The ABCs of Immunology: Structure and Function of TAP, the Transporter Associated with Antigen Processing

Rupert Abele and Robert Tampé
Institute of Biochemistry, Biozentrum Frankfurt, Johann Wolfgang Goethe-University, D-60439 Frankfurt am Main, Germany tampe@em.uni-frankfurt.de

The transporter associated with antigen processing (TAP) is essential for peptide delivery from the cytosol into the lumen of the endoplasmic reticulum (ER), where these peptides are loaded on major histocompatibility complex (MHC) I molecules. Loaded MHC I leave the ER and display their antigenic cargo on the cell surface to cytotoxic T cells. Subsequently, virus-infected or malignantly transformed cells can be eliminated. Here we discuss the structure, function, and mechanism of TAP as a central part of the peptide-loading complex. Furthermore, aspects of virus and tumor escape strategies are presented.

The Adaptive Immune System

To protect ourselves against various pathogens, two divisions of defense have evolved in vertebrates. The innate immune system present in all metazoa is the first and immediate barrier for invading microbes. This system is encoded by genes of the host germ line and recognizes molecular surface patterns shared by many microbes that are not present in the metazoa host. The adaptive immune system, which is found only in vertebrates, is encoded by gene elements that somatically rearrange. This results in the assembly of antigen-binding molecules specific for structures of intra- or extracellular pathogens. However, the innate and adaptive immune systems are interconnected.

In the adaptive immune system, two sets of cells have evolved for antigen recognition: B and T cells. The B cells carry the antigen-specific B cell receptor on their cell surface. The B cells deal with the humoral immune response. After activation of these cells, antibodies, such as the soluble form of the B cell receptor, are released to label the antigen for degradation by macrophages or other immune accessory cells. The cellular immune response is orchestrated by T cells. These cells recognize antigenic peptides presented on the surface of host cells by major histocompatibility complex (MHC) molecules.

There are two branches of MHC molecules. MHC I molecules are type I membrane glycoproteins found on all nucleated cells. MHC I molecules mainly present peptides of endogenous proteins to CD8+ cytotoxic T cells. These T cells scan the peptide repertoire on the cell surface of the target cell and eventually kill cells that present nonself peptides derived from endogenous pathogens or mutated proteins. MHC II molecules found only on the cell surface of specialized immune cells present peptide fragments of exogenous proteins. CD4+ T helper cells recognize peptide-MHC II complexes and stimulate B cells to produce antibodies. The dogma that peptides derived from endogenous pathogens are presented by MHC I and that peptides from exogenous pathogens are displayed by MHC II has recently been challenged. In some professional antigen-presenting cells (e.g., dendritic cells), peptides from exogenous pathogens are also bound and displayed by MHC I in an alternative processing and presentation pathway (65).

MHC I Assembly Pathway

Generally, endogenous proteins are degraded in the cytoplasm by the proteasome to a length of 3–22 residues (FIGURE 1). After interferon-γ stimulation, as in the case of inflammation, immunoproteasomes are formed (12). The immunoproteasome switches the degradation pattern by exchanging the catalytically active subunits and by partially changing the cap structures (26), thus resulting in a higher quantity of antigenic peptides with COOH-terminal amino acids preferred by MHC I (14). However, most of these peptides have to be trimmed by amino exopeptidases in the cytosol and/or lumen of the endoplasmic reticulum (ER) for MHC I binding (12). Some of these peptides are delivered by the transporter associated with antigen processing (TAP) under consumption of ATP from the cytosol into the lumen of the ER. Interestingly, only a small fraction of the protein fragments produced by the proteasome are transported by TAP and loaded onto MHC I.

In elegant experiments, Princiotta and colleagues (77) have shown that on average the degra-
The presence of 1 out of 2,000 proteins leads to a peptide-loaded MHC I on the cell surface. Folding and loading of MHC I with peptides requires the interplay of various ER-resident chaperones. MHC I heavy chain (45 kDa) is cotranslationally inserted in the ER membrane and glycosylated. Calnexin and the immunoglobulin-binding protein (BiP) interact transiently with the newly synthesized heavy chain, promoting folding and assembly with soluble β₂-microglobulin. Calnexin is replaced by calreticulin after the heterodimer of heavy chain and β₂-microglobulin has folded and assembled correctly. Together with the oxioreductase ERp57, tapasin, and TAP, this complex forms the peptide-loading complex.

The human MHC I heavy chain genes are located on three loci of chromosome 6 and are called human leukocyte antigen (HLA)-A, -B, and -C. Up to six different MHC I heavy chains can be found per individual, because both alleles are expressed and all of these loci show a high polymorphism. Peptides with a length from 8 to 10 amino acids bind in a groove formed by two flanking α-helices sitting on a β-sheet of the α1- and α2-domains of the heavy chain. They are bound to MHC I by the free NH₂ and COOH terminals of the peptide and two to three anchor residues. The peptide specificity of MHC I is determined by these anchor residues, which include most often the COOH-terminal residue of the peptide and one or two additional residues of the peptide. Upon peptide binding, MHC I is released from the loading complex and translocated via the Golgi apparatus to the cell surface. Cytotoxic T cells scan the MHC I-bound peptide via the T cell receptor in combination with the CD8 co-receptor. Cells exposing peptides derived from non self proteins or mutated self proteins are recognized and eliminated by cytotoxic T cells.

For presentation of extracellular antigens via MHC I, two different cross-presentation pathways are discussed: 1) Extracellular antigens are taken up by phagocytosis or endocytosis and are released from phagosomes or endosomes into the cytosol, where they enter the classical MHC I pathway (1, 30, 37). 2) Exogenous antigens are internalized and degraded in a specialized endosomal compartment. Subsequently, the peptides bind to empty MHC I derived by internalization or delivered from the ER in complex with the invariant chain that normally targets MHC II to this compartment. Loaded MHC I will be transported to the cell surface, presenting...
protein fragments from exogenous antigens (63).

**TAP as Central Part of the Peptide-Loading Complex**

A focal element of the MHC I pathway is formed by the peptide-loading complex. This macromolecular machinery is built by TAP associated with four tapasin and four MHC I molecules (72). Furthermore, the lectin-like chaperones calreticulin, calnexin, and the oxidoreductase ERp57 were found to be associated in this complex in variable ratios. The functions of the auxiliary proteins of the loading complex for loading of MHC I are still under intensive investigation. Calreticulin seems to be important for the stabilization of the loading complex and could be involved in concert with the other accessory proteins in optimization of peptide loading of MHC I (23, 90). ERp57 in the loading complex is covalently linked to tapasin via a labile disulfide bridge (20). This thiol-dependent oxidoreductase is found to be associated first with calnexin and heavy chain during MHC I maturation. In a later stage, ERp57 seems to be responsible in the peptide-loading complex for formation of the correct disulfide bonds of MHC I (58, 59). The type I membrane glycoprotein tapasin fulfills several functions:

- **It works as a facilitator or editor of peptide binding to some MHC I** (54, 95, 97). Cells missing tapasin have a reduced surface expression of loaded MHC I (56). Moreover, peptide-bound MHC I shows a decreased cell surface stability in the absence of tapasin (28, 78). Surprisingly, the binding affinities of the MHC I-associated peptides are not altered in the presence or absence of tapasin (97). However, the number and varieties of bound peptides are increased when tapasin is associated with MHC I.

- **It retains unloaded MHC I in the ER** (82).

- **It recruits the other members of the loading complex** (88).

- **It increases the local concentration of peptides for MHC I loading by bridging TAP with MHC I.**

- **It stabilizes TAP by increasing the half-life, resulting in higher amount of TAP and subsequently higher peptide transport rate** (8, 56, 79). The $K_m$ value for peptide transport of TAP is not affected by tapasin. The influence of tapasin on peptide binding of TAP is controversially discussed (57, 79).

TAP also fulfills the function of a chaperone for the members of the loading complex. The assembly of MHC I with ERp57, calreticulin, and tapasin is less efficient in the absence of TAP than in its presence (66). Moreover, MHC I adopts a different conformation in the absence of TAP than in its presence (73). TAP may also serve as a relay to transmit a signal for dissociation of peptide-loaded MHC I. This model is supported by the finding that peptide-mediated dissociation of MHC I from the loading complex is blocked when no nucleotide is bound to rat TAP (45). The lateral mobility of the loading complex in the ER membrane is also strongly influenced by the activity of TAP, most likely reflecting different conformations of TAP. The mobility of the loading complex increases when TAP is inactive and decreases when ATP and peptide are present (80).

**Structural Organization of the TAP Complex**

TAP belongs to the large family of ATP-binding cassette (ABC) transporters, which, under consumption of ATP, translocate a vast variety of solutes across membranes (33). ABC transporters can be found in each organism. Common to all ABC transporters is a four-domain structure with two hydrophobic transmembrane domains (TMDs) and two hydrophilic nucleotide-binding domains (NBDs). The TMDs provide the passage of solutes and the substrate-binding site in the case of exporters. The two NBDs are located in the cytoplasm and are characterized by the highly conserved Walker A, Walker B, and C loop sequences, which are involved in ATP binding and/or hydrolysis.

The peptide transporter TAP forms a heterodimer consisting of TAP1 and TAP2 (50). Both subunits are essential for antigen processing (76, 87). TAP is localized in the ER and cis-Golgi (44). Neither an NH$_2$-terminal signal peptide for ER import nor a retention signal for any subunit is known. TAP1 and TAP2 are composed of an NH$_2$-terminal TMD followed by a COOH-terminal NBD (FIGURE 2). The topology of TAP is still under controversial discussion. As determined by hydrophobicity analysis and sequence comparison with members of the ABC-B subfamily, TAP1 and TAP2 contain 10 and 9 transmembrane helices, respectively. Only the last six transmembrane helices of both subunits show sequence homology to other ABC transporters. Strikingly, a peptide transporter missing these NH$_2$-terminal domains of four and three putative transmembrane helices of TAP1 and TAP2 (FIGURE 2), respectively, is fully active with respect to peptide binding and transport (46). The NH$_2$-terminal extensions are involved in recruitment of tapasin. The peptide-binding region is localized to the last
The NBDs of TAP convert the energy of ATP hydrolysis to peptide transport. Recently, the X-ray structure of the NBD of TAP1 in complex with MgADP was published (24). Like other NBDs of bacterial ABC transporters, the NBD forms an L-shaped structure. The longer arm I is built up by a mixed α-β structure and contains the Walker A and B sequences as well as the highly conserved D loop and switch region (also called the H loop). The shorter arm II is composed of an α-helical domain bearing the Q loop and C loop. Structural and biochemical studies provide evidence that the NBDs form a dimer in the presence of MgATP (16, 21, 36, 39, 61, 86). Two molecules of ATP are sandwiched at the interface of both subunits where the Walker A and B loops from one subunit and the C loop of the other subunit are binding one ATP (FIGURE 3).

Peptide Binding and Transport: A Question of Affinity, Specificity, and Diversity

A prerequisite for peptide transport is peptide binding to TAP. This step is ATP independent (6, 93). In contrast, peptide transport strictly requires ATP hydrolysis (67). TAP most efficiently binds peptides with a length of 8–16 amino acids, whereas the most efficient transport is restricted to peptides with 8–12 amino acids (6, 93). However, peptides with a length up to 40 amino acids as well as sterically restricted peptides are transported via TAP (29, 70, 92).

With the help of combinatorial libraries, the peptide specificity of TAP was deciphered (91). For binding, the first three and the COOH-terminal residues are important. Obviously, there is a coevolution between the cleavage selectivity of the immunoproteasome and the binding specificity of TAP, MHC I, and the T cell receptor. The immunoproteasome produces peptides with COOH-terminal residues favored for TAP and MHC I binding. The preference for the NH2-terminal residues differs between TAP and MHC I. Therefore, an NH2-terminal trimming by ER-resident proteases has to take place (84). The sequence in between both ends of the peptides presented to the T cell receptor can be highly promiscuous with respect to TAP and MHC I binding. This ensures that a limited set of peptide transporter and MHC I molecules can offer a maximal peptide diversity, protecting the organ-
The peptide binding is composed of a fast, probably diffusion-controlled peptide association, followed by a slow structural rearrangement, which includes ~25% of the residues of TAP (68, 70). The conformational change might be the switch to activate the ATP hydrolysis. With TAP reconstituted in proteoliposomes, the direct coupling between peptide binding, ATP hydrolysis, and, subsequently, peptide transport was proven (27). The $K_m$ for ATP is 0.3 mM, and the turnover number for ATP hydrolysis is 5 ATP per second per TAP. If two ATPs are hydrolyzed per transported peptide as reported for the OpuA system of Lactococcus lactis (74) and the molecules of TAP are estimated at $10^9$ molecules per cell, then the delivery of peptides into the lumen of the ER is not the rate-limiting step in the MHC I presentation pathway.

**Functional Asymmetry of the TAP Subunits**

The ATP hydrolysis of the single subunits in the TAP complex during peptide transport was deciphered in so-called BeF$_4^-$ trapping experiments where, after ATP hydrolysis, inorganic phosphate is replaced by BeF$_4^-$, which together with MgADP forms a very stable complex in the nucleotide-binding pocket (17). Subsequently, nontrapped nucleotides are washed out and trapped nucleotides are covalently cross-linked to TAP by using photoactive nucleotide analogs. Applying this method, it became clear that both subunits hydrolyze ATP during peptide transport. The ATPase activity of both subunits is stimulated in the presence of peptide in the same way, suggesting an equal contribution of both NBDs for peptide transport. However, the nonequivalence of both subunits was derived from mutational studies. Exchanging the NBDs of TAP1 and TAP2 resulted in a chimeric peptide transporter with transport activity (7, 18). In contrast, TAP complexes harboring two identical NBDs translocated peptides with strong lowered efficiency. Moreover, mutating the highly conserved lysine residue in the Walker A sequence (ATP binding site II) abrogates peptide transport, whereas the same mutation in TAP1 (site I) showed a decreased transport activity as reported in two out of three studies (42, 52, 81). Site I is defined as the ATP binding pocket composed of residues of the Walker A and B motifs of NBD1 and the C loop of NBD2 (FIGURE 2). Whether the asymmetry is also reflected in the nucleotide-binding properties of the two subunits is under discussion. Nucleotide binding was analyzed by 8-azido-nucleotide photocrosslinking or nucleotide-agarose binding to single expressed subunits or TAP complexes of wild-type or mutated TAP (4, 17, 42, 52, 53, 81). Some groups report that TAP2 binds preferentially ADP, whereas TAP1 binds both. Other publications show that TAP1 and TAP2 bind ATP and ADP with approximately the same affinity. Moreover, it is discussed that site II (Walker A of TAP2) is in a closed state with a very slow dissociation kinetic for nucleotides. The nonequivalence of both NBDs is reflected in sequence variations in the highly conserved regions of ABC transporters (FIGURE 4). Sequence comparison of the regions of NBD1 and NBD2 involved in ATP binding with other NBDs reveals that the most significant deviations occur in site I. In TAP1, the catalytic base of the Walker B (usually

---

**FIGURE 2. Model of the ATP-bound dimer of NBD1 and NBD2**

NBD1 (residues 502–720) and NBD2 (residues 467–680) of TAP were modeled by using the structure of MJ0796 (PDB entry 1L2T) as template via the Swiss-Model web server (83). The figure was generated using PyMOL (http://www.pymol.org). The helices of arm II of NBD1 and NBD2 are colored orange and olive, respectively. The Walker A and C loop sequences are marked in black. Site I and site II, defined as ATP-binding pocket composed of residues of the Walker A and B motif of NBD1 and the C loop of NBD2 and vice versa, are indicated with circles. The 2 sandwiched ATP molecules are shown in stick presentation. The model is viewed along normal toward the cytosol.
glutamate) is replaced by aspartate and the central histidine of the H loop by glutamine. This histidine contacts the γ-phosphate of ATP and is essential for substrate transport in different ABC transporters (38, 85, 94). The C loop in TAP2, which interacts with the γ-phosphate of ATP bound to site I, is degenerated to LAAGQ instead of LSGGQ. Mainly, the exchange of the serine, which along with the second glycine is the residue with the highest conservation in the region and forms contact with the γ-phosphate, seems to regulate the ATPase activity as shown for other ABC transporters (13, 35). Recently, it was also shown that the nonhomologous COOH-terminal tails of both subunits affect the distinct nucleotide-binding behavior (11). Furthermore, it seems that the COOH terminals are regulatory elements in the coordinated process of ATP hydrolysis.

**Transport Mechanism of TAP**

We propose the following model (FIGURE 5) of a peptide transport mechanism of TAP: Peptide and ATP bind independently to TAP (step 1). However, in living cells TAP will be loaded with ATP because the ATP concentration in the cytosol (1–10 mM) is far above the affinity for ATP (~5 μM) (53). ATP binding is sensed by the Q loop and induces a rigid body movement of arm II of the NBD, which enables the movement of arm II of the NBD, which enables the ATP to bind independently to TAP (step 2). Peptide binding (step 3) induces a structural rearrangement in the TMDs of both subunits (step 4), which weakens the interaction between the L and Q loops (68, 70). As a result, the ATP-loaded NBDs form a dimer, which subsequently induces peptide release into the ER lumen (step 5). ATP hydrolysis and phosphate release first at the NBD2 (step 6) weaken the interaction of the NBDs (36, 39, 86). After dimer dissociation (step 7), ADP is released and replaced by ATP (step 8). Obviously, ATP at NBD2 is hydrolyzed first because 1) the ATP-binding site II is composed of canonical ABC transporter sequences, whereas the ATP-binding site I shows deviations as discussed above, probably resulting in a decreased ATP hydrolysis rate, and 2) mutation in Walker A of NBD2 (site II) disrupts peptide transport, whereas the same mutation in NBD1 (site I) is still active (42, 52). Remarkably, ATP hydrolysis in NBD2 is sufficient for peptide transport by weakening the dimer interface. ATP hydrolysis in NBD1 alone does not interrupt dimer interface, or ATP can only be hydrolyzed at NBD1 after ATP hydrolysis occurred at NBD2. The movement of the NBDs during dimerization can be very small, as speculated from the X-ray structure of the vitamin B12 transporter (60).

**Malfunction of TAP in Human Diseases**

Different mechanisms for TAP-dependent inhibition of antigen presentation have evolved, which are reflected in genetic diseases, tumor development, and viral infections.

Bare lymphocyte syndrome (BLS) I is a rare genetic disease in which the cell surface expression of MHC I is drastically reduced (51). The reduced MHC I level is manifested in necrotizing granulomatous skin lesions and recurrent bacterial infections, mostly of the respiratory tract. In one subgroup of BLS I, this disease is due to a defect in TAP1 or TAP2. The defect in TAP1 is caused by a frame shift in the first third of the coding sequence. Interestingly, in these patients TAP2 cannot be detected either, which is in agreement with observations that TAP2 stability is drastically increased in the absence of TAP1.
in the presence of TAP1 (32). Defective TAP2 generated by a premature stop codon is found in siblings homozygous for this defect. Surprisingly, these patients showed no increased susceptibility for viral infections (19).

Many tumors escape the cytotoxic T cell recognition by shutting down peptide delivery. Depending on the tumor cell line, the defective peptide transport results from different mechanisms. Often low levels of TAP1 and/or TAP2 mRNA are detected, which can be restored by interferon-γ treatment (40, 64). Recently in one melanoma cell line, a strongly reduced TAP1 mRNA level was discovered that could not be restored by interferon-γ treatment (86). The deficient expression of TAP is due to a single nucleotide deletion at position 1489 of tap1, resulting in higher instability of the TAP1 mRNA. Also, mutations of TAP genes can lead to tumor escape as reported for a small-cell lung cancer (15). These cells express normal levels of TAP. However, a mutation in the tap1 gene exchanging residue 659 located between the C loop and the Walker B sequence disrupts peptide transport.

In addition to other members of the antigen-presenting machinery, TAP is also a potent target for viral escape strategies. Some viruses, such as adenovirus 12 E1A and the human papillomavirus, inhibit peptide transport by downregulation of TAP expression (25). The factors of both oncogenic DNA viruses, which inhibit TAP expression, exhibit a significant similarity in structure and function.

Proteins from herpes simplex virus 1 and 2 (HSV) and cytomegalovirus that inhibit peptide delivery into the ER lumen by direct interaction with TAP were identified (2, 22, 31, 34, 55). The cytosolic protein ICP47 from HSV inhibits peptide binding in a competitive manner (3, 89). For TAP inhibition, the NH2-terminal region of the immediate early gene product is sufficient (69). The active domain is unstructured in aqueous solution and forms a helix-loop-helix structure at lipid interfaces (9, 75).

The type I membrane glycoprotein US6 from human cytomegalovirus binds with its ER luminal domain, most likely to the short ER luminal loops of the core TAP complex (FIGURE 2) (46). The ER luminal domain of US6 is sufficient to inhibit TAP function (2). US6 impedes ATP binding but not ADP binding to TAP, with an IC50 value of 1 μM, which results in peptide transport deficiency (32, 49). Obviously, US6 induces a structural rearrangement in TAP over a distance of >5 nm.

The mK3 protein from herpesvirus 68 and the E19 protein from adenovirus inhibit the antigen-presenting machinery by interacting with TAP without affecting peptide transport (10, 62). In the case of mK3, the interaction is needed for ubiquitination and subsequent degradation of TAP/tapasin-associated MHC I. Binding of E19 interrupts the tapasin-TAP interaction, resulting in ineffective MHC I loading.

Recently, defects of peptide transport in HIV- or bovine herpes virus-infected human cells and pseudorabies virus-infected porcine cells have been reported (5, 47, 48). However, the factors and the molecular mechanisms of transport inhibition for these viruses have yet to be elucidated. 

We thank Dr. Lutz Schmitt for help with the PyMOL presentations and for helpful discussions as well as Christine Le Gal for preparation of the manuscript.

The Deutsche Forschungsgemeinschaft, via grants of the SFB 628 - Functional Membrane Proteomics division, has supported our work.

References

5. Ambagala AP, Hinkley S, and Srikumaran S. An

10. Bennett EM, Bennink JR, Yewdell JW, and

12. Brooks P, Murray RZ, Mason GG, Hendil KB, and

16. Chen J, Lu G, Lin J, Davidson AL, and Quiao FA. A
tweezer-like motion of the ATP-binding

ATP hydrolysis at both subunits of the transporter associated

18. Daumke O and Knittler MR. Functional asymmetry
of the ATP-binding-cassettes of the ABC trans-
porter TAP is determined by intrinsic properties of


21. Fetsch EE and Davidson AL. Vanadate-catalyzed
photocleavage of the signature motif of an ATP-


23. Higgins CF. ABC transporters: from microorgan-

24. Hill A, Jugovic P, York I, Russ G, Bennink J, Yewdell J, Ploegh H, and Johnson D. Herpes simple-

virus turns off the TAP to evade host immu-

25. Hoof T, Demmer A, Hadam MR, Riordan JR, and


27. Houde M, Bertholet S, Gagnon E, Brunet S, Gayette G, Laplante A, Prince MF, Thibault P, Sacks D, and Desjardins M. Phagosomes are com-

28. Grandea AG 3rd, Lehner PJ, Cresswell P, and

29. Higgins CF. ABC transporters: from microorgan-


virus turns off the TAP to evade host immu-

31. Hoof T, Demmer A, Hadam MR, Riordan JR, and

32. Horn C, Bremer E, and Schmitt L. Nucleotide

33. Higgins CF. ABC transporters: from microorgan-

34. Hill A, Jugovic P, York I, Russ G, Bennink J, Yewdell J, Ploegh H, and Johnson D. Herpes simple-

virus turns off the TAP to evade host immu-

35. Hoof T, Demmer A, Hadam MR, Riordan JR, and

36. Horn C, Bremer E, and Schmitt L. Nucleotide
51. Lankat-Buttgereit B and Tampé R. The trans-
49. Kyritsis C, Gorbulev S, Hutschenreiter S, 
53. Lapinski PE, Raghuraman G, and Raghavan M. 
54. Lauvau G, Gubler B, Cohen H, Daniel S, Caillat-
64. Matsui M, Machida S, Itani-Yohda T, and Akatsuka 
63. MacAry PA, Lindsay M, Scott MA, Craig JI, Luzio JP, and Lehner PJ. Mobilization of MHC class I molecules from late endosomes to the cell sur-
59. Neumann L, Kraas W, Uebel S, Jung G, and 
67. Neefjes JJ, Momburg F , and Hämmerling GJ. 
71. Nijenhuis M and Hämmerling GJ. Multiple 
72. Ortmann B, Copeman J, Lehner PJ, Sadasivan B, 
74. Patzlaff JS, van der Heide T, and Poolman B. The 
75. Phillips RB. Amino acid sequence changes of the MHC class I heavy chain. 
76. Powis SJ, Townsend AR, Deverson EV, Bastin J, 
85. Shyamala V, Baichwal V, Beall E, and Ames GF. 
86. Smith PC, Karpowich N, Millen L, Moody JE, 
87. Spies T and DeMars R. Restored expression of 
88. Spooner R, Wellinger RJ, Piskur J. SWISS-MODEL: an automo-
89. Tomazin R, Hill AB, Jugovic P, York I, van Endert P, 
92. Uebel S, Meyer TH, Kraas W, Kienle S, Jung G, Wiesmuller KH, and Tampé R. Requirements for peptide binding to the human transporter associ-
93. Van Endert PM, Tampé R, Meyer TH, Tisch R, Bach JF, and McDevitt HO. A sequential model for peptide binding and transport by the trans-

PHYSIOLOGY • Volume 19 • August 2004 • www.physiologyonline.org