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Minireview

Modulation of the antigen transport machinery TAP by friends and enemies

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Abstract The transporter associated with antigen processing (TAP) is a key factor of the major histocompatibility complex (MHC) class I antigen presentation pathway. This ABC transporter translocates peptides derived mainly from proteasomal degradation from the cytosol into the ER lumen for loading onto MHC class I molecules. Manifold mechanisms have evolved to regulate TAP activity. During infection, TAP expression is upregulated by interferon-γ. Furthermore, the assembly and stability of the transport complex is promoted by various auxiliary factors. However, tumors and viruses have developed sophisticated strategies to escape the immune surveillance by suppressing TAP function. The activity of TAP can be impaired on the transcriptional or translational level, by enhanced degradation or by inhibition of peptide translocation. In this review, we briefly summarize existing data concerning the regulation of the TAP complex.

Keywords: ABC transporter; Antigen presentation; Herpes virus; Membrane transport; Peptide-loading complex; Transporter associated with antigen processing; Tumor progression; Viral escape

1. Function of TAP

The transporter associated with antigen processing (TAP) is a central component in the major histocompatibility complex (MHC) class I dependent antigen presentation pathway. TAP translocates peptides derived mainly from proteasomal degradation from the cytosol into the lumen of the endoplasmic reticulum (ER), where these peptides are loaded onto MHC class I molecules (Fig. 1). Stable peptide-MHC complexes are transported to the cell surface to present their antigenic cargo to $CD8^+$-cytotoxic T-lymphocytes. The recognition of viral or tumor antigens leads to an efficient elimination of the infected or malignant cell.

TAP belongs to the family of ATP-binding cassette (ABC) transporters, which translocate a large variety of substrates across membranes driven by ATP hydrolysis [1–3]. Human TAP forms a heterodimer consisting of TAP1 (748 aa) and TAP2 (686 aa) [4]. Both subunits are essential and sufficient for peptide transport [5–7]. TAP is localized in the ER and *cis*-Golgi [8]. Each subunit contains a transmembrane domain (TMD), followed by a cytosolic nucleotide-binding domain (NBD) (Fig. 2). The TMDs comprise the peptide binding pocket and the translocation pathway for the substrate. From hydrophobicity analysis and sequence alignment with P-glycoprotein, 10 and 9 transmembrane helices have been predicted for TAP1 and TAP2, respectively [9]. The peptide-binding pocket is located to a region enclosing the last cytosolic loop and a stretch of 15 residues following the last transmembrane helix of both subunits [10]. Remarkably, TAP1 and TAP2 lacking the first predicated four and three transmembrane helices, respectively, are targeted to the ER membrane and assemble into a fully functional heterodimeric transport complex, demonstrating that the extra N-terminal regions (N-domains) of both subunits are not required for peptide binding and transport [11,12]. These N-terminal regions have been identified to be essential for tapasin binding and the assembly of the peptide-loading complex (see below) [11]. The NBDs containing the highly conserved Walker A/B motifs and the C-loop (ABC-signature) energize peptide transport by ATP binding and hydrolysis.

The transport cycle is a multi-step process composed of ATP and peptide binding, ATP hydrolysis and peptide translocation. Peptide binding follows a two step reaction with a fast association preceding a slow conformational rearrangement, which comprises one-fourth of all residues of TAP [13,14]. A second conformational change seems to occur after ATP binding, since the lateral membrane mobility of TAP decreases drastically in the presence of peptide and ATP [15]. TAP binds and transports most efficiently peptides with a length of 8–16 and 8–12 amino acids, respectively [16,17]. The peptide specificity of TAP is restricted to the three N-terminal residues and the C-terminal residue [18]. The specificity for the C-terminal residue is very similar between the TAP complex, immuno-proteasomes, and MHC class I molecules, suggesting a co-evolution of these factors. However, the length of the peptides as well as the specificity for the N-terminal residue are distinct between TAP, the proteasome

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Abbreviations: ABC, ATP-binding cassette; Ad, adenovirus; BHV, bovine herpes virus; EGFP, enhanced green fluorescent protein; ER, endoplasmic reticulum; HPV, human papillomavirus; HSV, herpes simplex virus; ICP47, infected cell protein 47; IFN-γ, interferon-γ; MHC, major histocompatibility complex; NBD, nucleotide-binding domain; PLC, peptide-loading complex; TAP, transporter associated with antigen processing; TMD, transmembrane domain; UL49.5, unique long region protein 49.5; US6, unique short region protein 6; vhs, virion host shut-off; wt, wild-type

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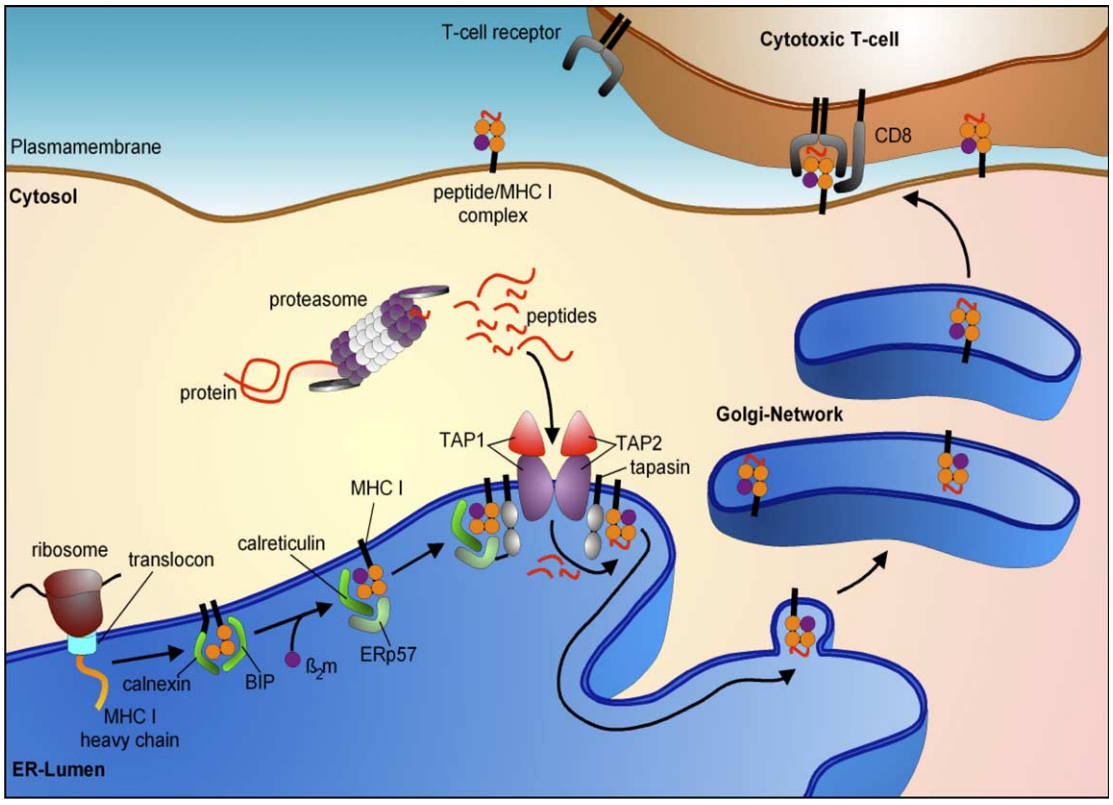

Fig. 1. Antigen presentation pathway via MHC class I molecules. The MHC I heavy chain is co-translationally translocated into the ER, where it folds and assembles with β_2-microglobulin assisted by the immunoglobulin binding protein (BiP) and calnexin. Subsequently, MHC class I molecules are recruited into a macromolecular peptide-loading complex (PLC) composed of calreticulin, ERp57, tapasin, TAP1 and TAP2. Peptides derived mainly by proteasomal degradation in the cytosol are translocated by TAP into the lumen of the ER, where they are loaded onto pre-assembled MHC class I molecules. Kinetically stable peptide-MHC complexes can escape the ER quality control and are transported via the Golgi to the cell surface. Binding of T-cell receptor and CD8 co-receptor to trimeric MHC class I molecules triggers the killing of the target cell (adapted from [99]).

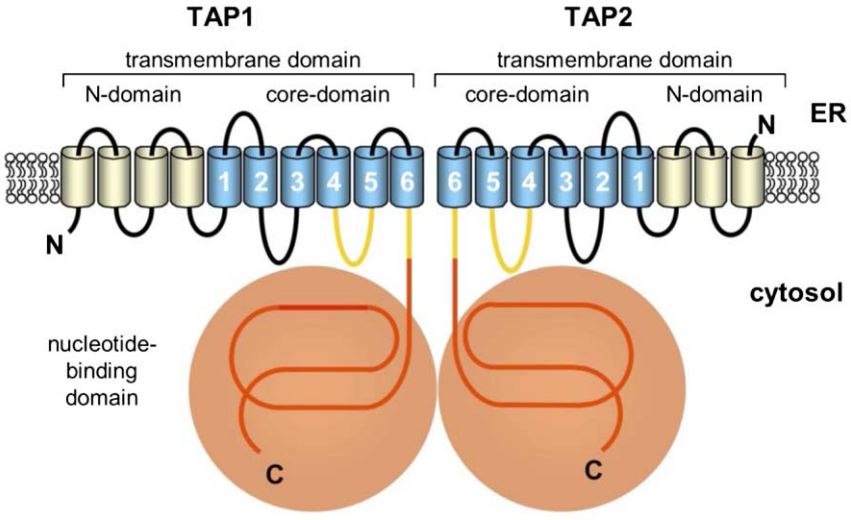

Fig. 2. Schematic model of the TAP complex. TAP forms a heterodimer composed of TAP1 and TAP2. Each subunit comprises an N-terminal transmembrane domain and a C-terminal, cytosolic NBD (red). The transmembrane domain can be subdivided into a six helices containing core domain and an NH_2-terminal extension of four and three helices for TAP1 and TAP2, respectively. Beside the translocation pathway, the TMDs also form the peptide-binding region (orange).

and MHC class I molecules. Peptides transported by TAP are subsequently trimmed by amino exopeptidases in the ER [19–22]. The sequence in between both anchor regions, which is recognized by the T-cell receptor, is highly divers in respect of TAP and MHC class I binding. This kind of clustered promiscuity ensures that one TAP complex in combination with