B, Tampe R (2003) Functional cysteine-less subunits of the transporter associated with antigen processing (TAP1 and TAP2) by de novo gene assembly. FEBS Lett 533:42–46

Herget M, Oancea G, Schrodt S, Karas M, Tampé R, Abele R (2007) Mechanism of substrate sensing and signal transmission within an ABC transporter: use of a Trojan horse strategy. J Biol Chem 282:3871–3880

Higgins CF, Linton KJ (2004) The ATP switch model for ABC transporters. Nat Struct Mol Biol 11:918–926

Hofacker M, Gompf S, Zutz A, Presenti C, Haase W, van der Does C, Model K, Tampé R (2007) Structural and functional fingerprint of the mitochondrial ATP-binding cassette transporter Mdl1 from *Saccharomyces cerevisiae*. J Biol Chem 282:3951–3961

Hollenstein K, Frei DC, Locher KP (2007) Structure of an ABC transporter in complex with its binding protein. Nature 446:213–216

Hosokawa N, Wada I, Hasegawa K, Yorihuzi T, Tremblay LO, Herscovics A, Nagata K (2001) A novel ER alpha-mannosidase-like protein accelerates ER-associated degradation. EMBO Rep 2:415–422

Hvorup RN, Goetz BA, Niederer M, Hollenstein K, Perozo E, Locher KP (2007) Asymmetry in the structure of the ABC transporter-binding protein complex BtuCD-BtuF. Science 317:1387–1390

Janas E, Hofacker M, Chen M, Gompf S, van der Does C, Tampé R (2003) The ATP hydrolysis cycle of the nucleotide-binding domain of the mitochondrial ATP-binding cassette transporter Mdl1p. J Biol Chem 278:26862–26869

Jensen TJ, Loo MA, Pind S, Williams DB, Goldberg AL, Riordan JR (1995) Multiple proteolytic systems, including the proteasome, contribute to CFTR processing. Cell 83:129–135

Kartner N, Riordan JR, Ling V (1983) Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. Science 221:1285–1288

Karttunen JT, Lehner PJ, Gupta SS, Hewitt EW, Cresswell P (2001) Distinct functions and cooperative interaction of the subunits of the transporter associated with antigen processing (TAP). Proc Natl Acad Sci U S A 98:7431–7436

Keusekotten K, Leonhardt RM, Ehses S, Knittler MR (2006) Biogenesis of functional antigenic peptide transporter TAP requires assembly of pre-existing TAP1 with newly synthesized TAP2. J Biol Chem 281:17545–17551

Knop M, Finger A, Braun T, Hellmuth K, Wolf DH (1996) Der1, a novel protein specifically required for endoplasmic reticulum degradation in yeast. EMBO J 15:753–763

Koch J, Tampé R (2006) The macromolecular peptide-loading complex in MHC class I-dependent antigen presentation. Cell Mol Life Sci 63:653–662

Koch J, Guntrum R, Heintke S, Kyritsis C, Tampé R (2004) Functional dissection of the transmembrane domains of the transporter associated with antigen processing (TAP). J Biol Chem 279:10142–10147

Koch J, Guntrum R, Tampé R (2006) The first N-terminal transmembrane helix of each subunit of the antigenic peptide transporter TAP is essential for independent tapasin binding. FEBS Lett 580:4091–4096

Koppers-Lalic D, Reits EA, Ressing ME, Lipinska AD, Abele R, Koch J, Marcondes Rezende M, Admiraal P, van Leeuwen D, Bienkowska-Szewczyk K et al (2005) Varicelloviruses avoid T cell recognition by UL49.5-mediated inactivation of the transporter associated with antigen processing. Proc Natl Acad Sci U S A 102:5144–5149

Lehner PJ, Surman MJ, Cresswell P (1998) Soluble tapasin restores MHC class I expression and function in the tapasin-negative cell line .220. Immunity 8:221–231

Lilley BN, Ploegh HL (2004) A membrane protein required for dislocation of misfolded proteins from the ER. Nature 429:834–840

Lindquist JA, Jensen ON, Mann M, Hammerling GJ (1998) ER-60, a chaperone with thiol-dependent reductase activity involved in MHC class I assembly. EMBO J 17:2186–2195

Linton KJ (2007) Structure and function of ABC transporters. Physiology (Bethesda) 22:122–130

Lipinska AD, Koppers-Lalic D, Rychlowski M, Admiraal P, Rijsewijk FA, Bienkowska-Szewczyk K, Wiertz EJ (2006) Bovine herpesvirus 1 UL49.5 protein inhibits the transporter associated with antigen processing despite complex formation with glycoprotein M. J Virol 80:5822–5832

Loch S, Tampé R (2005) Viral evasion of the MHC class I antigen-processing machinery. Pflugers Arch 451:409–417

Locher KP, Lee AT, Rees DC (2002) The *E. coli* BtuCD structure: a framework for ABC transporter architecture and mechanism. Science 296:1091–1098

Loo TW, Bartlett MC, Clarke DM (2006a) Transmembrane segment 1 of human P-glycoprotein contributes to the drug-binding pocket. Biochem J 396:537–545

Loo TW, Bartlett MC, Clarke DM (2006b) Transmembrane segment 7 of human P-glycoprotein forms part of the drug-binding pocket. Biochem J 399:351–359

Lou Y, Vitalis TZ, Basha G, Cai B, Chen SS, Choi KB, Jeffries AP, Elliott WM, Atkins D, Seliger B et al (2005) Restoration of the expression of transporters associated with antigen processing in lung carcinoma increases tumor-specific immune responses and survival. Cancer Res 65:7926–7933

Lybarger L, Wang X, Harris MR, Virgin HWT, Hansen TH (2003) Virus subversion of the MHC class I peptide-loading complex. Immunity 18:121–130

McCracken AA, Brodsky JL (2005) Recognition and delivery of ERAD substrates to the proteasome and alternative paths for cell survival. Curr Top Microbiol Immunol 300:17–40

Meusser B, Hirsch C, Jarosch E, Sommer T (2005) ERAD: the long road to destruction. Nat Cell Biol 7:766–772

Molinari M, Calanca V, Galli C, Lucca P, Paganetti P (2003) Role of EDEM in the release of misfolded glycoproteins from the calnexin cycle. Science 299:1397–1400

Neefjes JJ, Momburg F, Hämmerling GJ (1993) Selective and ATP-dependent translocation of peptides by the MHC-encoded transporter. Science 261:769–771

Neumann L, Abele R, Tampé R (2002) Thermodynamics of peptide binding to the transporter associated with antigen processing (TAP). J Mol Biol 324:965–973

Ortmann B, Androlewicz MJ, Cresswell P (1994) MHC class I/beta 2-microglobulin complexes associate with TAP transporters before peptide binding. Nature 368:864–867

Ortmann B, Copeman J, Lehner PJ, Sadasivan B, Herberg JA, Grandea AG, Riddell SR, Tampé R, Spies T, Trowsdale J et al (1997) A critical role for tapasin in the assembly and function of multimeric MHC class I-TAP complexes. Science 277:1306–1309

Pagant S, Kung L, Dorrington M, Lee MC, Miller EA (2007) Inhibiting endoplasmic reticulum (ER)-associated degradation of misfolded Yor1p does not permit ER export despite the presence of a diacidic sorting signal. Mol Biol Cell 18:3398–3413

Papadopoulos M, Momburg F (2007) Multiple residues in the transmembrane helix and connecting peptide of mouse tapasin stabilize the transporter associated with the antigen-processing TAP2 subunit. J Biol Chem 282:9401–9410

Parcej D, Tampé R (2007) Caught in the act: an ABC transporter on the move. Structure 15:1028–1030

Pinkett HW, Lee AT, Lum P, Locher KP, Rees DC (2007) An inward-facing conformation of a putative metal-chelate-type ABC transporter. Science 315:373–377

Ploegh HL (1998) Viral strategies of immune evasion. Science 280:248–253

Rabinovich E, Kerem A, Frohlich KU, Diamant N, Bar-Nun S (2002) AAA-ATPase p97/Cdc48p, a cytosolic chaperone required for endoplasmic reticulum-associated protein degradation. Mol Cell Biol 22:626–634

Schmitt L, Tampé R (2002) Structure and mechanism of ABC transporters. Curr Opin Struct Biol 12:754–760

Schrodt S, Koch J, Tampé R (2006) Membrane topology of the transporter associated with antigen processing (TAP1) within an assembled functional peptide-loading complex. J Biol Chem 281:6455–6462

Seliger B, Ritz U, Abele R, Bock M, Tampe R, Sutter G, Drexler I, Huber C, Ferrone S (2001) Immune escape of melanoma: first evidence of structural alterations in two distinct components of the MHC class I antigen processing pathway. Cancer Res 61:8647–8650

Shepherd JC, Schumacher TN, Ashton-Rickardt PG, Imaeda S, Ploegh HL, Janeway CA Jr, Tonegawa S (1993) TAP1-dependent peptide translocation in vitro is ATP dependent and peptide selective. Cell 74:577–584

Smith PC, Karpowich N, Millen L, Moody JE, Rosen J, Thomas PJ, Hunt JF (2002) ATP binding to the motor domain from an ABC transporter drives formation of a nucleotide sandwich dimer. Mol Cell 10:139–149

Spies T, DeMars R (1991) Restored expression of major histocompatibility class I molecules by gene transfer of a putative peptide transporter. Nature 351:323–324

Sun F, Zhang R, Gong X, Geng X, Drain PF, Frizzell RA (2006) Derlin-1 promotes the efficient degradation of the cystic fibrosis transmembrane conductance regulator (CFTR) and CFTR folding mutants. J Biol Chem 281:36856–36863

Takahashi N, Morita M, Maeda T, Harayama Y, Shimozawa N, Suzuki Y, Furuya H, Sato R, Kashiwayama Y, Imanaka T (2007) Adrenoleukodystrophy: subcellular localization and degradation of adrenoleukodystrophy protein (ALDP/ABCD1) with naturally occurring missense mutations. J Neurochem 101:1632–1643

Tan P, Kropshofer H, Mandelboim O, Bulbuc N, Hämmerling GJ, Momburg F (2002) Recruitment of MHC class I molecules by tapasin into the transporter associated with antigen processing-associated complex is essential for optimal peptide loading. J Immunol 168:1950–1960

Uebel S, Kraas W, Kienle S, Wiesmuller KH, Jung G, Tampe R (1997) Recognition principle of the TAP transporter disclosed by combinatorial peptide libraries. Proc Natl Acad Sci U S A 94:8976–8981

van Endert PM, Tampe R, Meyer TH, Tisch R, Bach JF, McDevitt HO (1994) A sequential model for peptide binding and transport by the transporters associated with antigen processing. Immunity 1:491–500

Wakabayashi K, Nakagawa H, Tamura A, Koshiba S, Hoshijima K, Komada M, Ishikawa T (2007) Intramolecular disulfide bond is a critical check point determining degradative fates of ATP-binding cassette (ABC) transporter ABCG2 protein. J Biol Chem 282:27841–27846

Wang X, Ye Y, Lencer W, Hansen TH (2006) The viral E3 ubiquitin ligase mK3 uses the Derlin/p97 endoplasmic reticulum-associated degradation pathway to mediate down-regulation of major histocompatibility complex class I proteins. J Biol Chem 281:8636–8644

Wang X, Herr RA, Chua WJ, Lybarger L, Wiertz EJ, Hansen TH (2007) Ubiquitination of serine, threonine, or lysine residues on the cytoplasmic tail can induce ERAD of MHC-I by viral E3 ligase mK3. J Cell Biol 177:613–624

Ward CL, Omura S, Kopito RR (1995) Degradation of CFTR by the ubiquitin-proteasome pathway. Cell 83:121–127

Wiertz E, Hill A, Tortorella D, Ploegh H (1997) Cytomegaloviruses use multiple mechanisms to elude the host immune response. Immunol Lett 57:213–216

Yan FF, Lin CW, Cartier EA, Shyng SL (2005) Role of ubiquitin-proteasome degradation pathway in biogenesis efficiency of {beta}-cell ATP-sensitive potassium channels. Am J Physiol Cell Physiol 289:C1351–C1359

Ye Y, Meyer HH, Rapoport TA (2001) The AAA ATPase Cdc48/p97 and its partners transport proteins from the ER into the cytosol. Nature 414:652–656

Ye Y, Shibata Y, Yun C, Ron D, Rapoport TA (2004) A membrane protein complex mediates retro-translocation from the ER lumen into the cytosol. Nature 429:841–847

Zaitseva J, Oswald C, Jumpertz T, Jenewein S, Wiedenmann A, Holland IB, Schmitt L (2006) A structural analysis of asymmetry required for catalytic activity of an ABC-ATPase domain dimer. EMBO J 25:3432–3443

Zolnerciks JK, Wooding C, Linton KJ (2007) Evidence for a Sav1866-like architecture for the human multidrug transporter P-glycoprotein. FASEB J (in press)