

Antigen processing and presentation

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In antigen-presenting cells (APCs), such as dendritic cells (DCs) and B cells, heterogeneous intracellular pathways and mechanisms are responsible for generating complexes of MHC class I and class II molecules with peptide antigens, and complexes of CD1 molecules with lipid antigens, for presentation to T cells. This process — referred to as antigen processing and presentation — allows T cells to continuously assess the intracellular and extracellular milieu for signs of infection or abnormal cell growth. Although MHC class I molecules typically bind peptides derived from endogenous proteins and MHC class II molecules typically bind peptides derived from proteins that are endocytosed or

phagocytosed by APCs, this simple division is not strictly enforced. Indeed, exogenous proteins internalized by DCs can generate peptide–MHC class I complexes that are recognized by CD8⁺ T cells, a phenomenon referred to as cross-presentation. Similarly, endogenous and viral proteins can generate peptide–MHC class II complexes that are recognized by CD4⁺ T cells in a process involving autophagy. Understanding the processes and mechanisms by which antigens are captured, processed and loaded onto MHC molecules for presentation to T cells provides us with crucial insights that are necessary for the design of vaccines and therapeutic strategies to bolster T-cell responses.

The MHC class II pathway

MHC class II $\alpha\beta$ -chain dimers are assembled in the endoplasmic reticulum (ER) as a nonameric complex with the invariant chain (Ii), which protects against premature peptide or protein interactions in pre-lysosomal compartments. This complex traffics to the lysosome MHC class II compartment (MIIC), where Ii is subjected to sequential proteolysis. The final cleavage product, a peptide known as class II-associated Ii peptide (CLIP), occupies the peptide-binding groove and must be released prior to loading with high-affinity peptides, an exchange reaction that is catalysed by the chaperone-like molecule HLA-DM. HLA-DO, which is expressed by B cells, thymic epithelial cells and certain DC subsets, can bind HLA-DM and inhibit MHC class II peptide exchange. Exogenous proteins access the MIIC through phagocytosis and endocytosis, and endogenous proteins access the MIIC through autophagy. Peptide antigens of an appropriate length (~10–16 amino acids) for binding to MHC class II molecules are generated following reduction of disulphide bonds by interferon- γ -inducible lysosomal thiol reductase (GILT) and cleavage by lysosomal proteases. Once transported to the cell surface, peptide–MHC class II complexes are presented to CD4⁺ T cells.

Abbreviations

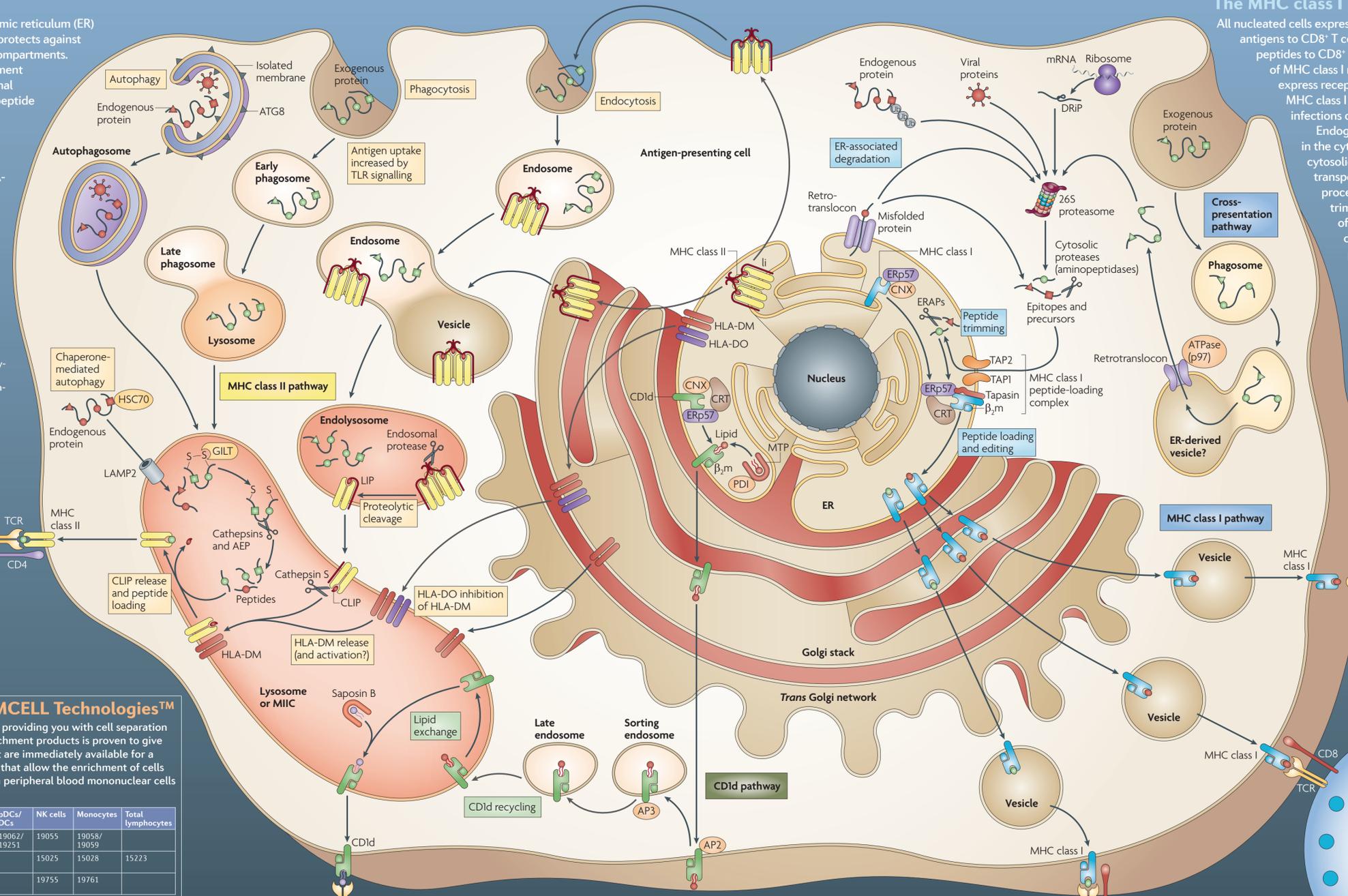
AEP, asparaginyl endopeptidase; AP, adaptor protein; ATG8, autophagy-related gene 8; CNX, calnexin; DRIP, defective ribosomal product; HSC70, heat-shock cognate protein 70; KIR, killer-cell immunoglobulin-like receptor; LAMP2, lysosomal-associated membrane protein 2; NK, natural-killer-cell receptor; PDI, protein disulphide isomerase; TCR, T-cell receptor; TLR, Toll-like receptor; Ub, ubiquitin.

The MHC class I pathway

All nucleated cells express MHC class I molecules and present endogenous peptide antigens to CD8⁺ T cells, but some DC subsets can also present exogenous peptides to CD8⁺ T cells through cross-presentation. Cell surface expression of MHC class I molecules is monitored by natural killer (NK) cells, which express receptors that trigger target-cell lysis when the expression of MHC class I is downregulated, such as occurs during some viral infections or cell transformation.

Endogenous peptides for MHC class I presentation are generated in the cytosol from a variety of sources by the proteasome and cytosolic proteases. These epitopes and precursors are then transported through the transporter associated with antigen processing (TAP) complex into the ER, where they are further trimmed by ER aminopeptidases (ERAPs) to produce peptides of 8–10 amino acids. The assembly of MHC class I heavy chain- β_2 -microglobulin (β_2m) heterodimers with the short peptides is coordinated by the peptide-loading complex, which is composed of a disulphide-linked dimer of tapasin and Erp57, calreticulin (CRT) and TAP molecules. Tapasin also supports peptide editing to select for the presentation of stable peptide–MHC class I complexes on the cell surface.

Exogenous proteins that are internalized by some DC and macrophage subsets via phagosomes or endosomes (not shown) can be retrotranslocated (possibly involving components of the ER-associated degradation system) into the cytosol, where they are fed into the MHC class I processing pathway. The minor TAP-independent pathway is not shown for simplicity.



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	T cells	CD4 ⁺ T cells	Naive/Memory CD4 ⁺ T cells	CD4 ⁺ CD25 ⁺ T cells	CD8 ⁺ T cells	B cells	pDCs/DCs	NK cells	Monocytes	Total lymphocytes
EasySep® (Human)	19051	19052	19155/19157	15862	19053	19054/19154	19062/19251	19055	19058/19059	
RosetteSep® (Human)	15021	15022		15862	15023	15024		15025	15028	15223
EasySep® (Mouse)	19751	19752		19782	19753	19754		19755	19761	

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The CD1d pathway

The MHC class I-like CD1 molecules assemble with β_2m and a lipid antigen, rather than a peptide antigen. Five CD1 isoforms are expressed in humans (CD1a–CD1e), but only CD1d is expressed in mice. Only the human CD1d pathway is shown for simplicity. Current models suggest that initial lipid binding by CD1d molecules occurs in the ER, possibly mediated by microsomal triglyceride transfer protein (MTP), and then additional lipids bind through saposin-mediated exchange during CD1d recycling through endocytic compartments. At the cell surface, CD1d molecules present lipid antigens to NKT cells.

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