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The Intracellular Antigen Transport Machinery TAP in Adaptive Immunity and Virus Escape Mechanisms

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The transporter associated with antigen processing (TAP) is a crucial element of the adaptive immune system, which translocates proteasomal degradation products into the endoplasmic reticulum, for transfer of these peptides on major histocompatibility complex (MHC) I molecules within a macromolecular peptide-loading complex. After loading and intracellular transport to the cell surface, these peptide/MHC complexes are monitored by cytotoxic T-lymphocytes. This review summarizes the structural organization and function of the ABC transporter TAP. Furthermore, we discuss human diseases and viral evasion strategies associated with TAP function.

KEY WORDS: ABC transporter; antigen presentation; herpes virus; immune evasion; membrane proteins; transport ATPases; transporter associated with antigen processing; virus persistence.

THE ADAPTIVE IMMUNE SYSTEM

Higher organisms have to protect themselves against the threat due to various pathogens such as bacteria, fungi, parasites, or viruses. During evolution, vertebrates evolved a tripartite protection system based on physical barriers and a highly specific immune system split into two different branches: (i) the innate immunity shaped by macrophages, granulocytes, natural killer cells, and humoral factors, such as lysozyme or C-reactive protein, and (ii) the adaptive immune system, in which destruction of pathogens is mainly based on clonal selection and expansion of antigen-specific B- and T-lymphocytes. In addition, memory cells arise during infection, enabling the immune system to detect and clear off pathogens more efficiently during recurrent infections.

B-lymphocytes bind soluble or matrix-assisted epitopes through their membrane-bound immunoglobulins. These antigens are then internalized, processed, and presented via MHC class II molecules on the surface of B-cells (Bryant and Ploegh, 2004; Trombetta and Mellman, 2005). Recognition of peptide/MHC II complexes by T-helper cells ($CD4^+$) causes the release of various cytokines, which drive differentiation of B-cells into antibody-secreting plasma cells. In contrast, MHC class I molecules present peptide epitopes derived from endogenous proteins, which are then recognized at the cell surface by cytotoxic T-lymphocytes ($CD8^+$) leading to destruction of infected or malignantly transformed cells by apoptosis or cell lysis (Grommé and Neefjes, 2002; Lehner and Cresswell, 2004; Williams *et al*., 2002a). The pathway of MHC I antigen processing is illustrated in Fig. 1.

TAP AS A KEY PLAYER WITHIN THE PEPTIDE-LOADING COMPLEX (PLC)

Usually cells abandon unwanted (damaged, misfolded, or short-lived regulatory) proteins or defective ribo-

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Abbreviations: ABC, ATP-binding cassette; MHC, major histocompatibility complex; NBD, nucleotide-binding domain; TAP, transporter associated with antigen processing; TMD, transmembrane domain.

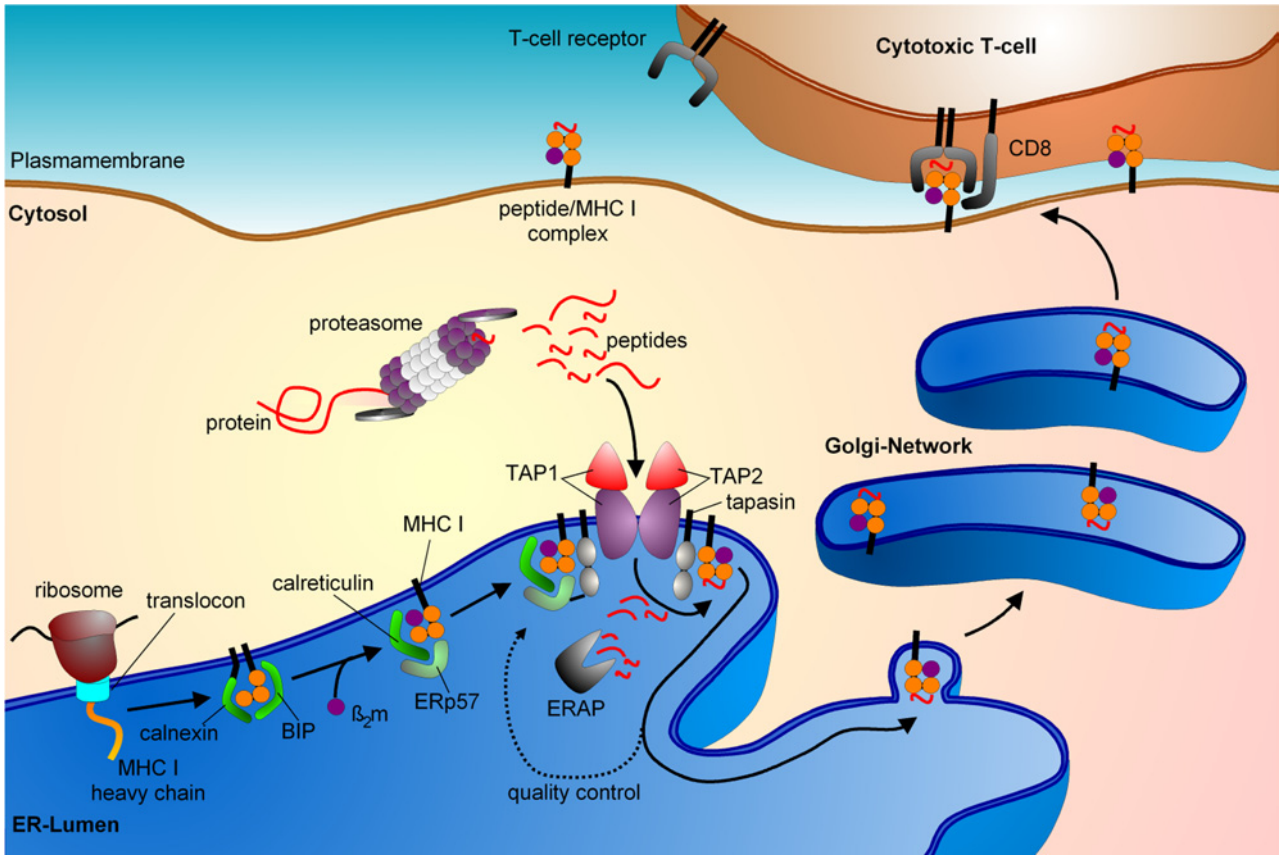

Fig. 1. The antigen-processing pathway via MHC I. *De novo* synthesized MHC I heavy chain initially associates with the chaperones BiP and calnexin and then binds to β_2-mircoglobulin (β_2m). Subsequently, calnexin is replaced by its soluble counterpart calreticulin. Henceforth, this complex is joined by the disulfide isomerase ERp57. Tapasin bridges the MHC I sub-complexes to transporter associated with antigen processing (TAP) leading to the multicomponent peptide-loading complex (PLC). This macromolecular assembly fulfills multiple functions. Peptides derived from proteasomal degradation are specifically recognized and translocated by the transporter TAP1 and TAP2 into the ER lumen, where chaperoning and peptide loading of MHC I occur. Peptides longer than 8–11 residues may be trimmed by the concerted action of the heterodimeric ER-aminopeptidases ERAP1/2. Kinetically stable peptide/MHC I complexes can leave the PLC, successfully pass the ER quality control, are finally are transferred via the Golgi network to cell surface, where they are inspected for their antigenic cargo by cytotoxic T-lymphocytes.

somal products (DRIPs) via ubiquitinylation to proteasomal degradation in the cytosol (Kloetzel, 2004; Yewdell, 2002). In the case of viral infection, especially newly synthesized viral gene products are preferentially degraded by the proteasome (Yewdell *et al*., 2003). A minor fraction of these degradation products are recognized and translocated via the transport complex TAP into the ER-lumen, where these peptides are transferred onto MHC I molecules. This process is assisted by various chaperones, such as tapasin, calreticulin, and the disulfide isomerase ERp57 (Abele and Tampé, 2004; Dick, 2004). Tapasin acts as a putative editor for peptide association with MHC I (Lauvau *et al*., 1999; Momburg and Tan, 2002; Williams *et al*., 2002b; Zarling *et al*., 2003). Loss of tapasin function leads to a reduced surface expression of MHC I (Lehner *et al*., 1998) and to a shortened half-life of TAP (Bangia *et al*., 1999; Garbi *et al*., 2003; Lehner *et al*., 1998; Raghuraman *et al*., 2002). Tapasin is disulfide-linked to ERp57, a thiol-dependent oxidoreductase, which is presumably required for correct disulfide-bond formation within the α_2 domain of MHC I (Dick, 2004; Lindquist *et al*., 2001). Interestingly, MHC I sub-complexes composed of MHC I heavy chain, β_2m, tapasin, ERp57, and calreticulin, bind independently to each TAP subunit in assembling a macromolecular peptide-loading complex (PLC) of approximately 1 MDa, which catalyzes efficient peptide transfer to MHC I (Antoniou *et al*., 2002; Raghuraman *et al*., 2002). Kinetically stable peptide/MHC complexes dissociate from the PLC and migrate to the cell surface via the classical secretion route.

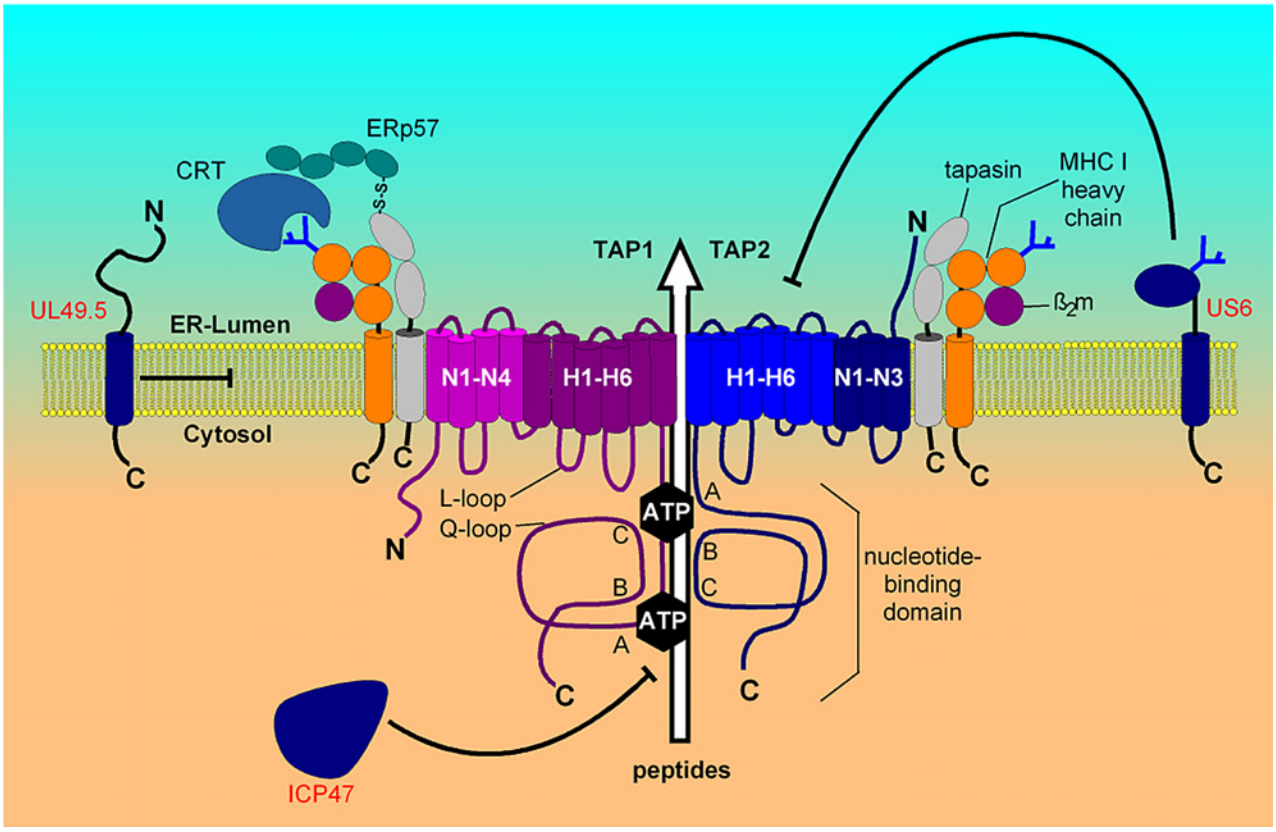

Fig. 2. Model of the peptide-loading complex. The PLC is composed of several proteins such as the TAP1/TAP2 complex, the MHC I heavy chain, β_2m, calreticulin, tapasin, ERp57, and the ER-resident aminopeptidase ERAP1/2. TAP contains a 6 + 6 TM core domain (H1–H6), which aligns the translocation pore. Walker A (A), Walker B (B), and C-loop (C) of the nucleotide-binding domain (NBD) are involved in ATP binding and hydrolysis, providing the energy for transport of antigenic peptides. Interaction of the L-loop with the Q-loop is proposed to link ATP binding/hydrolysis and peptide transport. In addition, viral interference of ICP47 from HSV I, US6 from HCMV, and UL49.5 from BHV with components of the PLC are illustrated (interference is indicated by black lines).

STRUCTURAL ASPECTS OF TAP

The ER-resident TAP complex consists of TAP1 (ABCB2) and TAP2 (ABCB3), both of which belong as "half-transporters" to the ATP-binding cassette (ABC) superfamily (Abele and Tampé, 2004). Common to all ABC transporters, TAP is composed of four major domains, two transmembrane domains (TMD) and two cytosolic nucleotide-binding domains (NBD). The NBDs possess the highly conserved Walker A (consensus sequence: G-X-X-G-X-G-K-S/T), Walker B (ϕ-ϕ-ϕ-ϕ-D; ϕ: hydrophobic amino acid), and characteristic C-loop (L-S-G-G-Q, ABC-signature) motifs, which convert the chemical energy of ATP into conformational changes within the TMDs moving the substrate across the membrane (Schmitt and Tampé, 2002). Recently, the membrane topology of the assembled, functional TAP complex was determined in semi-permeabilized "living" cells by cysteine-scanning mutagenesis and membrane-impermeable, thiol-specific fluorophors (Schrodt *et al.*, submitted). Experimental data together with hydrophobicity predictions and sequence alignments revealed 10 and 9 transmembrane helices for TAP1 and TAP2, respectively (Fig. 2). It has been further demonstrated that a 6 + 6 TM core complex of TAP1 and TAP2 is essential and sufficient for ER targeting, heterodimer assembly, peptide binding and transport, whereas the extra N-terminal domains, $TM_{(N1-N4)}$ of TAP1 and $TM_{(N1-N3)}$ of TAP2, are required for tapasin binding and assembly of the PLC (Koch *et al.*, 2004; 2005). By photo cross-linking experiments, peptide-binding regions have been mapped to the cytosolic loops in the core complex between TM_{H4} and TM_{H5}, and a stretch of 15 residues following TM_{H6} of each subunit (Nijenhuis and Hämmerling, 1996). Interestingly, mutations or polymorphic sites in TAP affecting the peptide specificity of TAP are located at cytosolic loops

or at the cytosolic interface of the membrane (reviewed by McCluskey *et al*., 2004).

Similar to X-ray structures of other ABC-NBDs (Hung *et al*., 1998; Karpowich *et al*., 2001), the NBD of human TAP1 revealed an L-shaped molecule with a RecA-like domain containing the Walker A/B motif and the switch region (H-loop) as well as and an α-helical domain enclosing the C-loop (Gaudet and Wiley, 2001). The conserved glutamine of the Q-loop is postulated to sense bound ATP via coordination of a single water molecule to the γ-phosphate (Chen *et al*., 2003; Smith *et al*., 2002; Zaitseva *et al*., 2005). In addition, the Q-loop contacts the L-loop of the TMD (Locher *et al*., 2002; Reyes and Chang, 2005) and may therefore be involved in the crosstalk of ATP-binding/hydrolysis and peptide translocation. ATP binding induces a slight rotation of the RecA-like domain towards the α-helical domain resulting in an optimal interface for dimer formation (Chen *et al*., 2003; Smith *et al*., 2002; Zaitseva *et al*., 2005). Within the NBD dimer, two ATPs are sandwiched by the Walker A/B motif of one and the C-loop of the opposite NBD (Fetsch and Davidson, 2002; Loo *et al*., 2002; Smith *et al*., 2002). Apart from the NBD of TAP1, no high-resolution structural data are available for the TAP complex. Single particle EM analysis revealed a TAP1/2 complex of approximately 10 nm in diameter with a central pocket of about 3 nm on the predicted ER-luminal side (Velarde *et al*., 2001).

SUBSTRATE SPECIFICITY OF TAP

The peptide binding motif of human TAP has been deciphered by combinatorial libraries (Uebel *et al*., 1997). In addition to free N- and C-termini, the first three N-terminal and the last C-terminal residues of the peptide are highly critical for TAP recognition. In particular, human TAP prefers peptides with hydrophobic or basic amino acids at the C-terminus, which fits well to the binding motif of MHC I molecules. Apart from these "anchor" residues, TAP is highly promiscuous in sequence and length, and hereby does not restrict the antigen diversity in a region, which is later recognized by the T-cell receptor. Thus, under evolutionary pressure of host–pathogen interactions, the immune system has been forced to fine-tune peptide affinity, selectivity, and diversity of TAP. Surprisingly, a functional polymorphism with distinct specificity patterns has been reported only for the rat TAP complex. The rat TAP^u allele sets preference to peptides with hydrophobic residues similar to mouse TAP, while the rat TAP^a allele favors basic and hydrophobic residues at the C-terminus, similar to human TAP (Momburg *et al*., 1994; 1996).

The TAP complex shows a remarkable structural flexibility in substrate recognition. TAP preferentially binds peptides with a length of 8–16 amino acids (Uebel *et al*., 1995; van Endert *et al*., 1994), which matches well with the peptide pool generated by the proteasome. Strikingly, even peptides with very bulky modifications, such as photo-probes, fluorophors, or branched peptides are recognized and transported by TAP (Grommé and Neefjes, 2002; Neumann and Tampé, 1999; Uebel *et al*., 1995). Peptides of 8–12 residues are transported most efficiently, but also the transport of peptides with a length of 40 residues has been observed (Androlewicz and Cresswell, 1994; Koopmann *et al*., 1996). To fit into the binding pocket of MHC I, longer peptides are N-terminally trimmed to 8–9 residues by the ER-resident aminopeptidases ERAP1/2 (Saric *et al*., 2002; Saveanu *et al*., 2005; Serwold *et al*., 2002; York, 2002). In consequence, C-termini created by proteasomal cleavage are in register with the binding motif of the TAP complex and MHC I molecules, and therefore most important to epitope generation.

TRANSPORT MECHANISM OF TAP

The transport mechanism of TAP can be subdivided into peptide binding and translocation steps. Peptide binding is ATP-independent and a multistep process (Androlewicz and Cresswell, 1994; Neumann and Tampé, 1999; Uebel *et al*., 1995; van Endert *et al*., 1994), whereas peptide translocation strictly requires ATP hydrolysis (Androlewicz *et al*., 1993; Meyer *et al*., 1994; Neefjes *et al*., 1993; Shepherd *et al*., 1993). Both subunits are essential and sufficient for peptide binding and translocation (Meyer *et al*., 1994; van Endert *et al*., 1994). Peptides associate with TAP in an initial fast bimolecular reaction followed by a slow structural reorganization of the TAP complex accompanied by very high activation energies for association and dissociation ($\sim$100 and $\sim$80 kJ/mol, respectively) (Neumann *et al*., 2002; Neumann and Tampé, 1999). By functional reconstitution of TAP in proteoliposomes, it has been demonstrated that peptide binding is tightly coupled to ATP hydrolysis (Gorbulev *et al*., 2001). Peptide-dependent ATPase activity follows Michaelis–Menten kinetics with a turnover of approximately 5 ATP/s. The K_d values of peptides directly correlate with the K_m values. ATP photo-crosslinking and nucleotide-trapping experiments provided evidence that peptide binding induces ATP hydrolysis at both TAP subunits. The NBDs of TAP1 and TAP2 can bind ATP or ADP independently (Müller *et al*., 1994). Crystal structures of NBD dimers of other ABC transporters as well as the analysis of different

dimeric intermediates revealed that ATP hydrolysis takes place only in the dimeric state (Janas *et al*., 2003; Smith *et al*., 2002; Verdon *et al*., 2003). However, whether one or two ATPs are hydrolyzed within one transport cycle and at which step the substrate is translocated across the membrane is still a matter of intense discussion (van der Does and Tampé, 2004). Thereby, two principle models are discussed: Crystal structures and trapped intermediates of isolated NBDs led to the processive-clamp model (Janas *et al*., 2003; Smith *et al*., 2002), where two ATPs are sandwiched between two NBDs. In this model, ATP binding and dimer formation drive transport of the peptide. Hydrolysis of two ATPs is required for dissociation of the two NBDs and resetting of the hydrolysis cycle (van der Does and Tampé, 2004). This model is supported by an ATP/substrate stoichiometry of 2:1 determined for the glycine betain ABC transporter OpuA (Patzlaff *et al*., 2003). In contrast, experiments with "transition-state" mutants and vanadate-trapped states of P-glycoprotein or the *E. coli* maltose transporter $MalFGK_2$ established only one nucleotide in the hydrolysis process (Senior *et al*., 1995; Sharma and Davidson, 2000; Urbatsch *et al*., 1995). Hence, the "alternating-site" model was proposed, where ATP hydrolysis occurs only in one catalytic site, followed by the opening of this domain while the second catalytic site remains closed. Reloading of the first site with ATP hydrolysis is initiated in the second catalytic domain (Senior *et al*., 1995). However, negative cooperativity between both catalytic sites has never been observed.

HUMAN DISEASES ASSOCIATED WITH TAP

TAP being a key element of the adaptive immune system, manifold strategies of TAP interference have been established during evolution. Few patients of the rare Bare Lymphocyte Syndrome (BLS) type I are reported to show a deficiency in TAP1 or TAP2 (de la Salle *et al*., 2002; Gadola *et al*., 2000). Genetic TAP defects are characterized by chronic inflammation of the respiratory tract as well as manifestation of necrotizing granulomatous skin lesions. Apart from TAP deficiencies, the role of TAP in autoimmune diseases has been reported, but discussed controversially.

Many tumors escape immune surveillance by downregulation of MHC I presentation of tumor-associated epitopes. In metastatic carcinoma, TAP function is frequently suppressed on the (post) transcriptional and translational level (Chen *et al*., 1996; Lankat-Buttgereit and Tampé, 2002; Seliger *et al*., 1997). Noticeably, the immune recognition of lung carcinomas could be restored *in vivo* by applying recombinant vaccinia or adenoviruses encoding the TAP1 gene (Alimonti *et al*., 2000; Lou *et al*., 2005). These strategies may be considered as part of immunotherapies for the treatment of carcinomas.

Viruses have evolved sophisticated strategies to evade immune surveillance by interfering with TAP function (Loch and Tampé, 2005). Especially DNA viruses, harboring large genomes (120–230 kb) and therefore slow replication rates, established several ways to achieve lifelong persistence in the host cell by blocking antigen presentation. For example, the immediate-early gene product ICP47 from herpes simplex virus (HSV-1) competes with high affinity for peptide binding to TAP, thereby impeding ATP hydrolysis and peptide transport into the ER (Ahn *et al*., 1996; Gorbulev *et al*., 2001). In contrast to ICP47, the early gene product US6 (unique short region) from the human cytomegalovirus (HCMV) binds to TAP via its ER-luminal domain, inhibiting ATP binding to the NBDs on the opposite side of the membrane (Hewitt *et al*., 2001; Kyritsis *et al*., 2001). In consequence, peptide transport is abolished. Most recently, an additional fascinating facette of immune evasion by varicelloviruses has been disclosed. The type I membrane protein UL49.5 (unique long region) from bovine and equine herpesvirus 1 (BHV 1, EHV 1) or pseudorabies virus (PrV), a nonessential envelope protein involved in maturation of the glycoprotein gM, causes a drastic suppression of MHC I cell surface expression by blocking TAP function (Ambagala *et al*., 2004; Koppers-Lalic *et al*., 2005). Inactivation of TAP involves two independent events: (i) inhibition of peptide translocation of the transporter and (ii) proteasomal degradation of TAP mediated by the short cytosolic, C-terminal tail of UL49.5 (Koppers-Lalic *et al*., 2005). These viral factors are not only important tools to study the cell biology of intracellular trafficking and maturation of proteins, but are also instrumental in investigating the structure, function, regulation, and mechanism of TAP as well as the entire PLC. However, key questions about where and how these pathogenic factors exactly bind and modulate TAP function still have to be resolved. Strikingly, no cellular homologues of these viral factors are found in the database. Thus, they appear to be prominent targets in structural biology and pharma research.

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REFERENCES

Abele, R., and Tampé, R. (2004). *Physiology* (*Bethesda*) **19**, 216–224.

Ahn, K., Meyer, T. H., Uebel, S., Sempé, P., Djaballah, H., Yang, Y., Peterson, P. A., Früh, K., and Tampé, R. (1996). *EMBO J.* **15**, 3247–3255.

Alimonti, J., Zhang, Q. J., Gabathuler, R., Reid, G., Chen, S. S., and Jefferies, W. A. (2000). *Nat. Biotechnol.* **18**, 515–520.

Ambagala, A. P., Gopinath, R. S., and Srikumaran, S. (2004). *J. Gen. Virol.* **85**, 349–353.

Androlewicz, M. J., Anderson, K. S., and Cresswell, P. (1993). *Proc. Natl. Acad. Sci. U.S.A.* **90**, 9130–9134.

Androlewicz, M. J., and Cresswell, P. (1994). *Immunity* **1**, 7–14.

Antoniou, A. N., Ford, S., Pilley, E. S., Blake, N., and Powis, S. J. (2002). *Immunology* **106**, 182–189.

Bangia, N., Lehner, P. J., Hughes, E. A., Surman, M., and Cresswell, P. (1999). *Eur. J. Immunol.* **29**, 1858–1870.

Bryant, P., and Ploegh, H. (2004). *Curr. Opin. Immunol.* **16**, 96–102.

Chen, H. L., Gabrilovich, D., Tampé, R., Girgis, K. R., Nadaf, S., and Carbone, D. P. (1996). *Nat. Genet.* **13**, 210–213.

Chen, J., Lu, G., Lin, J., Davidson, A. L., and Quiocho, F. A. (2003). *Mol. Cell* **12**, 651–661.

de la Salle, H., Saulquin, X., Mansour, I., Klayme, S., Fricker, D., Zimmer, J., Cazenave, J. P., Hanau, D., Bonneville, M., Houssaint, E., Lefranc, G., and Naman, R. (2002). *Clin. Exp. Immunol.* **128**, 525–531.

Dick, T. (2004). *Cell. Mol. Life Sci.* (*CMLS*), **61**, 547–556.

Fetsch, E. E., and Davidson, A. L. (2002). *Proc. Natl. Acad. Sci. U.S.A.* **99**, 9685–9690.

Gadola, S. D., Moins-Teisserenc, H. T., Trowsdale, J., Gross, W. L., and Cerundolo, V. (2000). *Clin. Exp. Immunol.* **121**, 173–178.

Garbi, N., Tiwari, N., Momburg, F., and Hämmerling, G. J. (2003). *Eur. J. Immunol.* **33**, 264–273.

Gaudet, R., and Wiley, D. C. (2001). *EMBO J.* **20**, 4964–4972.

Gorbulev, S., Abele, R., and Tampé, R. (2001). *Proc. Natl. Acad. Sci. U.S.A.* **98**, 3732–3737.

Grommé, M., and Neefjes, J. (2002). *Mol. Immunol.* **39**, 181–202.

Hewitt, E. W., Gupta, S. S., and Lehner, P. J. (2001). *EMBO J.* **20**, 387–396.

Hung, L. W., Wang, I. X., Nikaido, K., Liu, P. Q., Ames, G. F., and Kim, S. H. (1998). *Nature* **396**, 703–707.

Janas, E., Hofacker, M., Chen, M., Gompf, S., van der Does, C., and Tampé, R. (2003). *J. Biol. Chem.* **278**, 26862–26869.

Karpowich, N., Martsinkevich, O., Millen, L., Yuan, Y. R., Dai, P. L., MacVey, K., Thomas, P. J., and Hunt, J. F. (2001). *Structure* (*Camb*) **9**, 571–586.

Kloetzel, P. M. (2004). *Nat. Immunol.* **5**, 661–669.

Koch, J., Guntrum, R., Heintke, S., Kyritsis, C., and Tampé, R. (2004). *J. Biol. Chem.* **279**, 10142–10147.

Koch, J., Guntrum, R., and Tampé, R. (2005). *FEBS Lett.* **579**, 4413–4416.

Koopmann, J. O., Post, M., Neefjes, J. J., Hämmerling, G. J., and Momburg, F. (1996). *Eur. J. Immunol.* **26**, 1720–1728.

Koppers-Lalic, D., Reits, E. A., Ressing, M. E., Lipinska, A. D., Abele, R., Koch, J., Marcondes Rezende, M., Admiraal, P., van Leeuwen, D., Bienkowska-Szewczyk, K., Mettenleiter, T. C., Rijsewijk, F. A., Tampé, R., Neefjes, J., and Wiertz, E. J. (2005). *Proc. Natl. Acad. Sci. U.S.A.* **102**, 5144–5149.

Kyritsis, C., Gorbulev, S., Hutschenreiter, S., Pawlitschko, K., Abele, R., and Tampé, R. (2001). *J. Biol. Chem.* **276**, 48031–48039.

Lankat-Buttgereit, B., and Tampé, R. (2002). *Physiol. Rev.* **82**, 187–204.

Lauvau, G., Gubler, B., Cohen, H., Daniel, S., Caillat-Zucman, S., and van Endert, P. M. (1999). *J. Biol. Chem.* **274**, 31349–31358.

Lehner, P. J., and Cresswell, P. (2004). *Curr. Opin. Immunol.* **16**, 82–89.

Lehner, P. J., Surman, M. J., and Cresswell, P. (1998). *Immunity* **8**, 221–231.

Lindquist, J. A., Hämmerling, G. J., and Trowsdale, J. (2001). *FASEB J.* **15**, 1448–1450.

Loch, S., and Tampé, R. (2005). *Pflugers Arch. Eur. J. Physiol.* **451**, 409–417.

Locher, K. P., Lee, A. T., and Rees, D. C. (2002). *Science* **296**, 1091–1098.

Loo, T. W., Bartlett, M. C., and Clarke, D. M. (2002). *J. Biol. Chem.* **277**, 41303–41306.

Lou, Y., Vitalis, T. Z., Basha, G., Cai, B., Chen, S. S., Choi, K. B., Jeffries, A. P., Elliott, W. M., Atkins, D., Seliger, B., and Jefferies, W. A. (2005). *Cancer Res.* **65**, 7926–7933.

McCluskey, J., Rossjohn, J., and Purcell, A. W. (2004). *Curr. Opin. Immunol.* **16**, 651–659.

Meyer, T. H., van Endert, P. M., Uebel, S., Ehring, B., and Tampé, R. (1994). *FEBS Lett.* **351**, 443–447.

Momburg, F., Armandola, E. A., Post, M., and Hämmerling, G. J. (1996). *J. Immunol.* **156**, 1756–1763.

Momburg, F., Roelse, J., Howard, J. C., Butcher, G. W., Hämmerling, G. J., and Neefjes, J. J. (1994). *Nature* **367**, 648–651.

Momburg, F., and Tan, P. (2002). *Mol. Immunol.* **39**, 217–233.

Müller, K. M., Ebensperger, C., and Tampé, R. (1994). *J. Biol. Chem.* **269**, 14032–14037.

Neefjes, J. J., Momburg, F., and Hämmerling, G. J. (1993). *Science* **261**, 769–771.

Neumann, L., Abele, R., and Tampé, R. (2002). *J. Mol. Biol.* **324**, 965–973.

Neumann, L., and Tampé, R. (1999). *J. Mol. Biol.* **294**, 1203–1213.

Nijenhuis, M., and Hämmerling, G. J. (1996). *J. Immunol.* **157**, 5467–5477.

Patzlaff, J. S., van der Heide, T., and Poolman, B. (2003). *J. Biol. Chem.* **278**, 29546–29551.

Raghuraman, G., Lapinski, P. E., and Raghavan, M. (2002). *J. Biol. Chem.* **277**, 41786–41794.

Reyes, C. L., and Chang, G. (2005). *Science* **308**, 1028–1031.

Saric, T., Chang, S. C., Hattori, A., York, I. A., Markant, S., Rock, K. L., Tsujimoto, M., and Goldberg, A. L. (2002). *Nat. Immunol.* **3**, 1169–1176.

Saveanu, L., Carroll, O., Lindo, V., Del Val, M., Lopez, D., Lepelletier, Y., Greer, F., Schomburg, L., Fruci, D., Niedermann, G., and van Endert, P. M. (2005). *Nat. Immunol.* **6**, 689–697.

Schmitt, L., and Tampé, R. (2002). *Curr. Opin. Struct. Biol.* **12**, 754–760.

Schrodt, S., Koch, J., and Tampé, R. (submitted for publication). *J. Biol. Chem.*

Seliger, B., Maeurer, M. J., and Ferrone, S. (1997). *Immunol. Today* **18**, 292–299.

Senior, A. E., al-Shawi, M. K., and Urbatsch, I. L. (1995). *FEBS Lett.* **377**, 285–289.

Serwold, T., Gonzales, F., Kim, J., Jacob, R., and Shastri, N. (2002). *Nature* **419**, 480–483.

Sharma, S., and Davidson, A. L. (2000). *J. Bacteriol.* **182**, 6570–6576.

Shepherd, J. C., Schumacher, T. N., Ashton-Rickardt, P. G., Imaeda, S., Ploegh, H. L., Janeway, C. A., Jr., and Tonegawa, S. (1993). *Cell* **74**, 577–584.

Smith, P. C., Karpowich, N., Millen, L., Moody, J. E., Rosen, J., Thomas, P. J., and Hunt, J. F. (2002). *Mol. Cell* **10**, 139–149.

Trombetta, E. S., and Mellman, I. (2005). *Annu. Rev. Immunol.* **23**, 975–1028.

Uebel, S., Kraas, W., Kienle, S., Wiesmüller, K. H., Jung, G., and Tampé, R. (1997). *Proc. Natl. Acad. Sci. U.S.A.* **94**, 8976–8981.

Uebel, S., Meyer, T. H., Kraas, W., Kienle, S., Jung, G., Wiesmuller, K. H., and Tampé, R. (1995). *J. Biol. Chem.* **270**, 18512–18516.

Urbatsch, I. L., Sankaran, B., Weber, J., and Senior, A. E. (1995). *J. Biol. Chem.* **270**, 19383–19390.

van der Does, C., and Tampé, R. (2004). *Biol. Chem.* **385**, 927–933.

van Endert, P. M., Tampé, R., Meyer, T. H., Tisch, R., Bach, J. F., and McDevitt, H. O. (1994). *Immunity* **1**, 491–500.

Velarde, G., Ford, R. C., Rosenberg, M. F., and Powis, S. J. (2001). *J. Biol. Chem.* **276**, 46054–46063.
Verdon, G., Albers, S. V., van Oosterwijk, N., Dijkstra, B. W., Driessen, A. J., and Thunnissen, A. M. (2003). *J. Mol. Biol.* **334**, 255–267.
Williams, A., Peh, C. A., and Elliott, T. (2002a). *Tissue Antigens* **59**, 3–17.
Williams, A. P., Peh, C. A., Purcell, A. W., McCluskey, J., and Elliott, T. (2002b). *Immunity* **16**, 509–520.
Yewdell, J. (2002). *Mol. Immunol.* **39**, 139–146.
Yewdell, J. W., Reits, E., and Neefjes, J. (2003). *Nat. Rev. Immunol.* **3**, 952–961.
York, I. A., York, I. A., Chang, S. C., Saric, T., Keys, J. A., Favreau, J. M., Goldberg, A. L., and Rock, K. L. (2002). *Nat. Immunol.* **3**, 1177–1184.
Zaitseva, J., Jenewein, S., Jumpertz, T., Holland, I. B., and Schmitt, L. (2005). *EMBO J.* **24**, 1901–1910.
Zarling, A. L., Luckey, C. J., Marto, J. A., White, F. M., Brame, C. J., Evans, A. M., Lehner, P. J., Cresswell, P., Shabanowitz, J., Hunt, D. F., and Engelhard, V. H. (2003). *J. Immunol.* **171**, 5287–5295.