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Review

ER quality control in the biogenesis of MHC class I molecules

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ABSTRACT

Class I molecules of the major histocompatibility complex play a vital role in cellular immunity, reporting on the presence of viral or tumor-associated antigens by binding peptide fragments of these proteins and presenting them to cytotoxic T cells at the cell surface. The folding and assembly of class I molecules is assisted by molecular chaperones and folding catalysts that comprise the general ER quality control system which also monitors the integrity of the process, disposing of misfolded class I molecules through ER associated degradation (ERAD). Interwoven with general ER quality control are class I-specific components such as the peptide transporter TAP and the tapasin-ERp57 chaperone complex that supply peptides and monitor their loading onto class I molecules. This ensures that at the cell surface class I molecules will possess mainly optimal peptides with a long half-life. In this review we discuss these processes as well as a number of strategies that viruses have evolved to subvert normal class I assembly within the ER and thereby evade immune recognition by cytotoxic T cells.

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1. Introduction

Class I histocompatibility molecules are cell surface glycoproteins that are involved in the immune detection and elimination of virally infected or transformed cells. They sample the protein composition of a cell by binding to a broad array of intracellularly generated peptides which they then present to cytotoxic T cells at the cell surface. If the peptides are recognized as foreign, as in the case of viral or transformation-associated antigens, the afflicted cell may be killed. Over the past two decades, class I molecules have also proven to be excellent models for the study of general and class I-specific quality control processes within the ER. In fact, the molecular chaperone calnexin (Cnx) was discovered as an 88 kDa protein that could be cross-linked to newly synthesized mouse class I molecules during their assembly within the ER [1].

Class I molecules consist of three subunits: a polymorphic 45 kDa transmembrane heavy chain (HC) which may possess from 1 to 3 Asn-linked oligosaccharides, a soluble 12 kDa subunit termed β_2-microglobulin (β_2m) and an 8–9 residue peptide ligand (Fig. 1A). All three components are required for efficient export of the class I molecule to the cell surface and for long term stability

Abbreviations: Cnx, calnexin; Crt, calreticulin; CST, castanospermine; ER, endoplasmic reticulum; ERAD, ER associated degradation; β_2m, β_2-microglobulin; HC, heavy chain; HCMV, human cytomegalovirus; PDI, protein disulfide isomerase; PLC, peptide loading complex; TAP, transporter associated with antigen processing.

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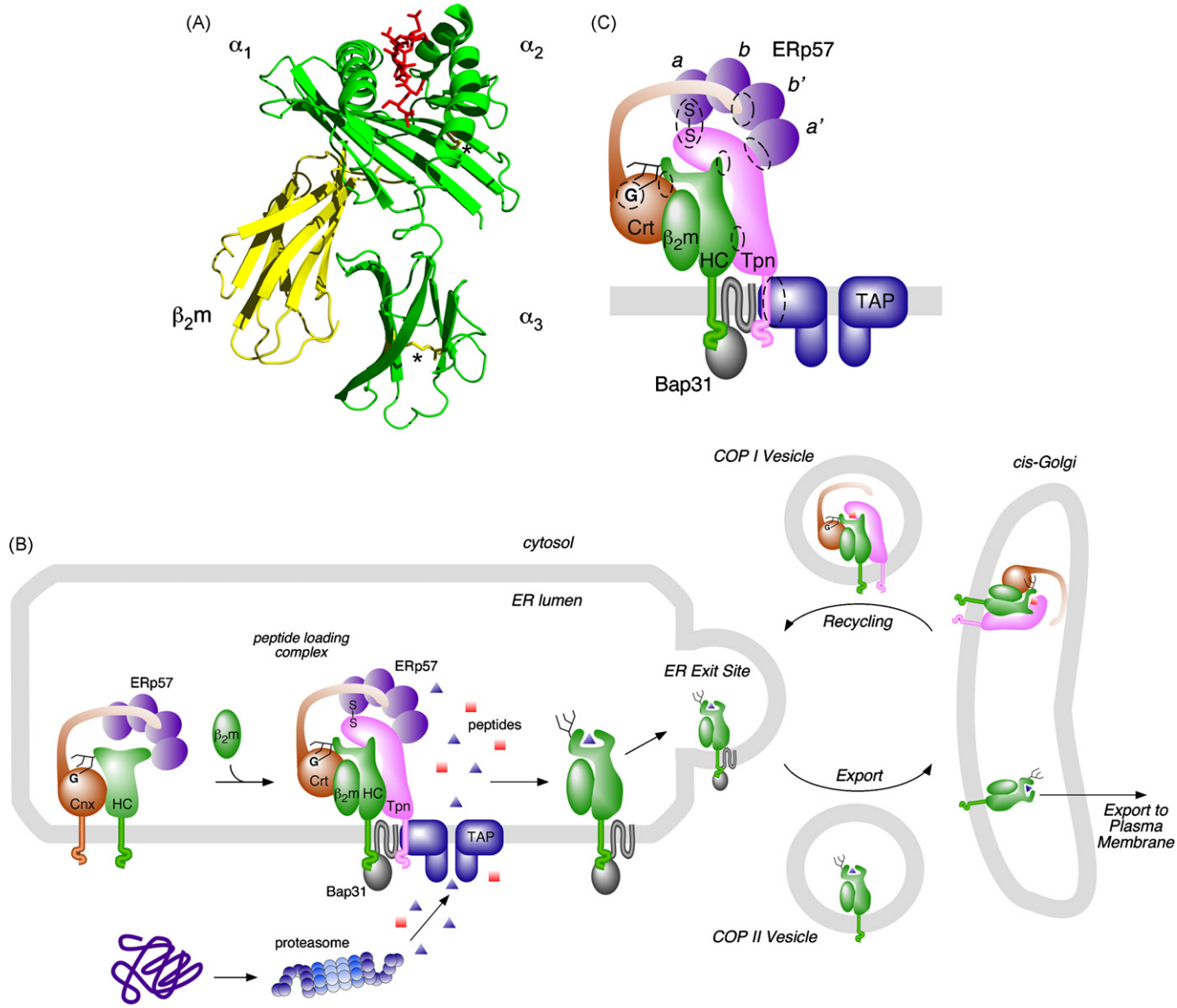

Fig. 1. Structure and assembly of class I molecules. (A) Structure of the mouse class I H-2D^{b} molecule with bound influenza nucleoprotein peptide (Protein Data Bank Accession: 1HOC). Only the soluble extracellular portion is shown with H chain in green, β_2m in yellow, and peptide in red. The individual H chain domains are indicated and the α_2 and α_3 domain disulfide bonds (yellow) are denoted by asterisks. (B) Assembly of class I molecules within the ER. The peptides that bind to class I molecules are the product of an extensive series of proteolytic events [79]. The proteasome generally creates peptides with C-termini compatible with class I binding but extended at their N-termini. Consequently, additional cytosolic proteases including the tricorn protease and various aminopeptidases participate as well. Following import into the ER via TAP, the ER aminopeptidase ERAAP may further trim peptides to the 8–9 residue length that is optimal for class I binding (optimal peptide: blue triangle, suboptimal peptide: pink square). Following release from the peptide loading complex, class I clusters at ER exit sites and is incorporated into COP II vesicles. Upon reaching the Golgi, class I is either exported on to the plasma membrane or recycled by tapasin and/or calreticulin back to the ER. Peptide loading and optimization may continue during this recycling until a high affinity peptide is able to occupy the peptide binding groove. (C) Multiple interactions stabilize the PLC (reviewed in [53]). Tapasin contacts TAP through transmembrane interactions, associates with the class I HC through both the HC α_2 and α_3 domains and makes multiple contacts with the redox-active *a* and *a*′ domains of ERp57, including a stable disulfide bond. In turn, ERp57 binds through its *b*′ domain to the tip of the arm domain of Crt and this chaperone associates with monoglucosylated oligosaccharides (G) on the class I HC through the lectin site of its globular domain as well as through polypeptide-based interactions. Bap31 is not required for PLC assembly but has been reported to interact with the HC through transmembrane contacts and also with tapasin. Adapted from [80].

following its arrival [2–4]. As shown in Fig. 1B, the newly synthesized HC binds rapidly, possibly cotranslationally, to the transmembrane chaperone Cnx and associated ERp57, a member of the protein disulfide isomerase (PDI) family of thiol oxidoreductases. Subsequently, binding to β_2m occurs and, at this stage in human cells, Cnx is fully replaced by its soluble ortholog calreticulin (Crt) whereas in mouse cells either Cnx or Crt may be present [2–4]. β_2m association alters the conformation of the HC, greatly enhancing its ability to bind peptide and rendering it competent to enter the peptide loading complex (PLC). The PLC consists of the HC-β_2m heterodimer, Crt (or Cnx), ERp57 and the additional components tapasin, TAP and Bap31. The peptides that bind to class I molecules are produced mainly in the cytosol, largely through the action of the proteasome. Peptides in the range of 8–16 residues are transported into the ER by the transporter associated with antigen processing (TAP) and those that match the binding requirements of the class I peptide binding groove are loaded onto class I with the assistance of the PLC. Following peptide binding, the class I molecule is released from the PLC and exported from the ER in a process involving Bap31 and possibly other export receptors [2–4]. In the following sections, we will discuss how the general and class I-specific quality control machinery participates in early heavy chain folding, peptide