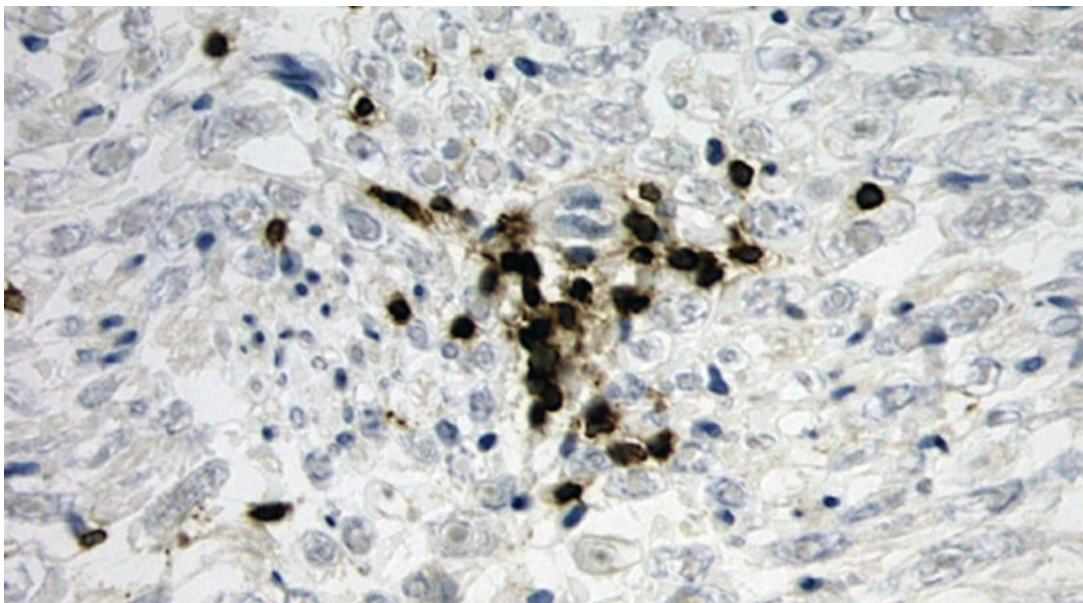


Antigen Processing and Presentation

[See online here](#)

All foreign antigens are recognized by the cells via specific receptors called the major histocompatibility complex. These MHC molecules encompass a wide diversity in structure and actions. What follows is a review of the MHC molecules and their interactions with an antigen.



Overview

Whenever a foreign organism invades our body, the [immune system](#) receives an alert. This is due to the presence of small **glycoprotein antigens** on the surface of these invading organisms that the body identifies as foreign.

All cells carry antigens on their surface; the body can distinguish the different **self- and non-self-antigens** because of the selection process during birth and in the early years of life. Initially, due to the great diversity of [DNA](#) splicing and recombination, the immune system creates billions of different antibodies with a limited number of genes by rearranging DNA segments during B cell development, prior to antigen exposure.

This results in the formation of **lymphocytes** complimentary to every possible antigen, even those of the fetus itself. Our lymphocytes are then matured, and **T-cells** are carried to the **thymus**, while **B-cells** are sent to the [bone marrow](#) for further processing.

In these locations, respective lymphocytes are exposed to every antigen in the fetus' body. Whichever lymphocyte reacts, it is killed on the spot. So, normally, a human being does not have those lymphocytes that correspond to the self-antigens.

Now, only those lymphocytes are present that will essentially attack foreign antigens.

However, these are stored in numerous **peripheral and central lymph node organs**, in an inactive state. An antigen needs to be transported to them for activation.

To perceive and battle the extensive variety of pathogens that an individual will experience in their lifetime, lymphocytes of the adaptive immune system have developed ways to identify an incredible assortment of various antigens from **micro-organisms, infections** and other.

Recognition of Antigens

Immunoglobulins

The antigen-identifying parts of B-cells are the **immunoglobulins (Ig)**. These proteins are created by B-cells in an array of antigen specificities, with every B-cell delivering an immunoglobulin of a single specificity. Some of these are bound to the B-cell surface and serve as the cell's antigen receptor. They are known as the **B-cell receptor (BCR)**.

Immunoglobulins of similar antigen specificity are released into the extracellular fluid (ECF) as an immune response by mature B-cells, the **plasma cells**. The discharge of antibodies, which bind pathogens in extracellular spaces of the body, is the fundamental effector capacity of B-cells.

T-cells

T-cells, on the other hand, have antigen-recognizing proteins on their cell membrane; they are called **TCRs (T-cell receptors)** and bear an enormous similarity to the antibodies of B-cells. They even have both the V and C regions and are produced by a process of variability not very different from that of B-cells, as mentioned above.

However, there is one difference: T-cells do not recognize antigens like B-cells do. On the contrary, T-cells need their antigens to be presented as short peptides, **bound to special Major Histocompatibility Complex (MHC) molecules**. Only then will the antigens be effective and will be able to activate the T-cells.

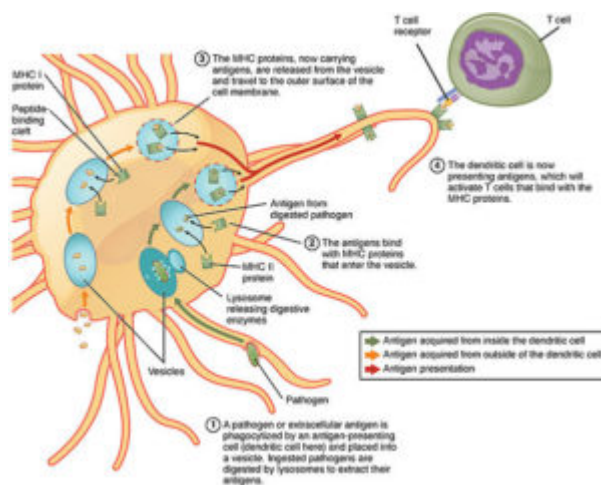


Image: "Antigen processing and presentation." by OpenStax College - Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

These antigens are presented to the T-cells via specific molecules, which are present on

the antigen presenting cells. The **protein antigens** are presented by the MHC molecules, which are coded by a specific segment of DNA. On the other hand, the **lipid antigens** are presented by the **CD1 molecules**. These are explained in more detail below.

It's important to note that T-cells only respond to processed antigens, which are short amino acid sequences called **peptides**. Therefore, only those antigens that have been broken down into peptides will be effective in eliciting a response. This is called **antigen processing**.

Invasion of foreign organisms

It all begins with the invasion of foreign organisms. These are ingested by the **antigen presenting cells**. Antigen presenting cells are of 3 types, but the majority of them include **dendritic cells**.

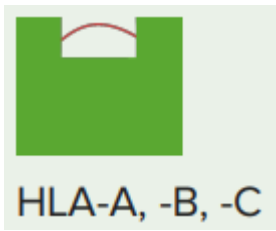
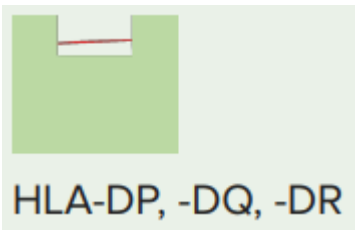
Once foreign organisms are phagocytosed, they form an **endosome**, which is fused with **lysosomes** that contain enzymes to kill and digest the organisms.

Antigens are, however, conserved. They are taken to the **endoplasmic reticulum** where they are processed to form small peptides. These **peptides** are then combined with **MHC molecules** and expressed on the cell surfaces. Thus, they are once again capable of activating T-cells by attaching to relevant T-cell molecules with complimentary TCRs.

Types of MHC Molecules

The function of MHC molecules is to bind and express antigen peptides—derived from pathogens—on the cell surface so that they are acknowledged by the appropriate T-cells. The outcome is quite often injurious to the pathogens, with common sequelae of infected cells being killed.

Classes of MHC

MHC class I	MHC class II
 <p>HLA-A, -B, -C</p>	 <p>HLA-DP, -DQ, -DR</p>
Present on all nucleated cells in the body	Present on professional APCs (dendritic cells, macrophages, B-cells) and on thymic epithelium
Alerts CD8 ⁺ cytotoxic T-cells to intracellular antigens	Alerts CD4 ⁺ helper T-cells and regulatory T-cells to extracellular antigens

There are two major classes of MHC molecules, each with their own specificities and functions. They both consist of two α - and β -chains from different sources. **MHC class I molecules** consist of a heavy α -chain spanning the membrane, which is coded by MHC genes, while β -chain is a light chain and is produced by the **β -microglobulin gene**.

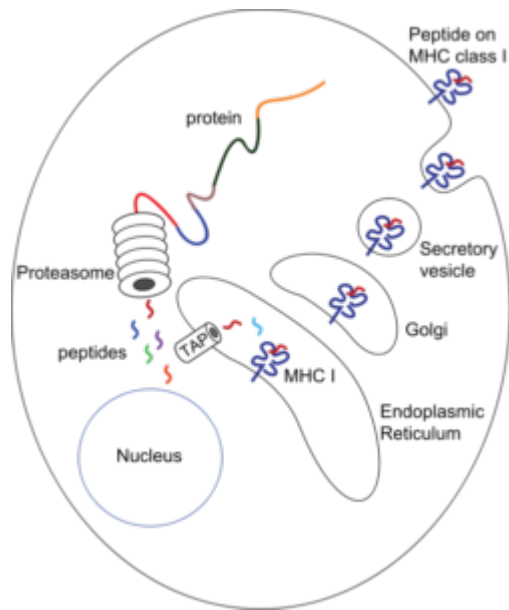


Image: "Simplified diagram of cytoplasmic protein degradation by the proteasome, transport into endoplasmic reticulum by TAP complex, loading on MHC class I, and transport to the surface for presentation" by Scray. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

MHC class II molecules contain 2 chains which span the membrane; they are both coded for by MHC genes.

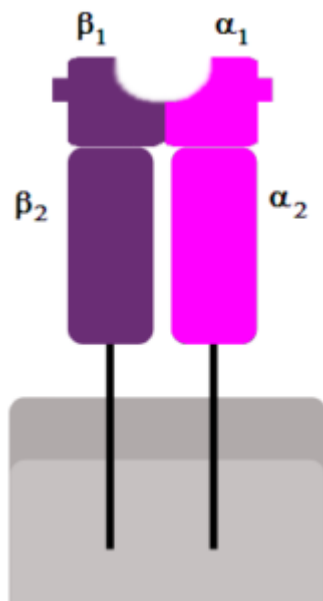


Image: "Summary Schematic representation of MHC class II molecule, consisting of two α -domains and two β -domains. The peptide-binding groove is situated between domains α_1 and β_1 ." by SanderB. License: [Public Domain](https://creativecommons.org/licenses/publicdomain/)

Both MHC molecules consist of a groove which binds the peptides; it forms a complex, which enables them to be presented to T-cells. The groove is known as a **peptide-binding groove**.

Functions of MHC

These molecules also play a major role in determining the **success of transplantation**. This is because transplanted cells can act just like regular antigens and stimulate an adaptive immune response. The MHC molecules are also often called the **HLA complex**, or **human leukocyte complex**, in the context of tissue matching.

MHC class I molecules are present **on all nucleated body cells**. They present those antigens that are present in the cellular cytoplasm. These can include foreign proteins, self-proteins, viral proteins and so on.

Once MHC class I molecules combine with antigenic peptides to be displayed on the cell surface, they mainly activate **cytotoxic T-lymphocytes**. Cytotoxic T-cells can then identify the potentially toxic cell and eliminate it. MHC molecules are basically part of the **HLA antigen group**. Those HLA antigens that correspond to MHC class I molecules include **HLA-A, B, and C**.

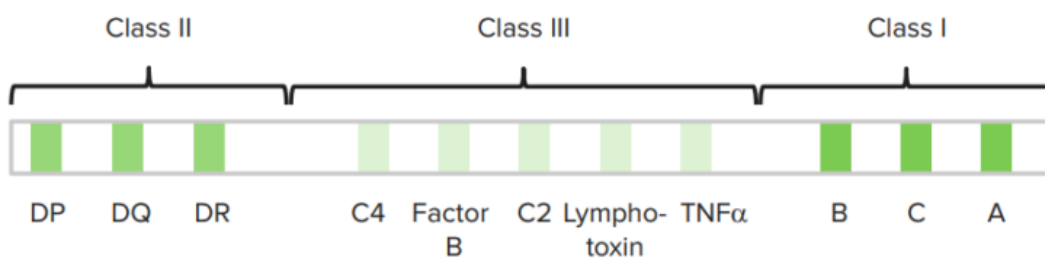
Peptides from the cytosol associate with class I MHC and are recognized by Tc cells. Peptides from within vesicles associated with class II MHC and are recognized by Th cells.

MHC class II molecules are **only present on antigen presenting cells**. These include **dendritic cells, macrophages, and B-lymphocytes**. These molecules are responsible for presenting antigens that are present extracellularly. This is done by phagocytosing the potentially harmful organism, degrading it, processing the antigen and then presenting it to T-cells.

Macrophages are stimulated to eliminate micro-organisms in their **intracellular vesicles**, and **B-cells** are stimulated to deliver antibodies that kill **extracellular pathogens**. Pathogens that manage to survive and thrive intracellularly (such as *M. Tuberculosis*), can proliferate in a manner that allows its escape from a presentation by an MHC molecule.

Once these **MHC class II molecules** combine with antigens and are displayed on the surface of antigen-presenting cells, they activate **T helper cells**. As mentioned, HLA antigens are the MHC molecules. Those HLA antigens that correspond to MHC class II molecules include **HLA-DP, DQ, DR, DM, DOA, and DOB**.

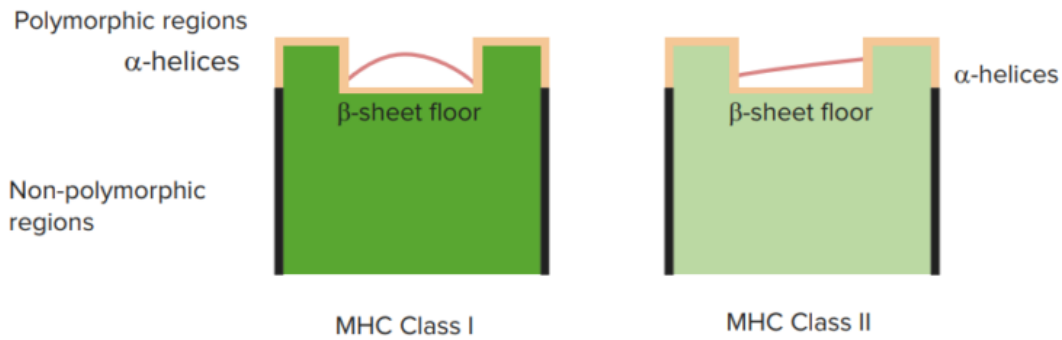
The different MHC proteins are coded by the **MHC gene**, which is located on **chromosome 6**. The initial part of the locus codes for MHC protein class II, while the latter part codes for MHC protein class I.



The MHC gene locus—chromosome 6. Image by Lecturio

Polymorphism of MHC Molecules

Two separate properties of MHC make it impossible for pathogens to avoid it. To start with, MHC is **polygenic**: it contains a few distinctive MHC class I and MHC class II qualities so that each person has an arrangement of MHC molecules that have varying specificities for different peptides.



Polymorphism of MHC class I and II molecules. Image by Lecturio

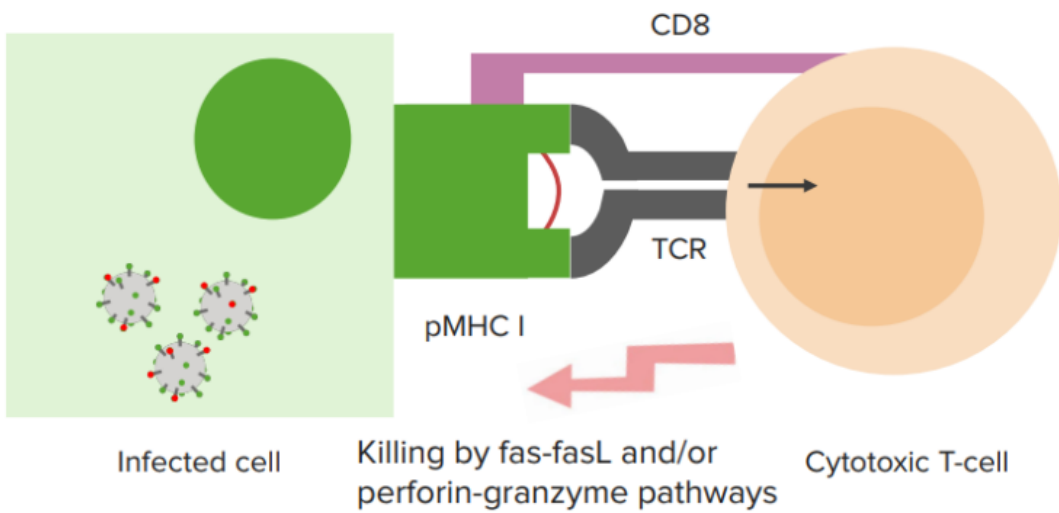
Second, MHC is **profoundly polymorphic**, i.e., there are multiple variants of every gene, giving rise to a magnificent diversity within the population. MHC qualities are, indeed, the most polymorphic qualities known.

	DP	DQ	DR	B	C	A	
M	24	91	4	8	17	84	
Number of allelic variants	α - chain	>40	>50	7	>4,000	>2,000	>3,000
	β - chain	>600	>900	-2,000	1	1	1
P	6	69	4	27	46	2	
	DP	DQ	DR	B	C	A	

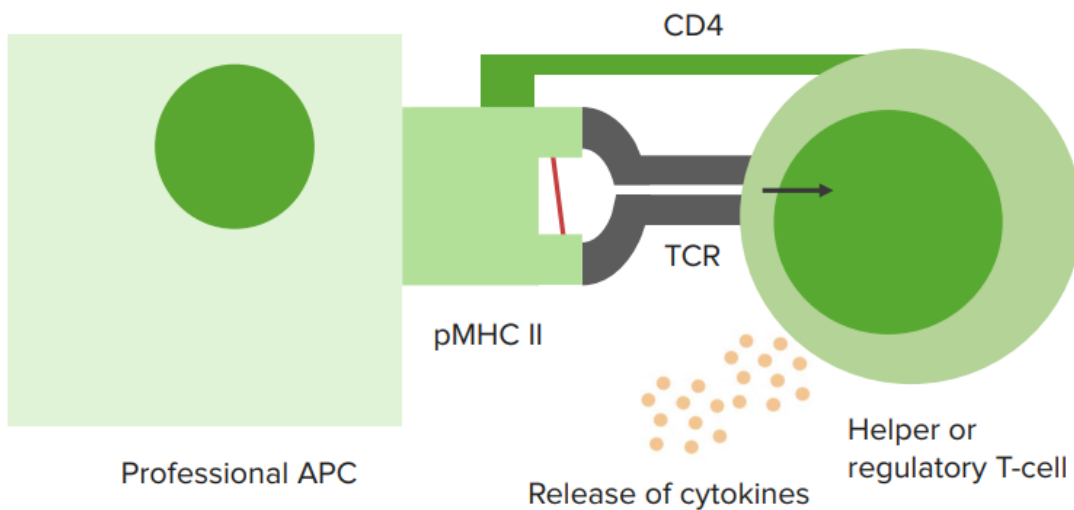
The diversity of the MHC. Image by Lecturio

TCR

Once the antigens are presented on the cellular surface, bound to the MHC molecules, they need to activate the T-cells as well. To ensure the attachment and action of these antigens, the T-cells possess TCRs. These **receptors** are specific for **specific antigens** and bind the antigen attached to the MHC molecules, stabilizing it. This allows the second messenger systems to come into play, which in turn activates the T-cells.



MHC class I presents peptides to CD8⁺ cytotoxic T-cells. Image by Lecturio



MHC class II presents peptides to CD4⁺ helper or regulatory T-cells. Image by Lecturio

Two Pathways of Antigen Processing

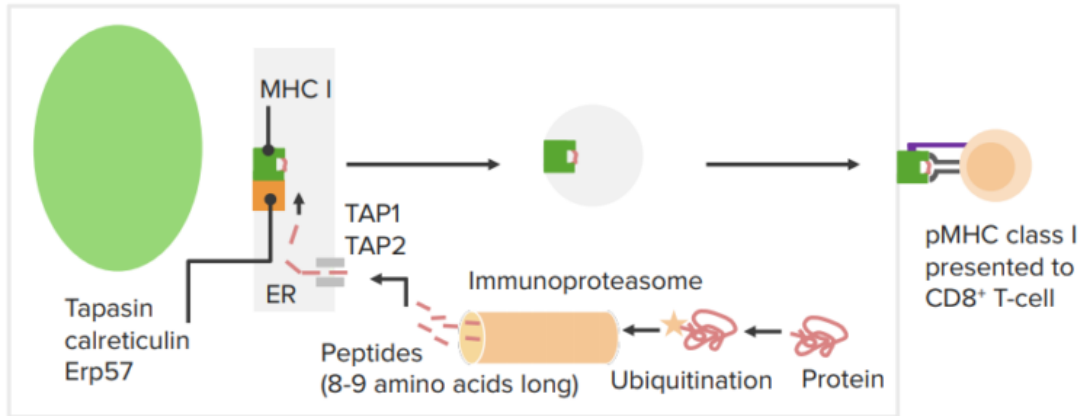
The method of antigen processing occurs in two distinct ways. Obviously, as there are two distinct types of antigens being processed, their processing pathways must be different also. Here we describe the two pathways separately.

The endogenous pathway

This pathway is used for the MHC class I molecules which are associated with all the endogenous antigens. The process starts with **ubiquitination** of the endogenous antigens, which marks them for **degradation by the proteasomes**.

The proteasomes function to break these antigenic proteins into small peptides of about 8–9 **amino acids** long, which are, in turn, transported with the TAP into the **endoplasmic reticulum**. TAP or **Transporter associated with antigen processing** is a member of the ATP-binding-cassette transporter family. It delivers cytosolic peptides into the endoplasmic reticulum (ER), where they bind to nascent MHC class I molecules.

At the same time, **chaperone proteins** within the rough endoplasmic reticulum help facilitate the proper folding of the MHC class I molecules and **β 2-microglobulin**. These partially folded MHC class I molecules are then associated with a TAP via another protein called **tapasin**. The molecules combine together and are then secreted from the cell by the **Golgi apparatus**, to be displayed on the cellular surface.



The endogenous antigen processing and presentation. Image by Lecturio

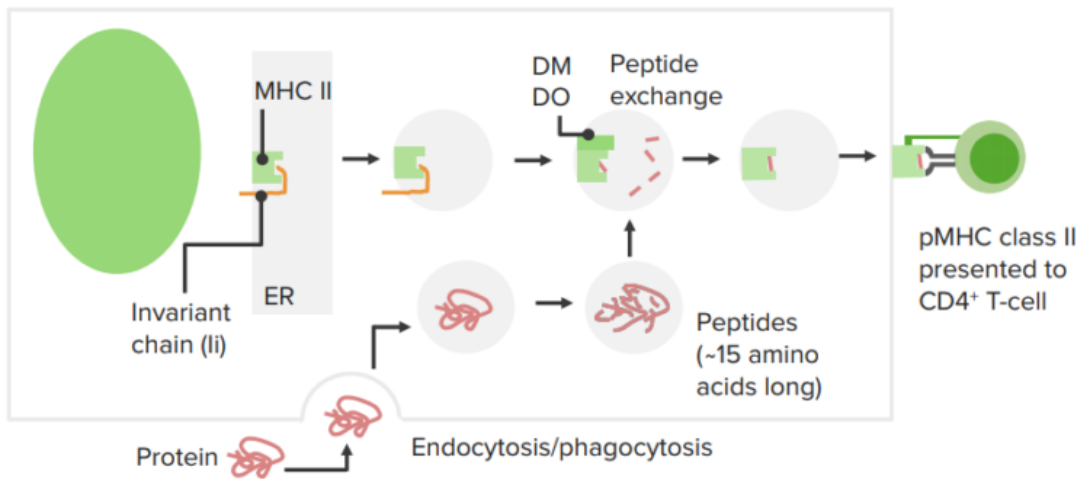
The exogenous pathway

This pathway is for the MHC class II molecules and is used by the **antigen presenting cells**. Initially, the **proteins are phagocytosed** and broken down by **proteases in endosomes** to **peptides** that are about 15 **amino acids** long.

In the **rough endoplasmic reticulum (ER)**, the naïve MHC class II molecules (alpha and beta chains) associated with each other and a third protein, called the “**invariant chain**” which stabilizes the complex. Without the invariant chain, the alpha and beta proteins will not associate. The Invariant chain (**Ii**), which trimerizes in the **ER**, associates with MHC class II molecules and is released from the **ER** as a nine subunit complex.

This MHC-invariant complex passes from the **RER** to, and out of, the Golgi body. **Before moving to the cell surface, the vesicle containing this complex fuses with the endosome containing the antigen peptides**. Here the invariant chain is proteolytically degraded and only a small part, called **CLIP**, remains attached to the **peptide binding groove**.

The antigen peptide from the external protein associates with the MHC II molecule in the channel between the α -1 and β -1 domains. Then another protein called **HLA-DM** removes CLIP and allows the chain to start attaching to the peptide. The resulting MHC II-peptide complex proceeds to the surface where it is expressed, ready for antigen presentation. MHC II molecules appear to be expressed on the surface of cells in pairs.



The exogenous antigen processing and presentation. Image by Lecturio

Cross-presentation

There is no clear differentiation between the endogenous and exogenous pathway. Peptides derived exogenously are presented via the MHC class I molecules. The cell begins the process by exogenous pathway but ends up diverting the antigens to the endogenous pathway; this allows the cell to skip some of the steps of the exogenous pathway.

As the exogenous pathway can involve infection before presenting the antigens, the cross-presentation allows the **dendritic cells** to process and present antigens without being infected.

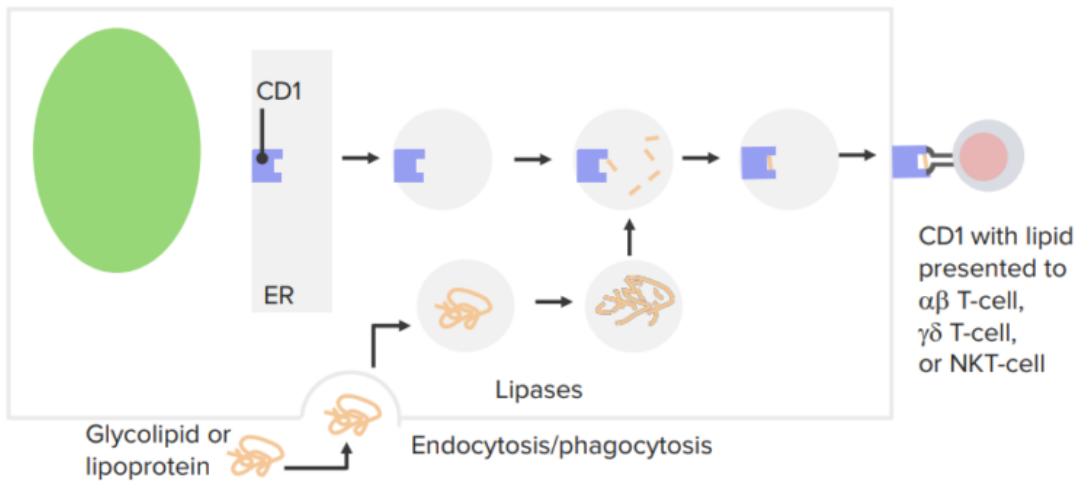
This allows the antigens to stimulate **different T-cells**, the endogenous antigens stimulating the **helper T-cells** via class II molecules and the exogenous ones cross-stimulating the **cytotoxic T-cells** via the class I molecules. However, not every antigen presenting cell can utilize the ability to cross-present.

Presentation of Lipid Antigens by CD 1

Aside from the **proteinaceous antigens**, some cells also possess **lipid antigens**. These cannot be presented via the MHC molecules. For these antigens, the body employs the **CD 1 molecules**, which are a **non-polymorphic family of glycoproteins** that are capable of presenting lipid antigens to T-cells. The molecules have a unique binding structure that allows them to bind to and present a wide variety of lipid antigens.

The process starts by **phagocytosis** of the antigens into the cell; then, **lipases** degrade them into the smallest pieces. The CD 1 molecule is present in the **endoplasmic reticulum**. The small pieces of lipid antigens are mixed and bound with the CD 1 molecules, which are then **exocytosed** to the cell surface. There they present their antigens to the T-cells and the natural killer cells.

In short, the body has the capability of expressing both lipid and protein antigens. Our immune system is equipped to fight every foreign invader with complex and intricate processes that are nothing short of a miracle.



Presentation of lipid antigens by CD1. Image by Lecturio

References

Janeway, Travers, Walport and Shlomchik. Immunobiology. 5th Edition

Robbins. Textbook of pathology.

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Notes