Review

The MHC I loading complex: a multitasking machinery in adaptive immunity

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Recognition and elimination of virally or malignantly transformed cells are pivotal tasks of the adaptive immune system. For efficient immune detection, snapshots of the cellular proteome are presented as epitopes on major histocompatibility complex class I (MHC I) molecules for recognition by cytotoxic T cells. Knowledge about the track from the equivocal protein to the presentation of antigenic peptides has greatly expanded, leading to an astonishingly elaborate understanding of the MHC I peptide loading pathway. Here, we summarize the current view on this complex process, which involves ABC transporters, proteases, chaperones, and endoplasmic reticulum (ER) quality control. The contribution of individual proteins and subcomplexes is discussed, with a focus on the architecture and dynamics of the key player in the pathway, the peptide-loading complex (PLC).

Immune detection leads to pathogen and tumor clearance

Humans are threatened by numberless pathogens every second of their lives. Bacteria, fungi, and viruses all cause human diseases, and in some cases even pandemics. In addition, malignantly transformed cells are an enemy from within. To cope with these threats, evolution has built the sophisticated system of adaptive immunity. To identify and eliminate infected or transformed cells, information on the target cell must be transmitted to the effector cells of the immune system. The adaptive immune system is based on a constant turnover of cellular proteins, which are converted into peptides. These are loaded onto MHC I molecules in the context of the multisubunit PLC (Figure 1). This macromolecular machinery is centered on the transporter associated with antigen processing (TAP), an ABC transporter that translocates antigenic peptides into the ER lumen [1]. The PLC further includes, besides MHC I heavy chain and β_2-microglobulin (β_2m), the adapter chaperone tapasin (Tsn), the ER-resident oxidoreductase ERp57, and lectin-like chaperone calreticulin (Crt). $CD8^+$ cytotoxic T cells scan MHC I complexes for antigenic cargo derived from virus- or tumor-associated proteins and eventually eliminate the target cell by inducing apoptosis to prevent systemic spread of the disease. In this review, we discuss the MHC I peptide-loading pathway, which spans multiple compartments and involves a set of specialized and generic receptors, chaperones, and transporters. Our main focus is on the PLC and its function, composition, and dynamics. The components and interplay of the PLC are covered, with special attention paid to the molecular architecture, stoichiometry, and dynamics of this macromolecular complex. To begin, the origin of antigenic peptides is discussed.

The generation of antigenic peptides

One source of peptides for MHC I presentation are defective ribosomal products (DRiPs), which are polypeptides that fail to acquire their native conformation and are rapidly delivered to the 26S/20S proteasome complex [2]. Hence, antigenic peptides can emerge very soon after protein translation and help in the very early detection of viral infection. In addition, unwanted or redundant proteins are, after ubiquitylation, subject to turnover by the proteasome, and thus provide an alternative source for MHC I ligands [3]. The relative contribution of DRiPs and proteasomal breakdown products to the pool of MHC I binding peptides, however, remains to be elucidated. Proteasomes come in different types: the 'standard' housekeeping proteasome and the immunoproteasome, which can be induced by interferon-γ and interferon-β, along with the TAP and MHC I [4]. The immunoproteasome is perfectly suited for production of peptides for the MHC I antigen presentation pathway because it preferentially cleaves after hydrophobic and basic amino acids, matching the preferences of TAP and MHC I for the C terminus of peptides. The N termini produced by the proteasome differ from those favored by TAP and MHC I. In addition, the peptides generated are approximately 3–22 residues long, so most of them are either too short or too long to be transported and loaded onto MHC I, which binds 8–11mers. After proteasomal degradation, the resulting peptides may be trimmed by cytosolic aminopeptidases such as leucine aminopeptidase, puromycin-sensitive

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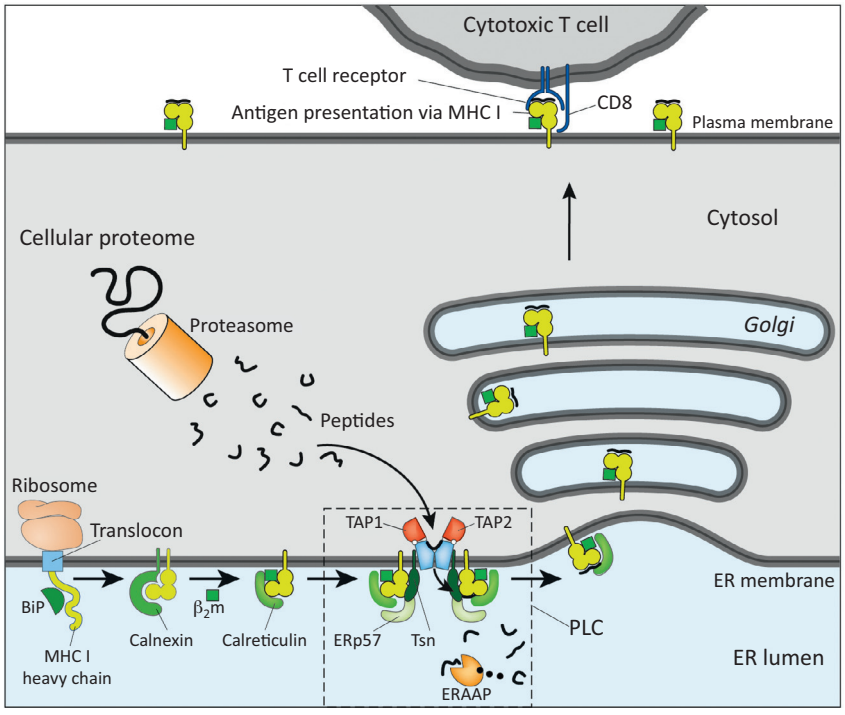

Figure 1. Antigen processing via MHC I molecules. After translation, the newly synthesized MHC I heavy chain associates with BiP and calnexin. Subsequently, assembly with soluble β_2m and exchange of calnexin with Crt take place. This MHC I/Crt subcomplex now associates with TAP/Tsn–ERp57 to form a fully assembled PLC, through which peptide transport and loading onto MHC I are spatiotemporally coordinated. The transmembrane and nucleotide-binding domains of TAP are colored in blue and red, respectively. The ER-associated aminopeptidase ERAAP might transiently interact with the PLC. After peptide loading, the peptide–MHC I complex dissociates from TAP/Tsn–ERp57 and traffics to the cell surface via the secretory pathway, where the peptide–MHC I complexes are monitored by cytotoxic $CD8^+$ T cells. BiP, binding immunoglobulin protein; MHC I, major histocompatibility complex class I; β_2m, β_2-microglobulin; PDI, protein disulfide isomerase; PLC, peptide-loading complex; Crt, calreticulin; TAP, transporter associated with antigen processing; Tsn, tapasin.

aminopeptidase, bleomycin hydrolase, and tripeptidyl peptidase-II (TPP-II). Besides these general trimming peptidases, nardilysin, thimetoligopeptidase, and the insulin-degrading enzyme are responsible for the generation of a few clearly defined epitopes. However, several studies have questioned the necessity of these peptidases; their real impact on the formation of antigenic peptides therefore remains unknown [5,6]. For example, a critical role in the generation of many MHC I ligands was proposed for TPP-II [7], but other studies using, for instance, TPP-II knockout mice, found no major defects in antigen presentation [8,9]. On the whole, although peptide trimming by cytosolic peptidases seems essential in some cases, the net effect might be a negative one, meaning that the peptidases destroy more MHC I ligands than they create [5].

Considering the short half-life of proteasome-generated peptides of less than 10 s [10], efficient MHC I antigen processing would benefit from a spatial link between the proteasome and TAP. However, such a direct connection has never been demonstrated convincingly. After transport into the ER lumen by TAP [1], peptides are further N-terminally processed by the ER aminopeptidase associated with antigen processing ERAAP (ERAP1/2 in humans) until they fit the length requirements for the MHC I binding pocket [11–13]. Taken together, the data suggest that antigenic peptides are derived from either DRiPs or native proteins and are shaped by the actions of the proteasome and additional peptidases. Before MHC I loading, peptides have to traverse the ER membrane, a task performed by the translocation complex TAP.

The core TAP complex: the gateway for peptide delivery into the ER

The heterodimeric TAP complex, composed of TAP1 (ABCB2) and TAP2 (ABCB3), is a member of the ABC transporter superfamily. The common blueprint for all ABC transporters is their organization into two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs). A cycle of engagement and disengagement of the two NBDs on ATP binding and hydrolysis is thought to be coupled to conformational changes in the TMDs to move proteasomal degradation products across the ER membrane [14]. TAP can be functionally dissected into the core TAP complex and N-terminal extensions at each subunit, called TMD_0 (Figure 2). As the central functional unit of the antigen translocation complex, core TAP comprises inner 2×6 transmembrane helices as well as the NBDs and is essential and sufficient for peptide binding and transport [15]. Peptide binding is ATP-independent [16,17], whereas peptide transport requires ATP hydrolysis [18]. The peptide-binding site was mapped to the cytosolic loop between transmembrane helices 4 and 5 and the cytosolic stretch following transmembrane helix 6 of core TAP1 and TAP2 [19].

TAP represents a prime example of how substrate specificity, selectivity, and diversity are combined. The