BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Code: BM35C6

Course Title: Immunology

Unit-I

Organs of the Immune system

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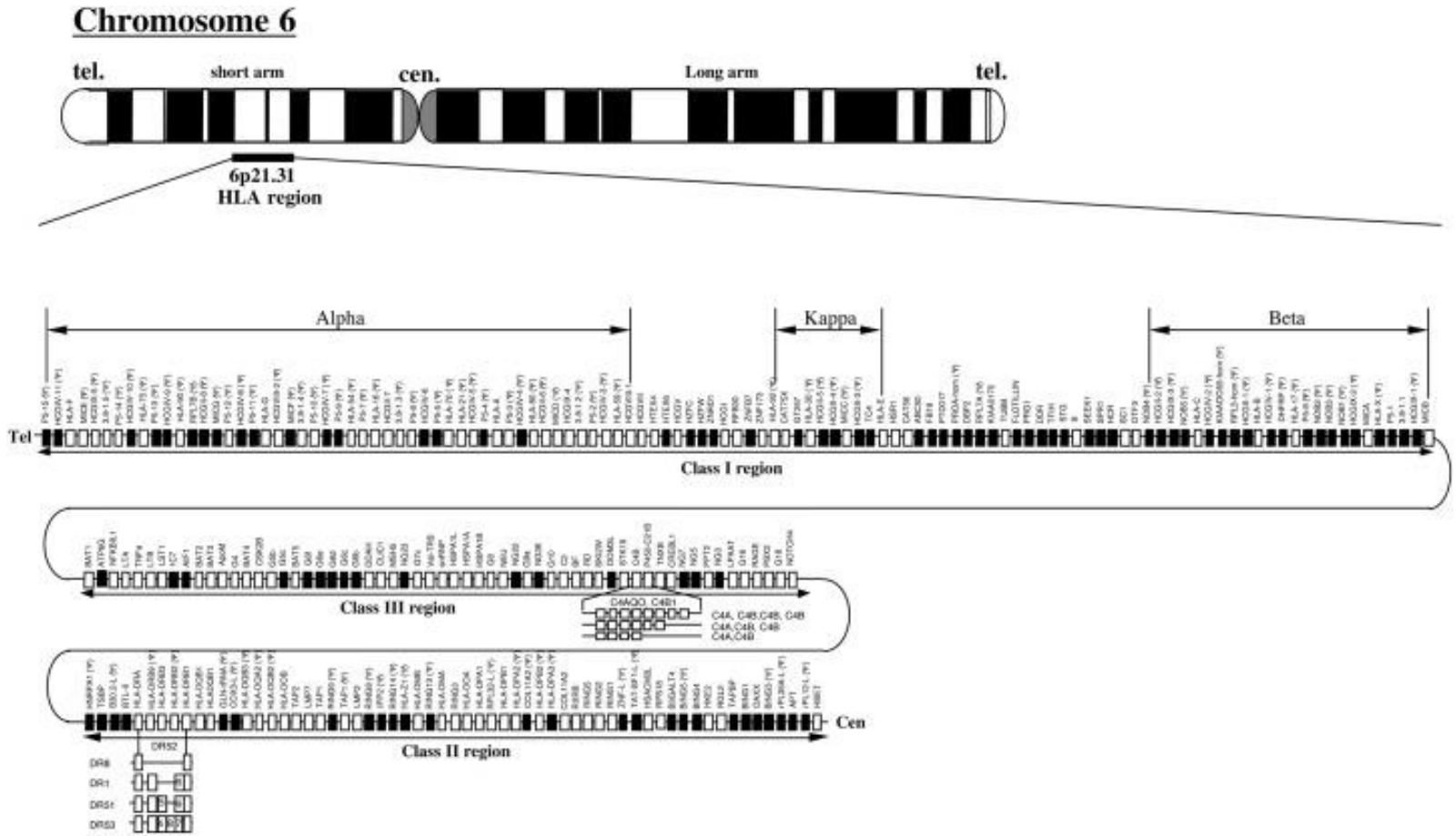
Unit I:

Organs of the immune system – Primary and secondary lymphoid organs- Types of immunity – Innate and acquired immunity. Innate immunity – Cellular components - Phagocytic cells, inflammatory cells and NK cells, Acquired immunity- Cellular components of adaptive immune system – T cells - B lymphocytes –lymphocytes trafficking between lymphoid tissues. Recognition molecules and receptors of innate immune systems - PAMPs, CD1 molecule and MBL (mannose binding lectins) - Pattern recognition receptors (PRRs), TLRs, KIR, Fc gamma receptors (FcγRIa, FcγRIIa and FcγRIIIa)- Complement receptors. Recognition molecules and receptors of adaptive immune systems - MHC molecules- genomic map of MHC genes, cellular distribution and expression, Antigen processing and presentation – the cytosolic pathway and endocytic pathway- Receptors of adaptive immune system – TCR and BCR.

PRESENTATION: 3

Genomic Map of MHC Genes



Genomic Map of MHC Genes:

- The Major Histocompatibility Complex (MHC) is a highly polymorphic region of the genome located on chromosome 6 in humans.
- It is divided into several classes, with the main regions being the **MHC class I**, **MHC class II**, and **MHC class III** regions.

1. MHC Class I Region:

Location: Found in the telomeric region of the MHC locus on chromosome 6.

Main Genes:

- **HLA-A**: Encodes one of the MHC class I molecules.
- **HLA-B**: Encodes another MHC class I molecule.
- **HLA-C**: Encodes a third MHC class I molecule.
- **HLA-E**, **HLA-F**, and **HLA-G**: Encode non-classical MHC class I molecules with roles in immune regulation and fetal-maternal interactions.

Genetic Organization: The MHC class I genes are located in a cluster, with HLA-A, HLA-B, and HLA-C being the classical class I genes most commonly studied.

2. MHC Class II Region:

Location: Located in the centromeric region of the MHC locus on chromosome 6.

Main Genes:

- **HLA-DP**: Includes the genes **HLA-DPA1** and **HLA-DPB1**, encoding MHC class II molecules.
- **HLA-DQ**: Includes the genes **HLA-DQA1** and **HLA-DQB1**, encoding additional MHC class II molecules.
- **HLA-DR**: Includes multiple genes such as **HLA-DRA**, **HLA-DRB1**, **HLA-DRB3**, **HLA-DRB4**, and **HLA-DRB5**, encoding various MHC class II molecules.

Genetic Organization: MHC class II genes are organized into several loci, with HLA-DP, HLA-DQ, and HLA-DR each containing α and β chains.

3. MHC Class III Region:

Location: Located between the MHC class I and class II regions on chromosome 6.

Main Genes:

- **Complement Component Genes**: Includes genes for complement components like **C2**, **C4A**, and **C4B**.
- **Cytokine Genes**: Includes genes for tumor necrosis factor (TNF) and lymphotoxin (LT).
- **Heat Shock Protein Genes**: Includes genes like **HSP70**.

Genetic Organization: The MHC class III region encodes various immune-related genes that are not directly involved in antigen presentation but support immune responses.

CELLULAR DISTRIBUTION AND EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX

- **Cellular distribution and expression** of Major Histocompatibility Complex (MHC) molecules are crucial for their roles in antigen presentation and immune system function. Here's a detailed overview of where and how MHC molecules are expressed on different cell types:

1. MHC Class I Molecules

- **Cellular Distribution**

- **Nucleated Cells**: MHC class I molecules are expressed on almost all nucleated cells in the body, including:
    - **Somatic Cells**: Such as epithelial cells, fibroblasts, and muscle cells.
    - **Hematopoietic Cells**: Including most types of blood cells (except mature red blood cells).

Expression and Function

- **Presentation to CD8+ T Cells**: MHC class I molecules present endogenous peptides (from intracellular proteins) to CD8+ cytotoxic T lymphocytes.
- **Role in Immune Surveillance**: This broad expression allows the immune system to monitor the health of all cells, detect viral infections, and identify tumor cells.

2. MHC Class II Molecules

Cellular Distribution

- **Antigen-Presenting Cells (APCs)**: MHC class II molecules are primarily expressed on specialized APCs, including:
  - **Dendritic Cells**: Found in tissues and lymphoid organs, these cells are crucial for initiating immune responses.
  - **Macrophages**: Present in tissues and organs, involved in phagocytosis and antigen presentation.
  - **B Cells**: Found in lymphoid organs and peripheral blood, where they help in antibody production and antigen presentation.
- **Induced Expression**: MHC class II expression can also be induced on other cells (e.g., endothelial cells and certain epithelial cells) during inflammatory responses.

Expression and Function

- **Presentation to CD4+ T Cells**: MHC class II molecules present exogenous peptides (from extracellular proteins that have been processed and presented by the APC) to CD4+ helper T lymphocytes.
- **Role in Immune Activation**: This interaction helps activate CD4+ T cells, which then provide help to B cells, cytotoxic T cells, and other immune cells.

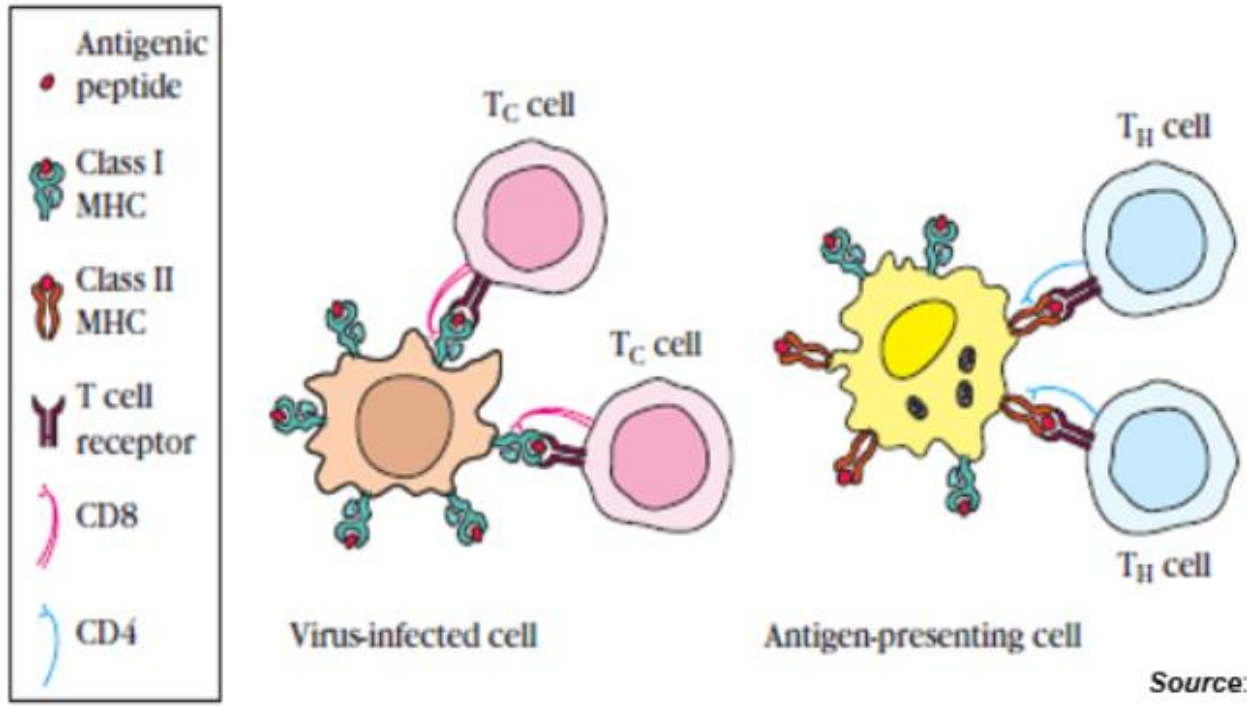
3. MHC Class III Molecules

Cellular Distribution

General Expression: MHC class III molecules are not restricted to specific cell types and are expressed broadly across various cells.

- **Expression and Function**

Supportive Role: MHC class III molecules are involved in various immune functions, including complement activation, inflammation, and stress responses, but do not directly present antigens to T cells.



Source: Kuby immunology 2007, 5th ed

Class I MHC molecules are expressed on nearly all nucleated cells. Class II MHC molecules are expressed only on antigenpresenting cells. T cells that recognize only antigenic peptides displayed with a class II MHC molecule generally function as T helper (TH) cells. T cells that recognize only antigenic peptides displayed with a class I MHC molecule generally function as T cytotoxic (TC) cells.

ANTIGEN PROCESSING AND PRESENTATION

1. Cytosolic /Endogenous Pathway (endogenous antigens, MHC Class I, CD8+ cytotoxic T cells)

The cytosolic pathway is primarily responsible for presenting endogenous antigens (i.e., peptides derived from proteins synthesized within the cell) to MHC class I molecules. This pathway is crucial for immune surveillance against intracellular pathogens like viruses and for detecting abnormal or cancerous cells.

Steps

1. **Protein Degradation**:
    1. **Proteasome**: Proteins synthesized within the cell are degraded into peptide fragments by the proteasome, a large protease complex in the cytoplasm.
    2. **Ubiquitination**: Proteins targeted for degradation are tagged with ubiquitin molecules, marking them for processing by the proteasome.

2. Peptide Transport:

1. **Transporter Associated with Antigen Processing (TAP)**: Peptides generated by the proteasome are transported into the endoplasmic reticulum (ER) by TAP, a heterodimeric transporter.

3. Peptide Loading:

1. **MHC Class I Molecule Assembly**: In the ER, the MHC class I molecule is assembled with its α chain and β2-microglobulin. The peptide-binding groove is formed by the α1 and α2 domains.
2. **Peptide Binding**: Peptides are loaded onto the MHC class I molecule within the ER. Only peptides that fit into the binding groove are stably associated with the MHC molecule.

4. Transport to Cell Surface:

1. **Golgi Apparatus**: The MHC class I-peptide complex is transported from the ER to the Golgi apparatus, where it undergoes further modifications.
2. **Cell Membrane**: The MHC class I-peptide complex is then transported to the cell surface, where it can be recognized by CD8+ cytotoxic T cells.

2. Endocytic/Exogenous Pathway- (exogenous antigens, MHC class II, CD4+ helper T cells)

The endocytic pathway is responsible for presenting exogenous antigens (i.e., peptides derived from extracellular proteins that are internalized by the cell) to MHC class II molecules. This pathway is crucial for the activation of CD4+ helper T cells and for coordinating the immune response.

Steps Antigen Uptake:

1. **Endocytosis/Phagocytosis**: Extracellular antigens are taken up by antigen-presenting cells (APCs) through endocytosis (for soluble antigens) or phagocytosis (for larger particles like bacteria).

1. Antigen Processing:

1. **Endosomal/Lysosomal Degradation**: Internalized antigens are transported to endosomes and lysosomes, where they are degraded into peptide fragments by proteolytic enzymes.

2. Peptide Loading:

1. **MHC Class II Molecule Assembly**: MHC class II molecules are synthesized in the ER and associated with an invariant chain (Ii), which blocks the peptide-binding groove and prevents premature peptide binding.
2. **Invariant Chain Removal**: The MHC class II molecules are transported to the endosomal compartment, where the invariant chain is degraded, leaving a small fragment known as CLIP (class II-associated invariant chain peptide) in the peptide-binding groove.
3. **Peptide Exchange**: CLIP is replaced by the antigenic peptide in the endosomal compartment.

3. Transport to Cell Surface:

1. **Cell Membrane**: The MHC class II-peptide complex is transported from the endosomal compartment to the cell surface, where it can be recognized by CD4+ helper T cells.

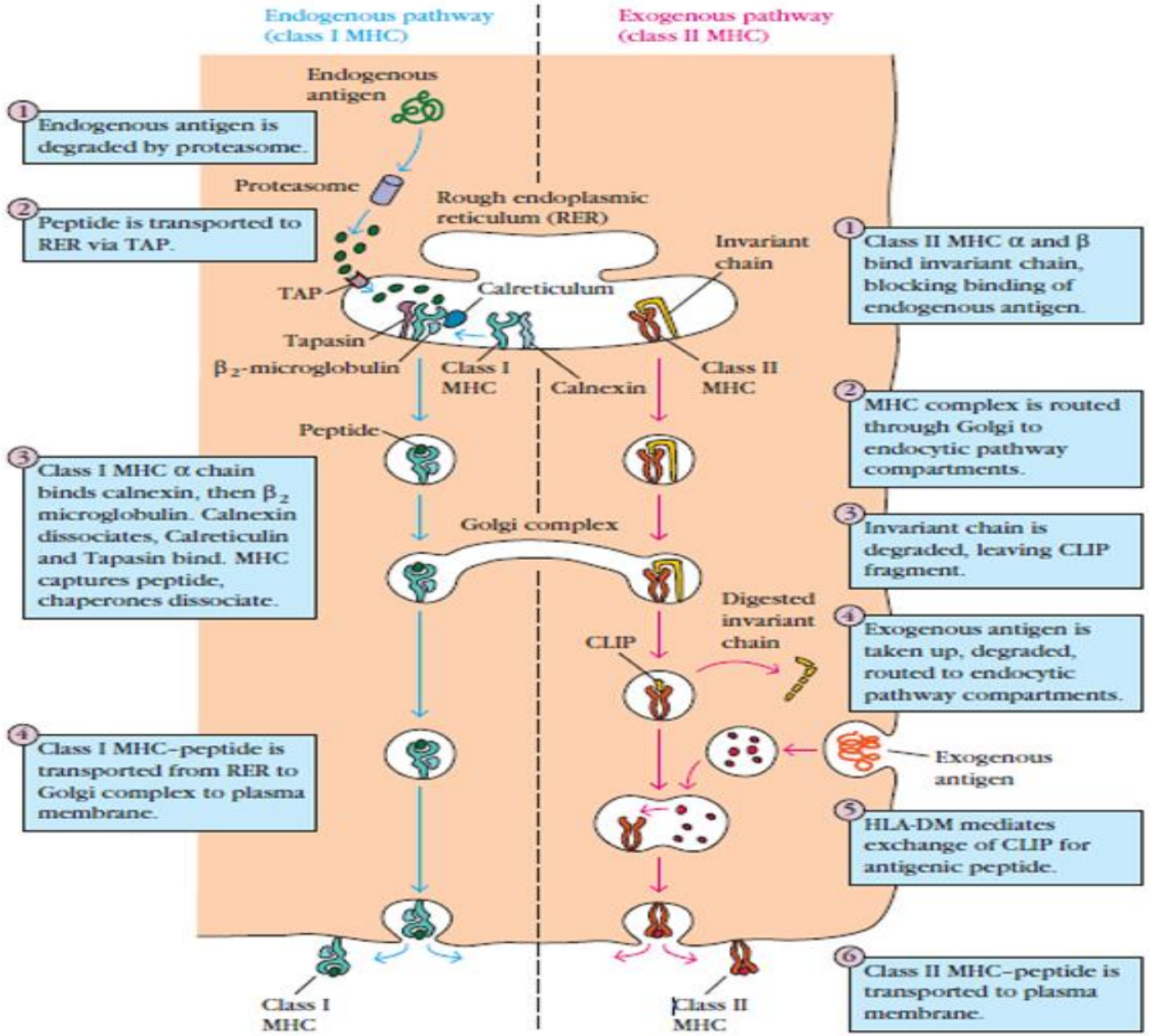


Figure2: Separate antigen-presenting pathways are utilized for endogenous (green) and exogenous (red) antigens. The mode of antigen entry into cells and the site of antigen processing determine whether antigenic peptides associate with class I MHC molecules in the rough endoplasmic reticulum or with class II molecules in endocytic compartments.

Summary

- **Cytosolic Pathway**:

  Processes and presents endogenous antigens via MHC class I molecules, primarily to CD8+ T cells.

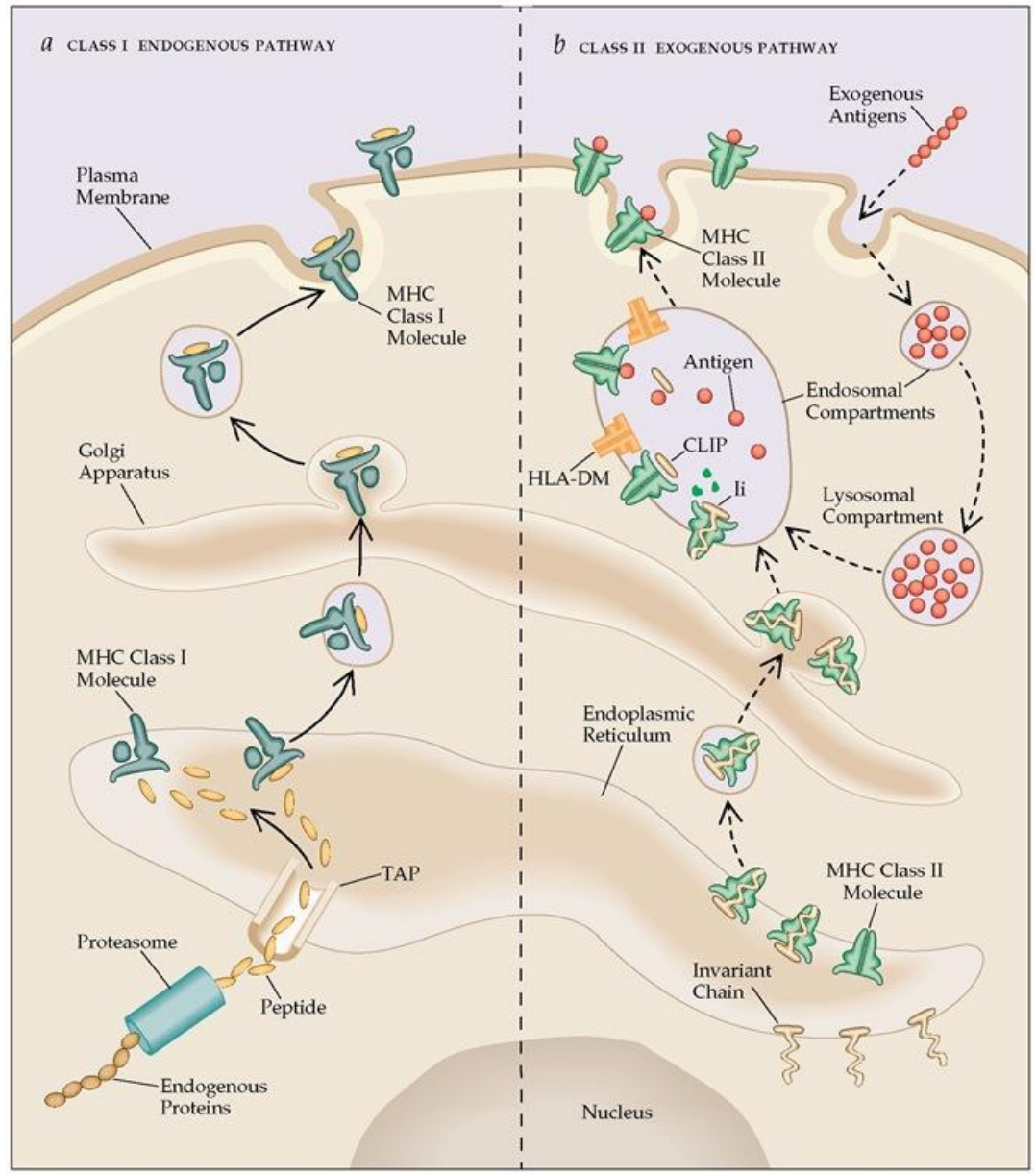
  It involves protein degradation by the proteasome, peptide transport by TAP, and peptide loading in the ER.

- **Endocytic Pathway**:

  Processes and presents exogenous antigens via MHC class II molecules, primarily to CD4+ T cells.

  It involves antigen uptake by endocytosis or phagocytosis, peptide processing in endosomes/lysosomes, and peptide loading after the removal of the invariant chain.

EXOGENOUS AND ENDOGENOUS PATHWAY



RECEPTORS OF ADAPTIVE IMMUNE SYSTEM

- **T Cell Receptors (TCRs)** and **B Cell Receptors (BCRs)** are important components of the adaptive immune system, responsible for recognizing and binding specific antigens.
- Each type of receptor has unique structures and functions that enable T cells and B cells to effectively respond to pathogens.

1. T Cell Receptors (TCRs)

Structure

Chains: TCRs are composed of two polypeptide chains, either α and β chains (in most T cells) or γ and δ chains (in some T cells).

- **Alpha/Beta TCRs**: The most common type, consisting of an α chain and a β chain.
- **Gamma/Delta TCRs**: Consist of a γ chain and a δ chain.

- **Variable and Constant Regions**: Each chain has a variable (V) region and a constant (C) region. The variable regions are involved in antigen recognition.
- **Antigen-Binding Site**: The antigen-binding site is formed by the combination of the variable regions of the α and β chains.

- **Function**
- **Antigen Recognition**: TCRs recognize specific peptide antigens presented by MHC molecules on the surface of antigen-presenting cells (APCs).
  - **MHC Class I**: Presents endogenous peptides to CD8+ cytotoxic T cells.
  - **MHC Class II**: Presents exogenous peptides to CD4+ helper T cells.
- **Activation**: Upon binding to the peptide-MHC complex, TCRs initiate intracellular signaling cascades that lead to T cell activation, proliferation, and differentiation.

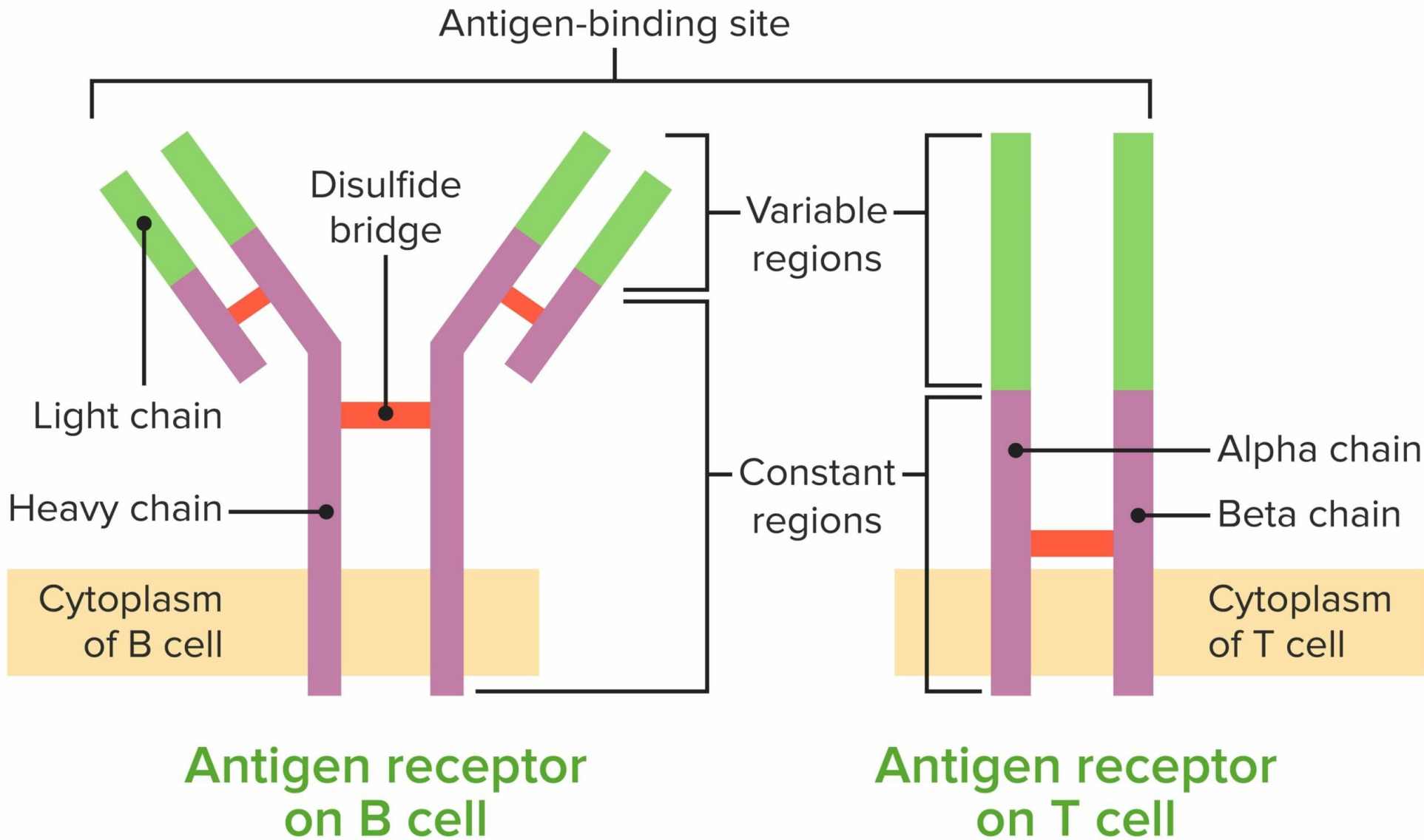
2. B Cell Receptors (BCRs)

Structure

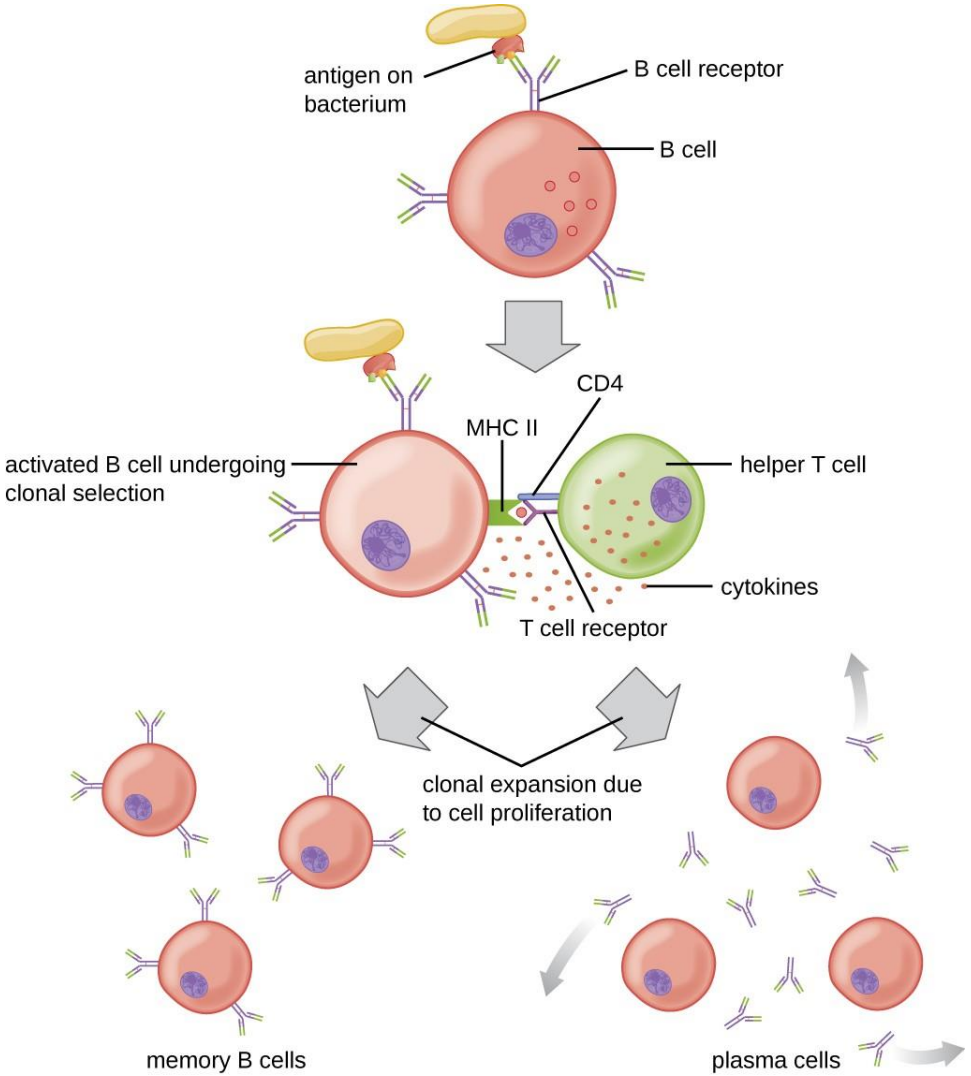
- **Immunoglobulin Structure**: BCRs are membrane-bound immunoglobulins (Ig) that have a similar structure to antibodies. They are composed of:
  - **Heavy Chains**: Two heavy chains form the main structure of the BCR.
  - **Light Chains**: Two light chains bind to the heavy chains to form a Y-shaped molecule.
  - **Variable and Constant Regions**: The variable regions of the heavy and light chains form the antigen-binding site, while the constant regions mediate effector functions.
- **Antigen-Binding Site**: Located at the tips of the Y-shaped molecule, the antigen-binding site recognizes specific antigens.

Functions:

- **Antigen Recognition**: BCRs bind directly to free-floating antigens, such as proteins, polysaccharides, or other molecules. The antigen-binding results in B cell activation.
- **Activation and Differentiation**: Upon antigen binding, B cells can differentiate into plasma cells that secrete antibodies or memory B cells that provide long-term immunity.


Antigen-binding site
Disulfide bridge
Variable regions
Light chain
Heavy chain
Constant regions
Alpha chain
Beta chain
Cytoplasm of B cell
Cytoplasm of T cell
Antigen receptor on B cell
Antigen receptor on T cell

B Cell Receptors (BCRs)



Summary

- **T Cell Receptors (TCRs)**:
  - **Structure**: Composed of α and β chains (or γ and δ chains), with variable and constant regions.
  - **Function**: Recognize peptide-MHC complexes on APCs, leading to T cell activation.
  - **Repertoire**: Generated through somatic recombination to recognize diverse antigens.
- **B Cell Receptors (BCRs)**:
  - **Structure**: Immunoglobulins with heavy and light chains, forming a Y-shaped molecule.
  - **Function**: Bind directly to antigens, leading to B cell activation and antibody production.
  - **Repertoire**: Generated through somatic recombination to recognize diverse antigens.

ACKNOWLEDGEMENT

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