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Important in **red**
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Immunology
MED438

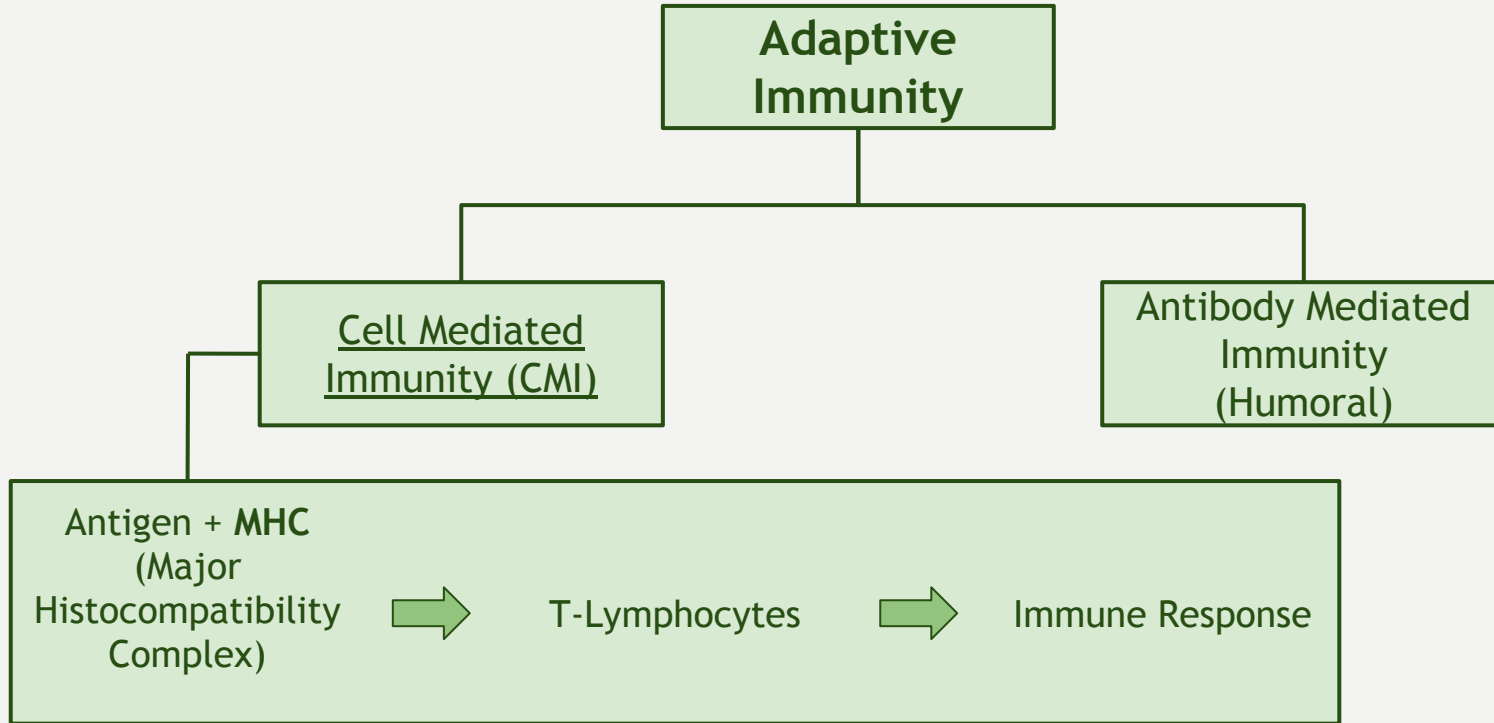
Cell Mediated Immunity



Objectives

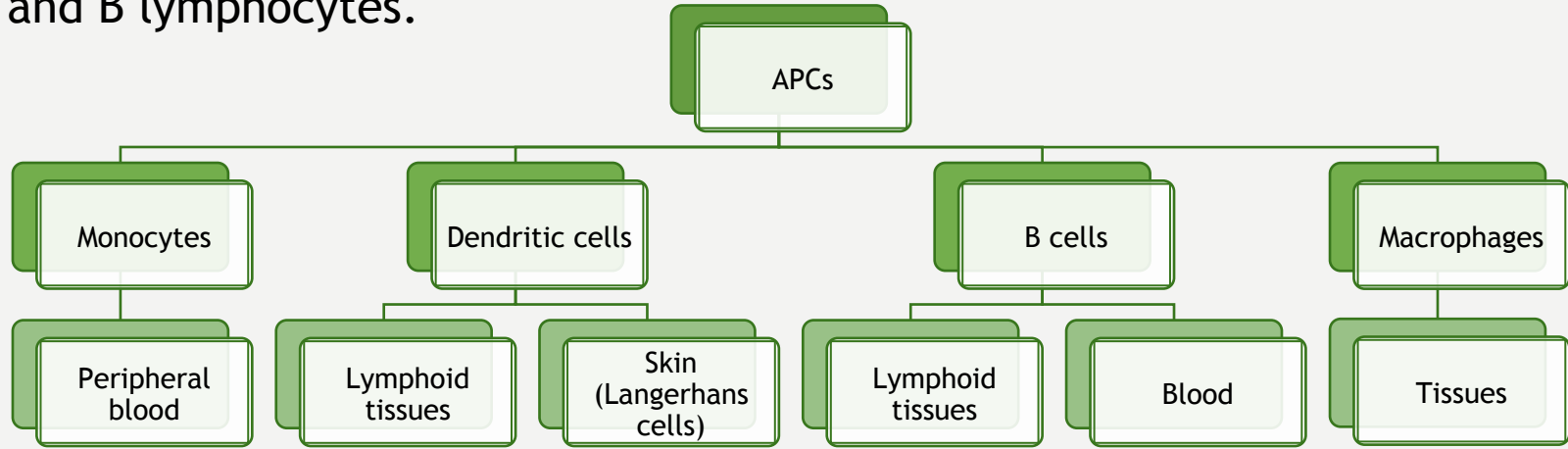
- To describe antigen recognition by T cells
- To describe the pathways involved in processing endogenous and exogenous antigens
- To discuss self MHC restriction in Ag presentation to T cells
- To describe the induction of cell mediated immunity (Chronic Inflammation)

Types of Adaptive Immunity

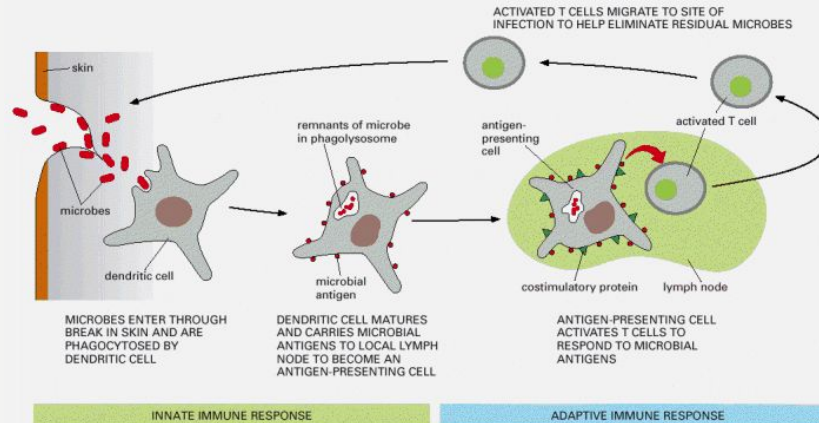


Lymphocytes (T,B and NK cells) and Monocytes are called mononuclear cells (consist of one round nucleus), and they are associated with inflammation (body's internal fire alarm).

Antigen Presenting Cells (APCs): Cells that process the antigen by “**breaking it down**” into amino acids and then **presenting** it to T and B lymphocytes.

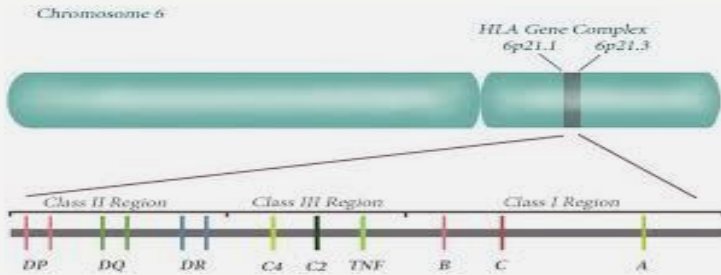


The process of a dendritic cell becoming an APC (also showing how innate and adaptive immune responses correlate).

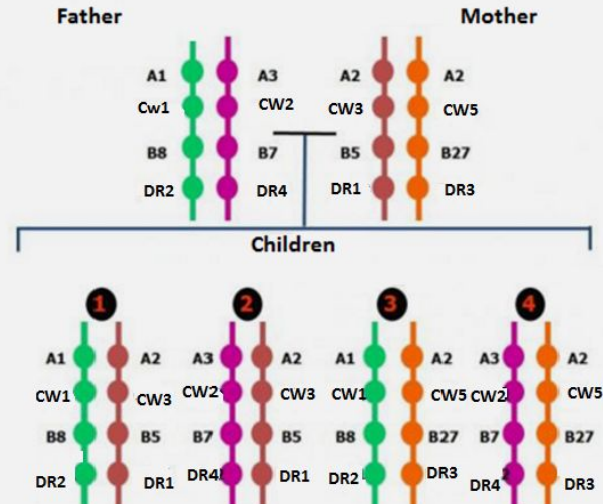


Major Histocompatibility Complex (MHC)

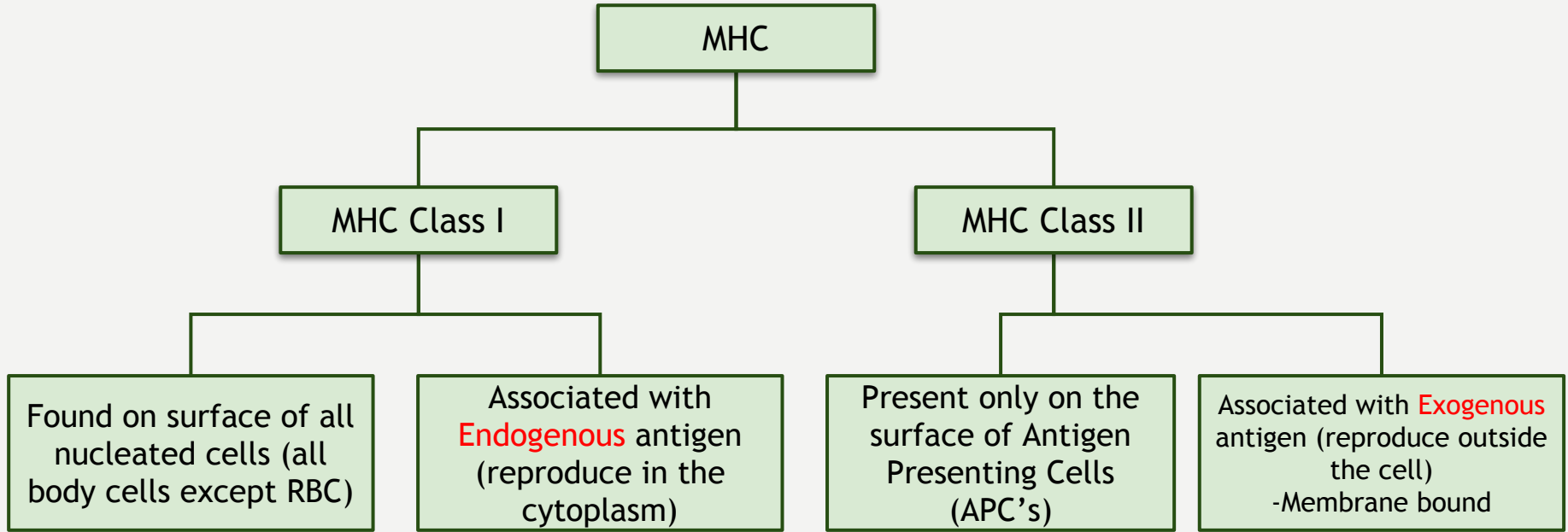
- MHC's are a group of proteins found on the surfaces of cells. They are essential for antigen **recognition** and organ **transplants**.
- Inside the MHC are Human Leukocyte Antigens (HLA), encoded by HLA genes clustered in the short arm of chromosome 6. In an organ transplant, the donor and recipient must have **matching** HLA's. *Note: HLA and MHC are basically different names of the same thing.*
- Each individual has two HLA gene haplotypes (one set from each parent).



The HLA genes are Co-dominant (both from are expressed)



MHC Classifications



Note:

MHC Class I molecules take peptides from our body's normal intracellular proteins and present them on the surface of the cell to inform cytotoxic (CD8) T cells that the cell is normal.

Can only recognize antigens in the form of MHC-peptide

APC's can express both MHC Classes since they are nucleated

Summary of MHC Biological Importance

01

Antigen Recognition
(Also called MHC
Restriction)

- Cytotoxic T cells (CD8) kill virus-infected cells in association with MHC Class I molecules
- Helper T cells (CD4) recognize antigens in association with MHC Class II molecules

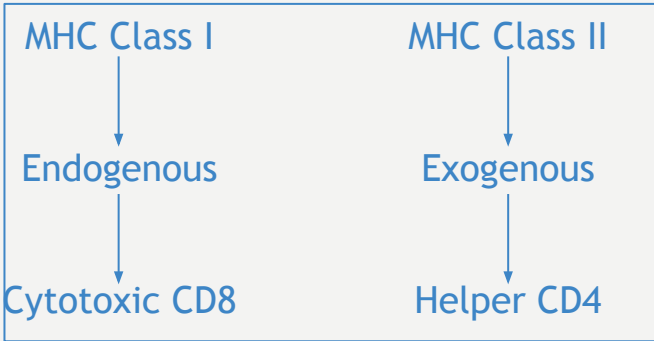
02

Organ Transplants

- Organ transplant success is determined by the compatibility of MHC genes

Endogenous and Exogenous Presenting Pathways Summary

There are **two** pathways in which an MHC molecule presents an Ag (antigen) to the T cells based on whether it is an **endogenous** or **exogenous** Ag.

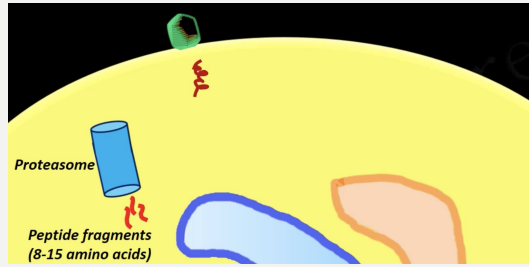


Endogenous Pathway:



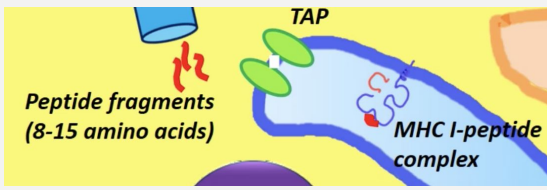
Dissociation

Viral proteins are taken inside Proteasome (where they are digested to peptide fragments)



MHC I Binding

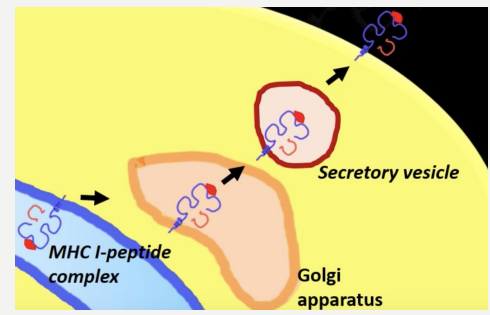
The fragments are transported by TAP (Transporters associated with Antigen Processing) to the Rough ER where they bind with MHC Class I molecules.



Why are MHC molecules synthesized in the RER?
Recall that RER is the site of protein synthesis

Surface Display

The MHC I-peptide complex is then transported to the Golgi Apparatus, where it secretes it to the surface of the cell. There, it interacts with the receptor of a Cytotoxic CD8 Cell.

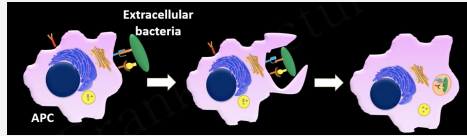


Endogenous and Exogenous Presenting Pathways Summary (Continued)

Exogenous Pathway:

Internalization

The extracellular antigen (e.g. bacteria) is engulfed by an APC and surrounded by an intracellular vesicle known as an endosome (hence the name membrane bound).



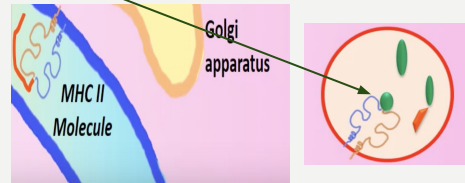
Fusion/Dissociation

The endosome fuses with lysosomes to form endolysosome, where the antigen is digested to peptide fragments.



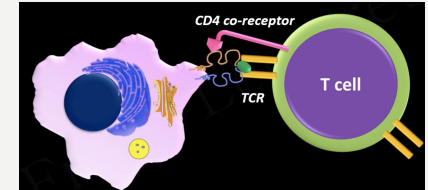
MHC II Binding

MHC Class II molecules are synthesized in the Rough ER. They are transported to the Golgi Apparatus, and then put inside a vesicle. This vesicle will bind with the endolysosome, where the antigen binds to the MHC class II molecule.

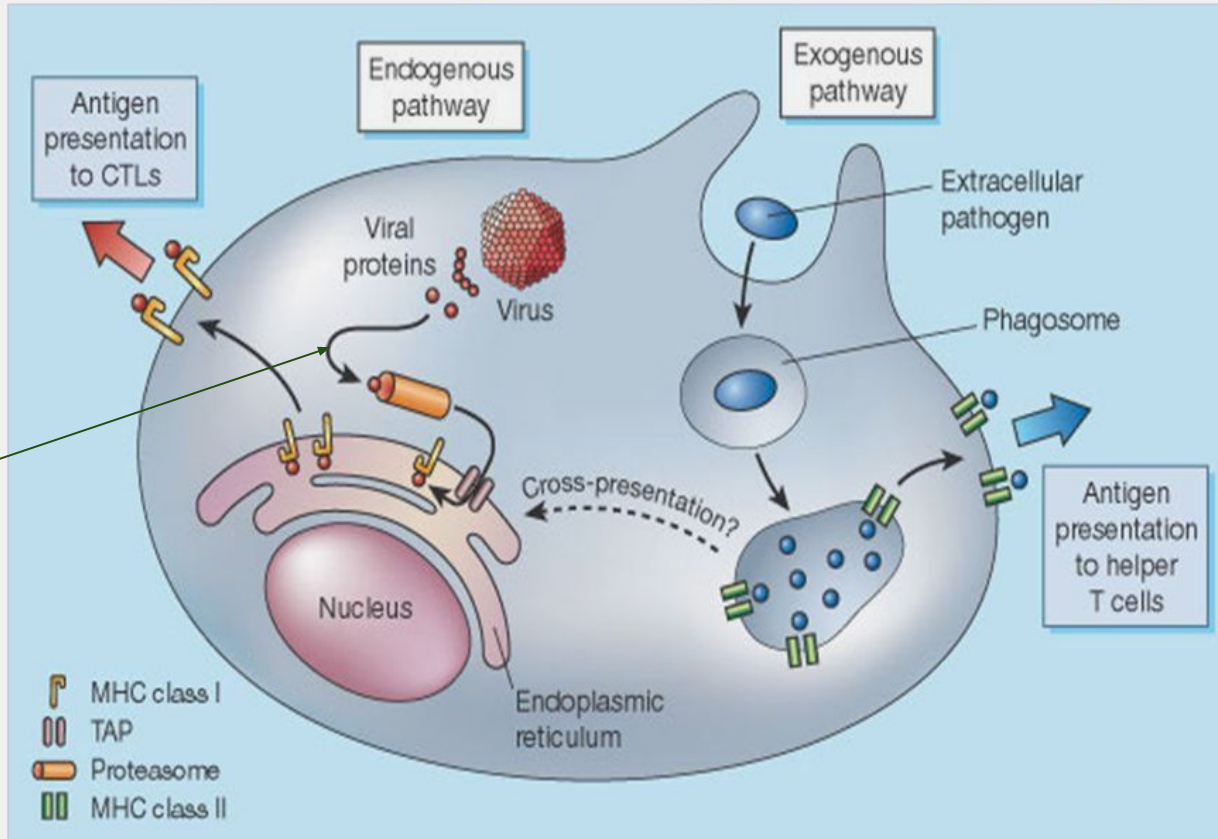


Surface Display

The MHC II-peptide complex is displayed on the surface of the cell, where it will interact with the receptor of a T helper (CD4) cell.



Endogenous and Exogenous Antigen Presenting Pathways

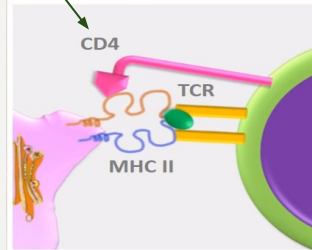


T-cell Activation

T-cell activation is a **TWO-SIGNAL** process.

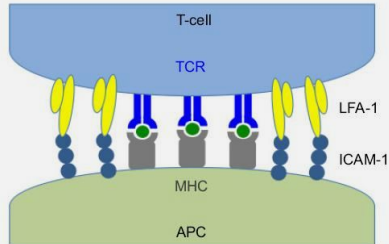
First Signal:

-Recognition and binding of MHC-peptide complex to **TCR** (T-Cell Receptor) and **CD4** (T-Cell Co-receptor)



-This step also includes stimulation from **accessory molecules** IL-1 (interleukin 1), and the binding of LFA-1 (Lymphocyte Function-associated Antigen) with its ligand ICAM-1 (Intercellular Adhesion Molecule)

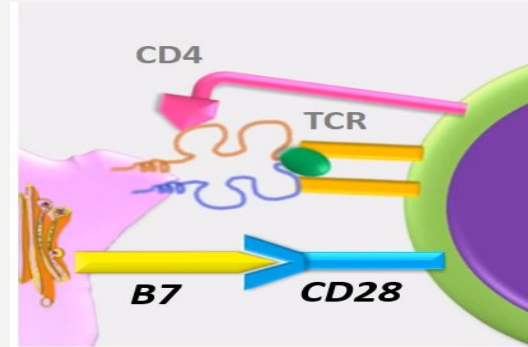
Without the accessory molecules, the first signal is impaired which causes a dysfunction in T helper cells, leading to intracellular infections.



Second Signal (known as **Costimulation**):

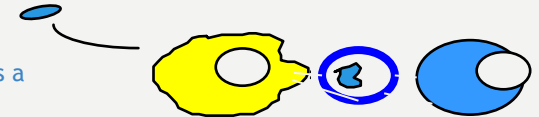
-Most important costimulators in this process are **B7** (CD80) and **CD28**, located in the APC and T-cell respectively.

-This signal involves the binding of B7 and CD28



Costimulators include cytokines or a pair of plasma membrane molecules

Side note:
MHC-peptide-T cell receptor is known as a trimolecular complex



T Cell Activation Outcome

-Production of IL-2

Once a T cell has been activated, it begins producing **Interleukin 2 (IL-2)** and its receptor (found on the T cell itself).

The IL-2 (also known as T cell growth factor) will then make the T-cell undergo the following:

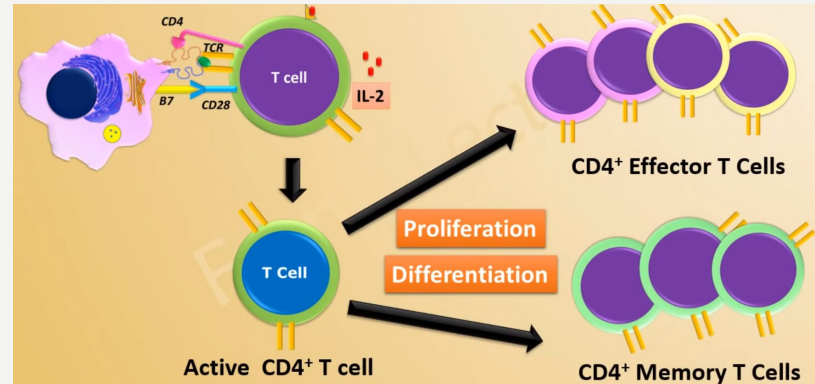
- 1- **Proliferation**: rapid multiplying
- 2- **Differentiation**: in this process, some T cells become **effectors** (CD4 or CD8), **regulators** (prevent autoimmunity), or **memory** T cells (large number at first to improve secondary response).

IL-2 also causes T Helper Cells to stimulate T Cytotoxic cells

(Recall the functions of Th1 and Th2)

Functions:

- Rapid response in future encounters
- Live for many years and have the capacity to multiply
- Produce greater amounts of Interleukins
- Activated by smaller amount of antigen



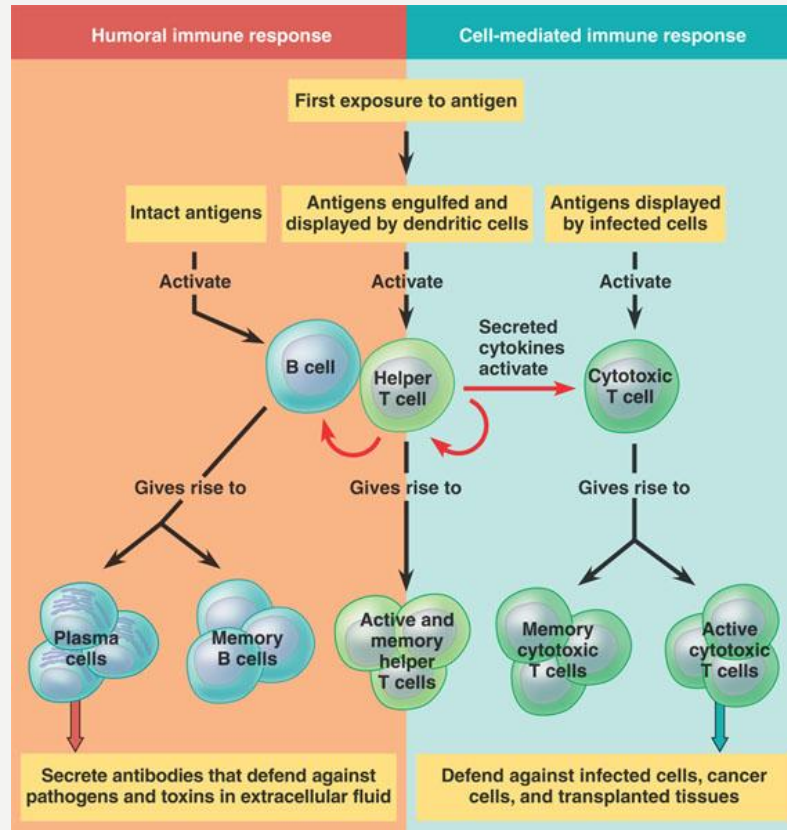
Proliferation: The CD4 helper T cell (effector) makes more copies of itself

Differentiation: The effector CD4 T cell differentiates into memory CD4 T cells

-Production of Interferons

Enhance anti-microbial activity of macrophages (boost the immune system)

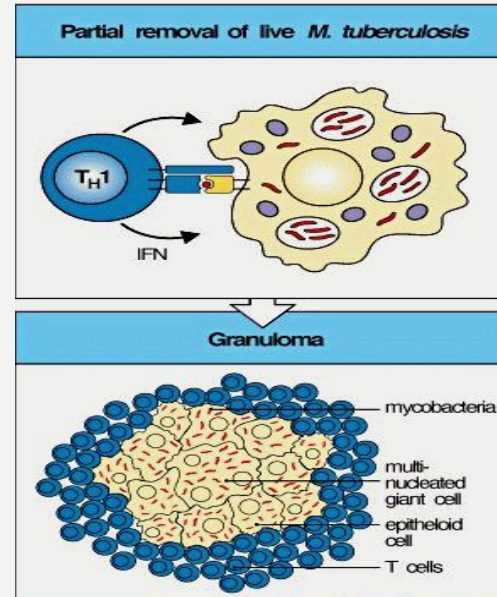
Short Summary of Humoral and Adaptive Immunities



Granuloma Formation

Granuloma is a collection of **macrophages** that form on the surface of wounds (inflammation). They form when the immune system tries to block foreign substances from spreading by **surrounding** them.

Since macrophages are APC's, they will have MHC Class II presented on their surface, which will lead to T helper cell (CD4) activation, triggering a CMI response.



Examples of Cell Mediated Immunity

Delayed type hypersensitivity (DTH) reaction:

The tuberculin test:

Some patients, when injected with the *M. tuberculosis* bacterium develop a delayed hypersensitivity reaction as a result of the immune system acting against that bacterium.

Mediated by **CD4+ T cells** and takes about 72 hours to develop



Contact hypersensitivity:

Many people develop rashes on their skin following contact with certain chemicals such as nickel, certain dyes, and poison ivy plant

The response takes some 24 hours to occur and like DTH, is triggered by **CD4+ T cells**

Contact dermatitis



Take Home Message

- Cell mediated adaptive immune response is specific and develops after exposure to a pathogen (antigen).
- Initial antigen exposure results in generation of memory cells for a stronger and a quicker response against future exposures to the same pathogen.
- It is usually associated with chronic infections.
- Antibodies are not involved.

Quiz:

1. Which of the following is the location of the HLA?

- a) Long arm of chromosome 6
- b) Short arm of chromosome 9
- c) Short arm of chromosome 6
- d) Long arm of chromosome 9

2. The Cell with no MHC Class I is:

- a) Muscle cell
- b) Red blood cell
- c) White blood cell
- d) Endothelial cell

3. In a virus-infected cell, which of the following will alert the T cells?

- a) MHC Class I molecules
- b) MHC Class II molecules
- c) B Lymphocytes
- d) None of the above

4. Where does the antigen bind to the MHC Class II molecule?

- a) Rough ER
- b) Golgi Apparatus
- c) Cytosol
- d) Endolysosome

5. Which of the following is considered a costimulator?

- a) MHC molecules
- b) CD80
- c) IL-2
- d) ICAM-1

6. In a granuloma, which type of cells will be largely activated to trigger an immune response?

- a) Cytotoxic T cells
- b) B Cells
- c) Helper T cells
- d) Basophils

Team Leaders:

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