Class I MHC mediated antigen processing & presentation

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 73

This document contains 4 pathways (see Table of Contents)
Class I MHC mediated antigen processing & presentation

Stable identifier: R-HSA-983169

Major histocompatibility complex (MHC) class I molecules play an important role in cell mediated immunity by reporting on intracellular events such as viral infection, the presence of intracellular bacteria or tumor-associated antigens. They bind peptide fragments of these proteins and presenting them to CD8+ T cells at the cell surface. This enables cytotoxic T cells to identify and eliminate cells that are synthesizing abnormal or foreign proteins. MHC class I is a trimeric complex composed of a polymorphic heavy chain (HC or alpha chain) and an invariable light chain, known as beta2-microglobulin (B2M) plus an 8-10 residue peptide ligand. Represented here are the events in the biosynthesis of MHC class I molecules, including generation of antigenic peptides by the ubiquitin/26S-proteasome system, delivery of these peptides to the endoplasmic reticulum (ER), loading of peptides to MHC class I molecules and display of MHC class I complexes on the cell surface.

Literature references


Antigen processing: Ubiquitination & Proteasome degradation

**Location:** Class I MHC mediated antigen processing & presentation

**Stable identifier:** R-HSA-983168

**Compartments:** cytosol

Intracellular foreign or aberrant host proteins are cleaved into peptide fragments of a precise size, such that they can be loaded on to class I MHC molecules and presented externally to cytotoxic T cells. The ubiquitin-26S proteasome system plays a central role in the generation of these class I MHC antigens.

Ubiquitination is the mechanism of adding ubiquitin to lysine residues on substrate protein leading to the formation of a polyubiquitinated substrate. This process involves three classes of enzyme, an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase. Polyubiquitination through lysine-48 (K48) generally targets the substrate protein for proteasomal destruction. The protease responsible for the degradation of K48-polyubiquitinated proteins is the 26S proteasome. This proteasome is a two subunit protein complex composed of the 20S (catalytic core) and 19S (regulatory) proteasome complexes. The proteasome eliminates most of the foreign and non-functional proteins from the cell by degrading them into short peptides; only a small fraction of the peptides generated are of the correct length to be presented by the MHC class I system. It has been calculated that between 994 and 3122 protein molecules have to be degraded for the formation of a single, stable MHC class I complex at the cell surface, with an average efficiency of 1 in 2000 (Kloetzel et al. 2004, Princiotta et al. 2003).

**Literature references**


**Editions**

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Antigen Presentation: Folding, assembly and peptide loading of class I MHC

Location: Class I MHC mediated antigen processing & presentation

Stable identifier: R-HSA-983170

Unlike other glycoproteins, correct folding of MHC class I molecules is not sufficient to trigger their exit from the ER, they exit only after peptide loading. Described here is the process of antigen presentation which consists of the folding, assembly, and peptide loading of MHC class I molecules. The newly synthesized MHC class I Heavy Chain (HC) is initially folded with the help of several chaperones (calnexin, BiP, ERp57) and then binds with Beta-2-microglobulin (B2M). This MHC:B2M heterodimer enters the peptide loading complex (PLC), a multiprotein complex that includes calreticulin, endoplasmic reticulum resident protein 57 (ERp57), transporter associated with antigen processing (TAP) and tapasin. Peptides generated from Ub-proteolysis are transported into the ER through TAP. These peptides are further trimmed by ER-associated aminopeptidase (ERAP) and loaded on to MHC class I molecules. Stable MHC class I trimers with high-affinity peptide are transported from the ER to the cell surface by the Golgi apparatus.

Literature references


Editions

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MHC class I molecules generally present peptide antigens derived from proteins synthesized by the cell itself to CD8+ T cells. However, in some circumstances, antigens from extracellular environment can be presented on MHC class I to stimulate CD8+ T cell immunity, a process termed cross-presentation (Rock & Shen. 2005). Cross-presentation/cross-priming is the ability of antigen presenting cells (APCs) to present exogenous antigens on MHC class I molecules to CD8+ T lymphocytes. Among all the APCs, Dendritic cells (DC) are the dominant antigen cross presenting cell types in vivo, although macrophages and B cells appear to cross present model antigens in vitro with a low degree of efficiency (Amigorena & Savina. 2010, Ackermann & Peter Cresswell. 2004). Compared to macrophages, DCs have low levels of lysosomal proteases and exhibit limited lysosomal degradation (Delamarre et al. 2005). This limited proteolysis of internalized antigens by DCs might contribute to their high efficiency for cross presentation (Monua & Trombetta. 2007). APCs acquire the exogenous antigens through endocytic mechanisms, especially phagosomes for particulate/cell-associated antigens and endosomes for soluble protein antigens. There does not seem to be a unique pathway for cross-presentation but rather different potential mechanisms of cross-presentation have been proposed. These proposed pathways can be classified according to the location where two key events occur: 1) processing of the antigenic protein and 2) loading of the processed peptide on to MHC I molecule (Blanchard & Shastri. 2010). Based on the requirement for TAP and cytosolic proteases two mechanisms have been described, a cytosolic pathway (TAP-dependent and proteasome-dependent) or a vacuolar pathway (TAP- and proteasome-independent) (Blanchard & Shastri. 2010, Amigorena & Savina. 2010). Regarding peptide-loading, MHC I could be loaded in the ER or in the phagosome and recycled to cell surface (Blanchard & Shastri. 2010). Exogenous soluble antigens are cross-presented by dendritic cells, albeit with lower efficiency than for particulate substrates. Soluble antigens destined for cross-presentation are taken up by distinct endocytosis mechanisms which route them into stable early endosomes and then to the cytoplasm for proteosomal degradation and peptide loading. The outcome of the cross presentation can be either tolerance or immunity (Rock & Shen. 2005).

**Literature references**


**Editions**

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