Review

Antigen Translocation Machineries in Adaptive Immunity and Viral Immune Evasion

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Abstract

Protein homeostasis results in a steady supply of peptides, which are further degraded to fuel protein synthesis or metabolic needs of the cell. In higher vertebrates, a small fraction of the resulting peptidome, however, is translocated into the endoplasmic reticulum by the transporter associated with antigen processing (TAP). Antigenic peptides are guided to major histocompatibility complex class I (MHC I) molecules and are finally displayed on the cell surface, where they mount an adaptive immune response against viral infected or malignantly transformed cells. Here, we review the structural organization and the molecular mechanism of this specialized antigen translocon. We discuss how the ATP-binding cassette (ABC) transporter TAP communicates and cooperates within the multi-component peptide loading machinery, mediating the proper assembly and editing of kinetically stable peptide/MHC I complexes. In light of its important role within the MHC I antigen processing pathway, TAP is a prime target for viral immune evasion strategies, and we summarize how this antigen translocation machinery is sabotaged by viral factors. Finally, we compare TAP with other ABC systems that facilitate peptide translocation.

Introduction

The proteome of eukaryotic cells is dynamically shaped by a fine-tuned balance between the *de novo* synthesis of proteins and their degradation. The turnover of intracellular proteins is a specific and highly regulated process, in which most proteins are degraded *via* two pathways, the autophagy-lysosome system and the ubiquitin-proteasome system [1]. The resulting peptides are short-lived intermediates because they are immediately processed by a variety of cytosolic peptidases that degrade such peptides within seconds [2]. Hence, these peptides serve as a steady supply of amino acids, which are used either as an energy source during starvation or for *de novo* synthesis of proteins, thereby closing the cycle.

Besides serving as fuel for cellular processes, small peptides have acquired a broad range of sophisticated functions during evolution. For instance, plant peptides are involved in the defense against infection by pathogens and in the regulation of growth and development [3]. Moreover, various peptides are utilized as signaling molecules. The yeast mating pheromones a-factor and α-factor are small signaling peptides, which are subjected to multiple rounds of posttranslational modification and proteolytic cleavage prior to their secretion [4]. Host defense peptides, also known as antimicrobial peptides, which are found in all phyla of life, were originally described to exhibit antimicrobial activity and also have immune modulatory properties including anti-infective, anti-inflammatory and wound-healing activities [5,6]. Moreover, small peptides play a key role in the adaptive immune system of jawed vertebrates, where they are presented on the cell surface for clonal recognition and expansion of lymphocytes or for the recognition and subsequent elimination of infected or malignantly transformed cells.

Elaborate translocation machineries regulate the correct compartmentalization of bioactive peptides, thereby mediating peptide transport from their site of production to the particular compartment, where they fulfill their physiological functions (Fig. 1). Many peptides, for example, the yeast α-factor mating pheromone [4], are sorted *via* the "classical" secretory pathway and released into the external milieu. In addition, certain bioactive peptides require specialized translocation machineries for their proper transport. Here, we summarize the current view on how peptides that serve as antigens in adaptive immunity are transported across the endoplasmic reticulum (ER) membrane *via* a specialized and unique class of translocation machineries, the ATP-binding cassette (ABC) transport systems.

Scanning Debris—The Role of Peptides in the MHC I Antigen Presentation Pathway

Organisms are under continuous assault by viruses, bacteria, fungi or parasites. Hence, mutual survival relies on a fine-tuned balance between pathogen replication and the clearance of pathogens by the host immune system. In addition, malignantly transformed cells attack the body from within. Cancer or infected cells are eliminated by $CD8^+$ cytotoxic T lymphocytes (CTLs) that recognize antigenic peptide epitopes in complex with major histocompatibility complex class I (MHC I) molecules on the surface of the threatened cell (Fig. 1). The majority of these peptides are derived from proteasomal degradation in the cytosol [7]. The

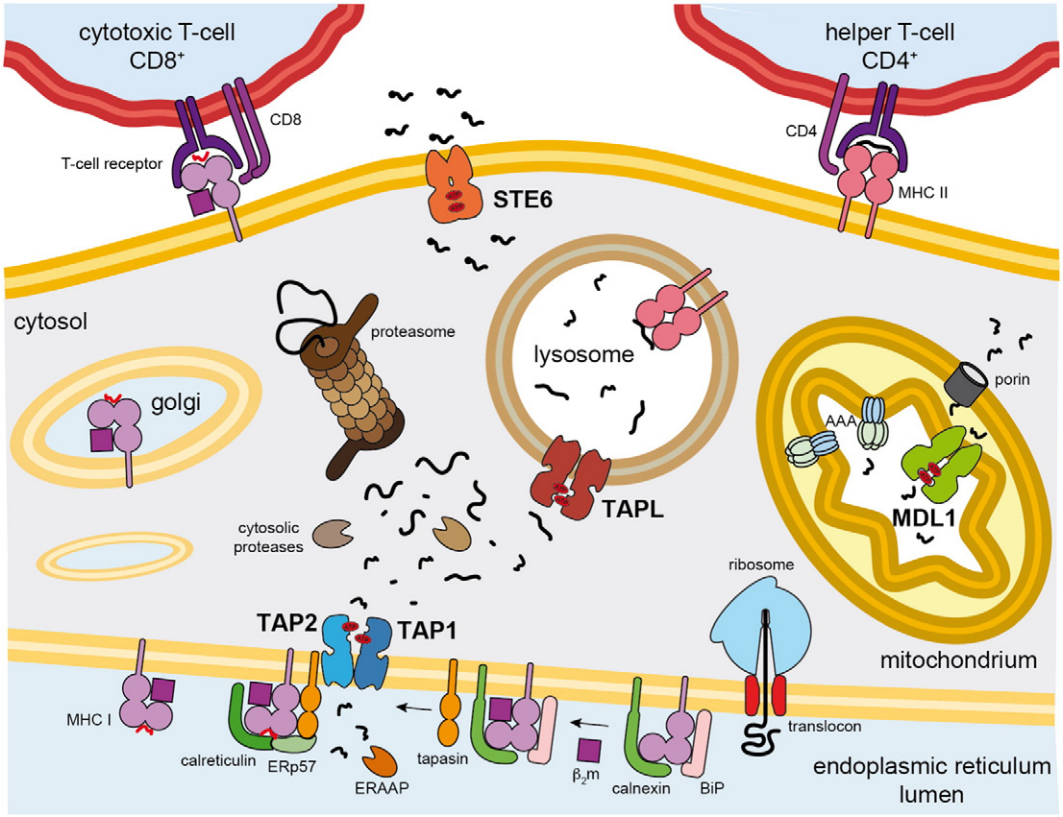

Fig. 1. Intracellular peptide trafficking and antigen processing. Various ABC transporters mediate peptide translocation across cell membranes, for example, the plasma membrane and intracellular membranes of mitochondria, lysosomes and the ER. Peptides derived from the ubiquitin-proteasome pathway are either degraded by cytosolic peptidases or translocated by TAP1/2 into the ER lumen, where they are trimmed by ERAAP proteases and further loaded onto MHC I molecules. *De novo* synthesized MHC I initially assembles with the chaperones BiP and calnexin. Subsequently, the PLC, composed of TAP1/2, tapasin, ERp57, calreticulin, β_2m and MHC I, is formed. Functional cooperation between PLC components catalyzes peptide loading onto MHC I. Stable peptide/MHC I complexes dissociate from the PLC and traffic *via* the Golgi network to the plasma membrane, where they are monitored by CTLs. Alternatively, peptides are translocated into lysosomes by the homodimeric TAPL complex for putative loading of MHC II molecules. MDL1, the yeast homolog of ABCB10, is proposed to be involved in the export of peptides derived from mitochondrial protein quality control mechanisms into the inter-membrane space. The ABC full-transporter STE6 of yeast (or Mdr49 of *Drosophila*) secretes prenylated peptides for cell–cell communication.