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Major Histocompatibility Complex

The major histocompatibility complex (MHC) was first detected as the genetic locus encoding the glycoprotein molecules (transplantation antigens) responsible for the rapid rejection of tissue grafts transplanted between genetically non identical individuals. It is now known that MHC molecules bind peptide antigens and present them to T cells

There are two major classes of MHC molecules

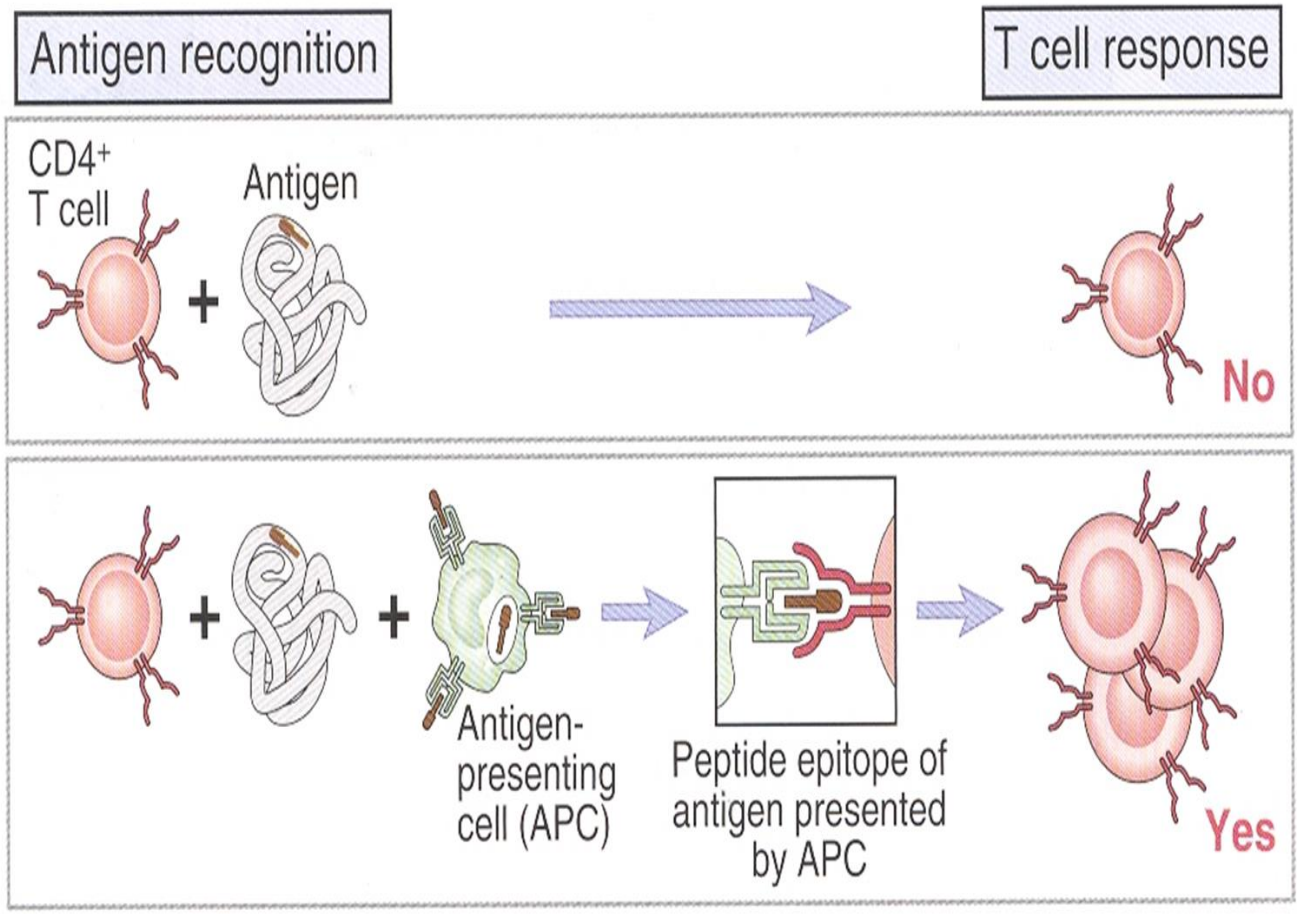
1- MHC class I molecules (MHC I) consist of one membrane .
2- MHC class II molecules (MHC II) consist of two membrane .

In each case, the MHC molecule has a groove that binds a peptide, which it can then present at the cell surface to a T cell to elicit an immune response, because T cells only recognize antigens as complexes with MHC molecules. The two classes of MHC proteins differ not only in their structure, but more importantly in their functional roles within the immune system: the two types of MHC molecules are specialized to present different types of antigens, thereby eliciting different responses.

MHC class I

MHC I glycoproteins are present by

- Every cell in the body
- Acting to present **endogenous antigens** that originate from the cytoplasm. These antigens include not only self-proteins, but also foreign proteins produced within the cell, such as **viral proteins** that take over the cell's machinery in order to replicate the virus. When these proteins become degraded, the peptide fragments can be transported to the **endoplasmic reticulum**, where they can bind to MHC I proteins, before being transported via the **Golgi apparatus** to the cell surface.
- Once at the cell surface, the membrane-bound MHC I protein displays the antigen for recognition by special immune cells known as cytotoxic T cell lymphocytes. MHC I proteins work to present the types of proteins being synthesized within a cell, which can then be monitored by killer T cells as part of a surveillance system that identifies and destroys any cell with over-abundant or unfamiliar peptide antigens, such as malignant cells or those harboring viruses.



MHC class II

MHC II glycoproteins are only present on specialized Antigen-Presenting immune Cells(APC) that include :

1- Macrophages that engulf foreign particles such as bacteria.

2- Dendritic cells that present antigen to T cells.

3- B cells that produce antibodies.

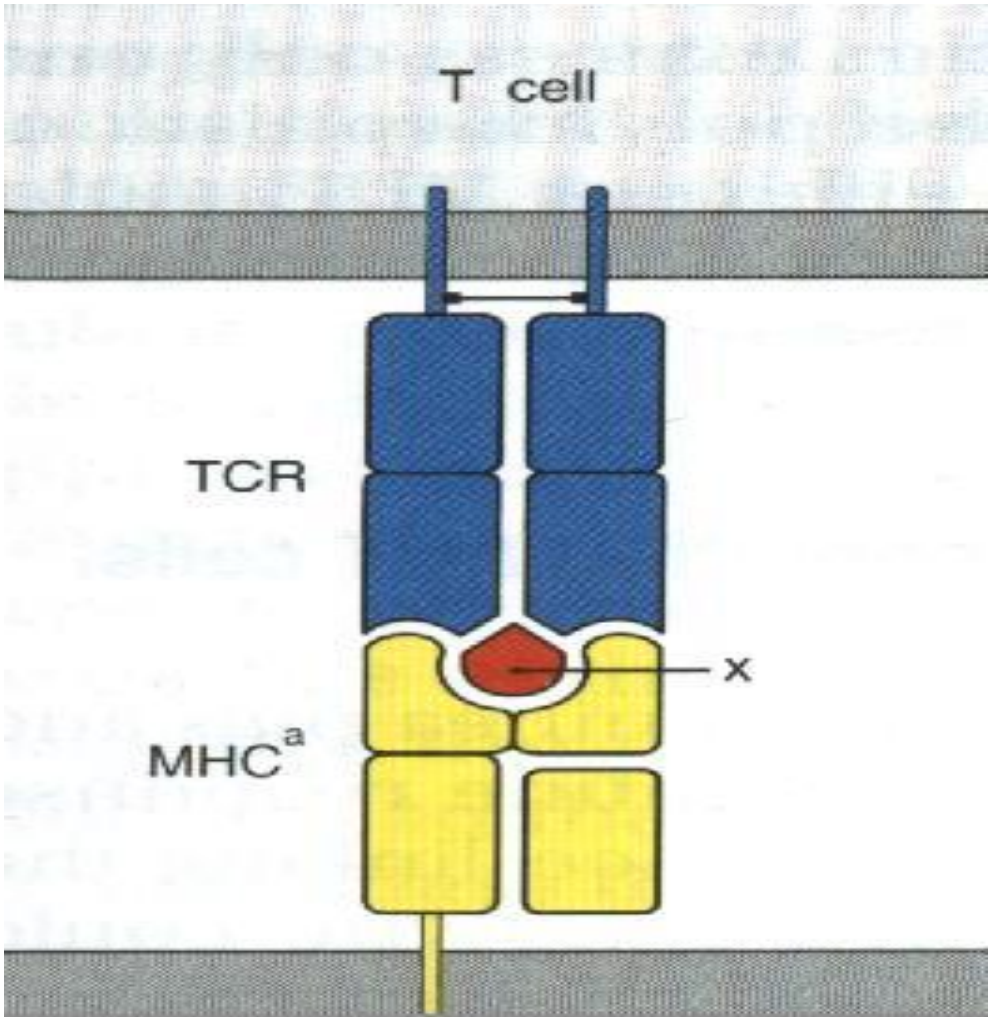
-MHC II proteins present **exogenous antigens** that originate extracellularly from foreign bodies such as **bacteria**. Upon encountering a pathogenic organism, proteins from the pathogen can be degraded into peptide fragments by the antigen-presenting cell, which then sequesters these fragments into the **endosome** so they can bind to MHC II proteins, before being transported to the cell surface.

A- Once at the cell surface, the membrane-bound MHC II protein displays the antigen for recognition by a different type of T cell, namely the helper T cell lymphocyte. These helper T cells are activated upon binding to macrophage or dendritic cell MHC II-antigen, causing the release of lymphokines that attract

other cells to the area of infection in an attempt to confine and destroy the antigenic material.

B- The binding of helper T cells to B cell MHC II-antigen stimulates the development of a clone of antibody-producing cells against the antigenic material.

In the cell-mediated , the antigen-MHC class II complex is recognized by T4 helper (CD4) T lymphocytes, while the antigen-MHC class I complex is recognized by T8 cytotoxic (CD8) T lymphocytes. Each class of T cells produces cytokines, becomes activated , and expands by clonal proliferation



Major differences between MHC classes I and II

MHC class I	MHC class II
Comprised of an MHC-encoded □chain and a □2-microglobulin chain	Comprised of MHC-encoded □and □ chains
Present on most cells	Present only on antigen-presenting cells
Bind endogenous antigens synthesized in a cell	Binds exogenous antigens
Present antigen to cytotoxic T cell lymphocytes	Present antigen to helper T cell lymphocytes
Bind CD8 adhesion molecules on cytotoxic T cells	Bind CD4 adhesion molecules on helper T cells
Presence of foreign or over-abundant antigens targets cell for destruction	Presence of foreign antigens induces antibody production, and attracts immune cells to area of infection

Cell-Mediated Immunity

In the following example, a bacterium, e.g., Mycobacterium tuberculosis, enters the body and is ingested by a macrophage. The bacterium is broken down, and fragments of it called antigens or epitopes appear on the surface of the macrophage in association with class II major histocompatibility complex (MHC) proteins. The antigen–class II MHC protein complex interacts with an antigen-specific receptor on the surface of a helper T lymphocyte Activation and clonal proliferation of this antigen-specific helper T cell occur as a result of the production of interleukins.

-Interleukin-1 (produced by macrophages) .

-Interleukin-2 (produced by lymphocytes).

These activated helper T cells, aided by activated macrophages, mediate one important component of cellular immunity i.e. a delayed Hypersensitivity reaction specifically against M. tuberculosis .

T lymphocytes are a type of lymphocyte that play a central role in cell-mediated immunity. They can be distinguished from other lymphocytes, such as B cells and natural killer cells (NK cells), by the presence of a T-cell receptor (TCR) on the cell surface. can effectively present antigens to other T cells . Type of T-
. lymphocyte:

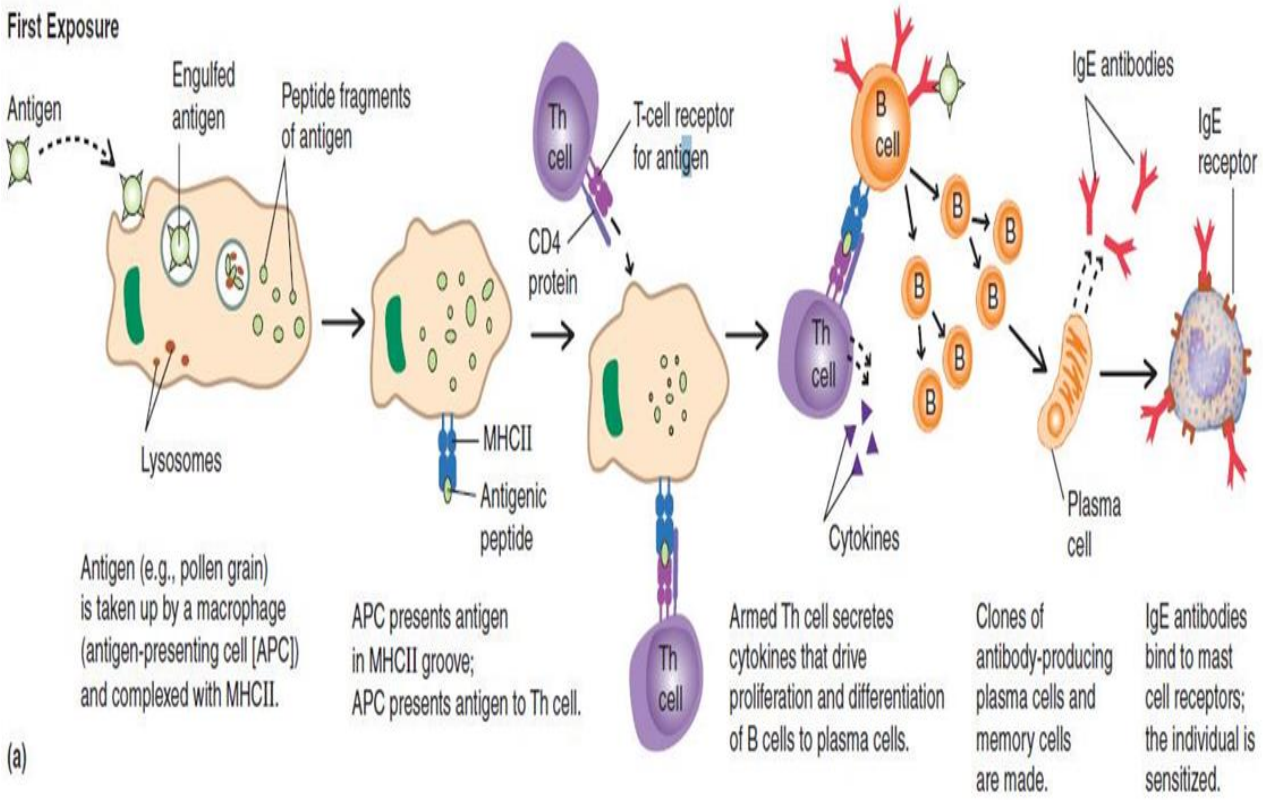
Helper :T helper cells assist other white blood cells in immunologic :
processes, including:

1- Maturation of B cells into plasma cells and memory B cells .

2-Activation of cytotoxic T cells and macrophages.

These cells are also known as CD4+ T cells because they express the CD4 glycoprotein on their surfaces **(cluster of differentiation).**

3- Secrete cytokines that regulate or assist in the active immune response



Cytotoxic

Cytotoxic T cells) destroy virus-infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T These cells recognize their targets by binding to antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells.

,In this example, a virus

1-e.g., influenza virus, is inhaled and infects a cell of the respiratory tract.

2- Viral envelope glycoproteins appear on the surface of the infected cell in association with class I MHC proteins.

3- A cytotoxic T cell binds via its antigen-specific receptor to the viral antigen–class I MHC protein complex and is stimulated to grow into a clone of cells by interleukin-2 produced by helper T cells.

4-These cytotoxic T cells specifically kill influenza virus–infected cells (and not cells infected by other viruses) by recognizing viral antigen–class I MHC

protein complexes on the cell surface and releasing perforins that destroy the .membrane of the infected cell

Memory T cells are a subset of antigen-specific T cells that persist long-term after an infection has resolved. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections.

Suppressor T cells, Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto reactive T cells , its have regulatory functions

Natural killer

They play a role in antibody-dependent cellular cytotoxicity (ADCC) and have a role in the early phases of infection with **herpes viruses** and other intracellular .pathogens

Natural killer (NK) cells are

1- Large granular lymphocytes that do not pass through the thymus

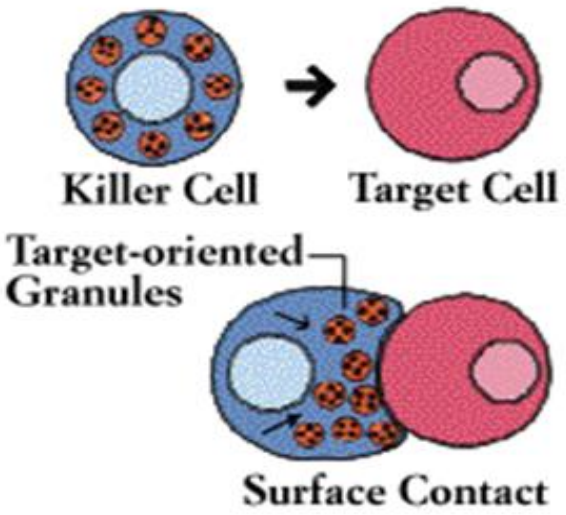
2-Do not have an antigen receptor, and do not bear CD4 or CD8 proteins.

3- They recognize and kill target cells, such as virus-infected cells and tumor cells, without the requirement that the antigens be presented in association with class I or class II MHC proteins.

Rather, NK cells target those cells to be killed by detecting that they do not display class I MHC proteins on the cell surface. This detection process is effective because many cells lose their ability to synthesize class I MHC proteins after they have been infected by a virus

Natural Killer (NK) cells are yet another type of lethal lymphocyte. Like cytotoxic T cells, they contain granules filled with potent chemicals. They are called "natural" killers because they, unlike cytotoxic T cells, do not need to recognize a specific antigen before swinging into action. They target tumor cells and protect against a wide variety of infectious microbes. In several immunodeficiency diseases, including AIDS, natural killer cell function is abnormal. Natural killer cells may also contribute to immunoregulation by .secreting high levels of influential lymphokines

Both cytotoxic T cells and natural killer cells kill on contact. The killer binds to its target, aims its weapons, and then delivers a lethal burst of chemicals that produces holes in the target cell's membrane



References:

Review of Medical Microbiology & Immunology: A Guide to Clinical Infectious Diseases, 15e.

Chapter 62: Major Histocompatibility Complex & Transplantation