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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: 2

Recognition Molecules and Receptors of Innate immune system

- The innate immune system relies on a set of recognition molecules and receptors to **detect pathogens and initiate an immediate response**. They are

1. Pathogen-Associated Molecular Patterns (PAMPs)

PAMPs are conserved molecular structures found on the **surface or within pathogens** that are recognized by the innate immune system's **pattern recognition receptors** (PRRs). PAMPs are typically essential for the survival of the pathogen, making them reliable targets for immune detection.

Examples of PAMPs

1. **Lipopolysaccharides (LPS)**: Found in the outer membrane of Gram-negative bacteria.
2. **Peptidoglycan**: Present in the cell walls of Gram-positive bacteria.
3. **Flagellin**: The protein that makes up bacterial flagella.
4. **Unmethylated CpG DNA**: Bacterial and viral DNA often contains unmethylated CpG motifs, which are rare in vertebrate DNA.
5. **Viral RNA**: Double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA) are often found in viruses.
6. **Mannans**: Complex polysaccharides found in fungal cell walls.

2. CD1 Molecule

The CD1 molecule is a family of glycoproteins **expressed on the surface of antigen-presenting cells (APCs)** that present lipid antigens to T cells. Unlike **MHC molecules, which present peptide antigens**, **CD1 molecules present lipid and glycolipid antigens.**

Types

1. **CD1a, CD1b, CD1c**: Present mainly in the thymus, skin, and dendritic cells, and are involved in presenting antigens from mycobacteria and other lipid-containing pathogens.
2. **CD1d**: Present on various APCs, including B cells and some epithelial cells, and is involved in the presentation of glycolipid antigens to natural killer T (NKT) cells.
3. **CD1e**: Involved in processing and loading of lipid antigens in the endosomal compartments.

Function:

- **Antigen Presentation**: CD1 molecules bind to lipid antigens and present them to T cells, particularly NKT cells, which can then produce cytokines and help coordinate the immune response.
- **Immune Surveillance**: Helps the immune system **recognize a broader range of pathogens** by presenting lipid antigens that are not typically recognized by MHC molecules.

3. Mannose-Binding Lectin (MBL)

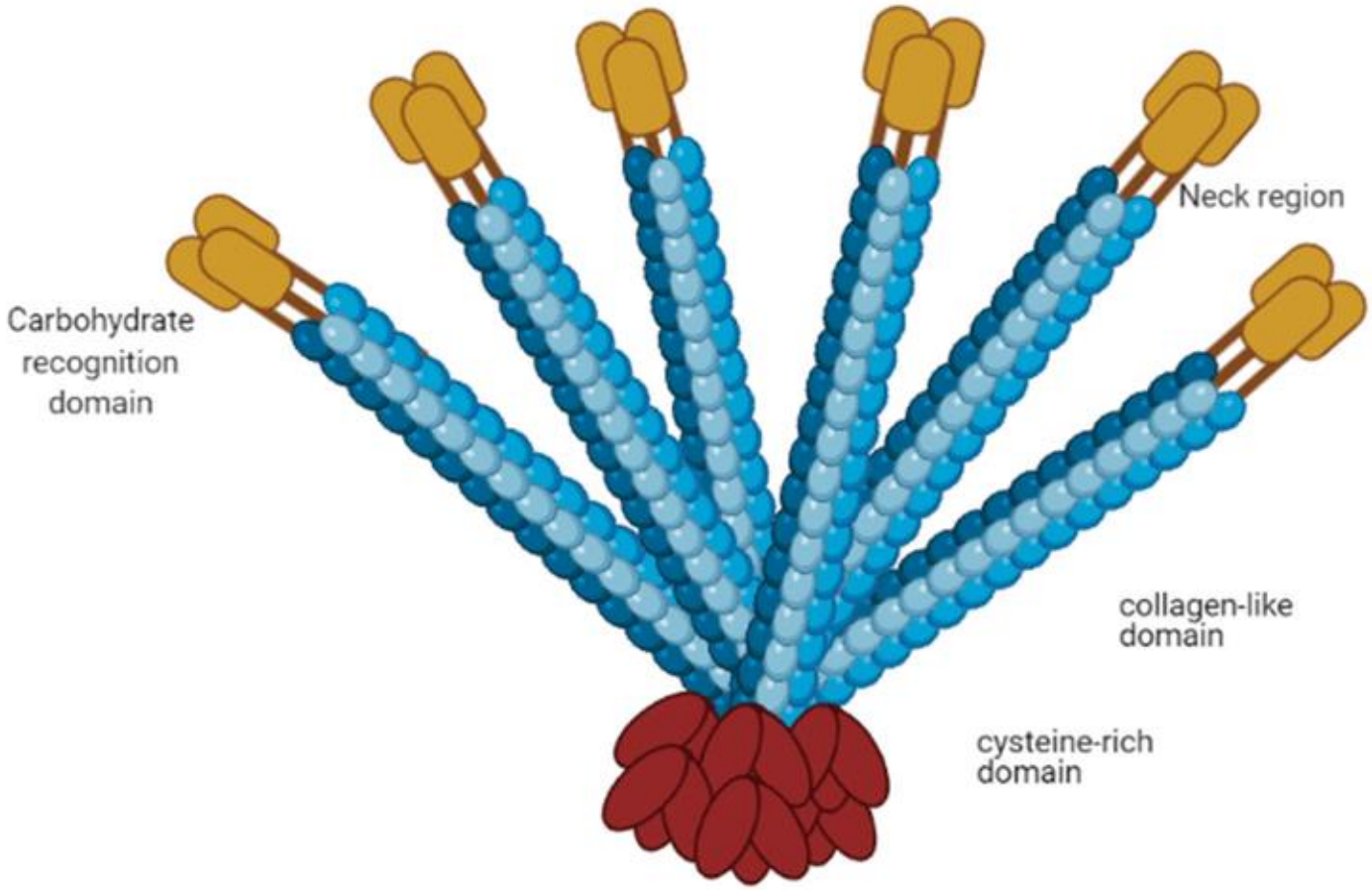
MBL is a crucial component of the innate immune system and is part of the lectin pathway of complement activation. It is a soluble pattern recognition molecule that binds to carbohydrate patterns on the surfaces of pathogens.

- **Structure and Function**
- **Structure**: MBL is a collagenous glycoprotein that forms a bouquet-like structure, allowing it to bind multiple sugar molecules on the surface of a pathogen simultaneously.

Functions:

- **Pathogen Recognition**: Binds to mannose and other sugars on the surfaces of bacteria, viruses, fungi, and protozoa.
- **Complement Activation**: Upon binding to a pathogen, MBL interacts with MBL-associated serine proteases (MASPs), leading to the activation of the lectin pathway of the complement system. This results in the opsonization of pathogens, making them more easily phagocytosed, and the formation of the membrane attack complex, which can lyse pathogen cells.
- **Opsonization**: Enhances phagocytosis by binding to pathogens and interacting with receptors on phagocytic cells.
- (Its an immune process which uses opsonins to tag foreign pathogens for elimination by phagocytes.)

MANNOSE BINDING LECTIN



Hexamer Structure of Mannose-Binding Lectin (MBL)

PATTERN RECOGNITION RECEPTORS

- Pattern Recognition Receptors (PRRs) are essential components of the innate immune system.
- They detect Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), which are molecular signatures associated with pathogens and cellular damage, respectively.
- PRRs trigger immune responses to eliminate infections and repair tissue damage.

Types of Pattern Recognition Receptors (PRRs)

1. Toll-Like Receptors (TLRs):

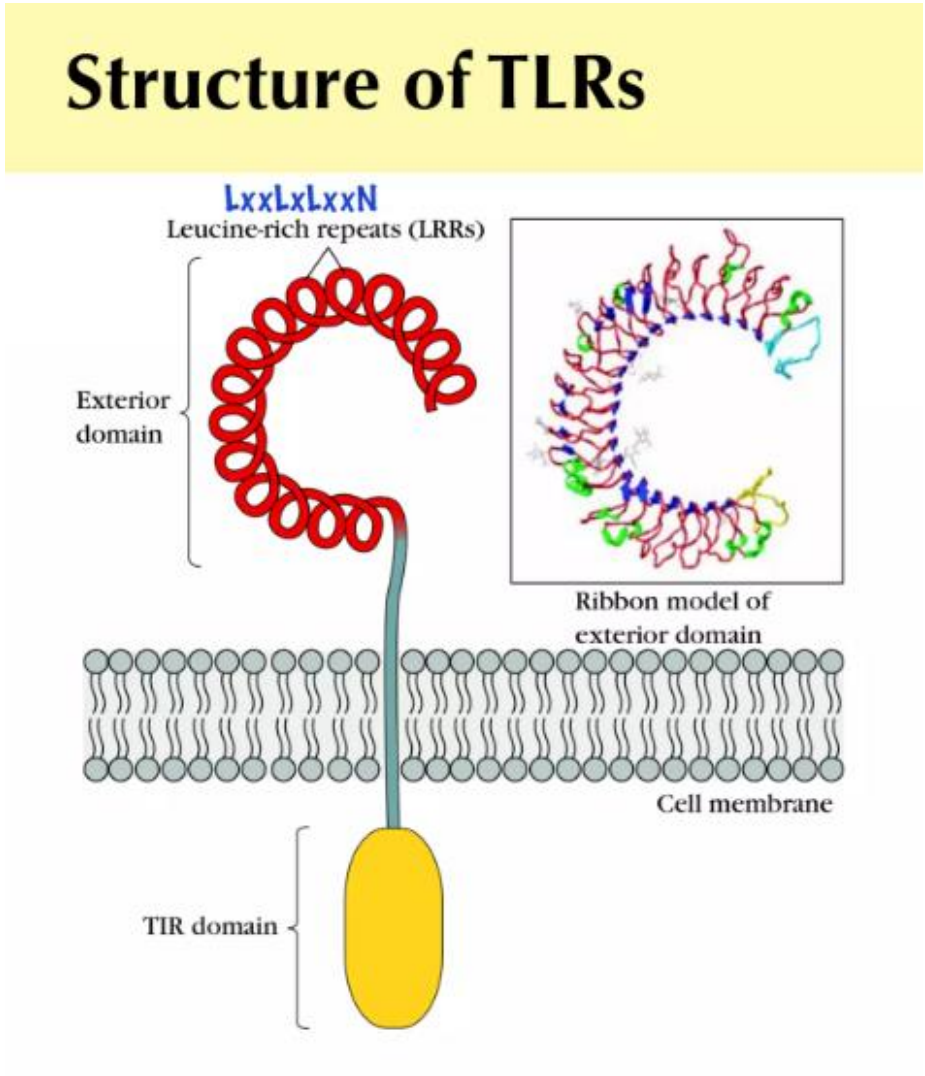
Toll-Like Receptors (TLRs) are a family of pattern recognition receptors (PRRs) that play a critical role in the innate immune system by **recognizing pathogen-associated molecular patterns (PAMPs)** and initiating immune responses.

- **Structure**: TLRs are transmembrane proteins with an extracellular domain that contains leucine-rich repeats (LRRs) for ligand binding and an intracellular Toll/IL-1 receptor (TIR) domain for signaling.
- **Location**: TLRs can be found on the cell surface or within endosomal compartments, depending on the specific TLR.

Examples and Ligands

1. **TLR1/TLR2**: Recognize bacterial lipopeptides.
2. **TLR2/TLR6**: Recognize lipoteichoic acid from Gram-positive bacteria and zymosan from fungi.
3. **TLR3**: Recognizes double-stranded RNA (dsRNA) from viruses.
4. **TLR4**: Recognizes lipopolysaccharides (LPS) from Gram-negative bacteria.
5. **TLR5**: Recognizes bacterial flagellin.
6. **TLR7/TLR8**: Recognize single-stranded RNA (ssRNA) from viruses.
7. **TLR9**: Recognizes unmethylated CpG DNA from bacteria and viruses.

Toll-Like Receptors (TLRs):



2. Killer-cell Immunoglobulin-like Receptors (KIRs)

- KIRs are family of receptors found on the surface of natural killer (NK) cells and some T cells. They are involved in the **regulation of NK cell activity**.
- **Structure**:

KIRs have extracellular immunoglobulin-like domains for ligand binding and cytoplasmic tails that contain either immunoreceptor tyrosine-based inhibitory motifs (ITIMs) or immunoreceptor tyrosine-based activating motifs (ITAMs).

- **Function**: KIRs recognize major histocompatibility complex (MHC) class I molecules on the surface of cells.

Types

1. **Inhibitory KIRs**:

Contain ITIMs (Immunoreceptor Tyrosine- based Inhibition Motifs) in their cytoplasmic tails. When they bind to MHC class I molecules, they **inhibit NK cell activation, preventing the killing of normal, healthy cells.**

1. Examples: KIR2DL1, KIR2DL2, KIR3DL1.

1. **Activating KIRs**:

Contain ITAMs (Immunoreceptor Tyrosine- based Activation Motifs) in their associated signaling adaptors. When they bind to their ligands, they **activate NK cell responses, including the killing of infected or transformed cells**.

1. Examples: KIR2DS1, KIR2DS2, KIR3DS1.

3. Fc Gamma Receptors (FcγRs)

- **FcγRs** are receptors that bind to the **Fc region of immunoglobulin G (IgG)** antibodies, mediating various immune responses.
- **Structure**: FcγRs are membrane-bound receptors with extracellular domains that **bind the Fc region of IgG and intracellular domains** that transmit **activation or inhibitory signals**.
- **Function**: FcγRs play a critical role in linking the adaptive immune system (via antibodies) to the innate immune system.

Types

1. **Activating FcγRs**:
    1. Examples: FcγRI (CD64), FcγRIIA (CD32A), FcγRIIIA (CD16).
    2. **Function**: These receptors have **ITAMs** in their cytoplasmic tails or associated signaling adaptors. Binding of IgG-opsonized pathogens to these receptors **triggers phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and the release of inflammatory mediators**.
2. **Inhibitory FcγRs**:
    1. Example: FcγRIIB (CD32B).
    2. **Function**: This receptor has **ITIMs** in its cytoplasmic tail. It provides **negative feedback to limit immune responses** and **prevent excessive inflammation and tissue damage**.
3. **Balanced Function**:
    1. The balance between activating and inhibitory FcγRs on immune cells ensures appropriate immune responses to pathogens while preventing autoimmunity and excessive inflammation.

Functions of PRRs

1. **Pathogen Detection**: PRRs recognize and **bind to PAMPs and DAMPs** (Damage –Associated Molecular Patterns), allowing the immune system **to detect infections and tissue damage**.
2. **Signal Transduction**: Upon ligand binding, **PRRs initiate signaling cascades that lead to the activation of transcription factors such as NF-κB, AP-1, and IRFs**. This results in the production of cytokines, chemokines, and type I interferons.
3. **Inflammatory Response**: The **activation of PRRs triggers inflammation**, recruiting immune cells to the site of infection or injury to contain and eliminate the threat.
4. **Activation of Adaptive Immunity**: PRRs help **activate the adaptive immune** system by enhancing antigen presentation and providing necessary co-stimulatory signals to T and B cells.

COMPLEMENT RECEPTORS

- **Complement receptors** are proteins found on the surface of various immune cells that recognize and bind to components of the complement system.
- These receptors play crucial roles in enhancing phagocytosis, promoting inflammation, and regulating immune responses.

Complement Receptors and Their Functions

1.CR1 (Complement Receptor 1, CD35)

1. **Structure**: A **large** glycoprotein with multiple complement-binding domains.
2. **Expression**: Found on erythrocytes, leukocytes (such as neutrophils, monocytes, macrophages, and B cells), and follicular dendritic cells.
3. **Functions**:
    1. **Immune Complex Clearance**: CR1 on erythrocytes helps transport immune complexes to the liver and spleen for removal.
    2. **Phagocytosis**: CR1 on phagocytes enhances the ingestion and destruction of opsonized pathogens.
    3. **Regulation**: Acts as a cofactor for the factor I-mediated cleavage of C3b and C4b, regulating complement activation.

CR2 (Complement Receptor 2, CD21)

- **Structure**: A membrane protein with multiple short consensus repeats.
- **Expression**: Primarily on B cells, follicular dendritic cells, and some epithelial cells.
- **Functions**:
  - **B Cell Activation**: CR2 is part of the B cell co-receptor complex, enhancing B cell responses to antigens tagged with C3d.
  - **Memory B Cells**: Plays a role in maintaining and recalling B cell memory by capturing and presenting antigens to B cells.

CR3 (Complement Receptor 3, CD11b/CD18, Mac-1)

- **Structure**: An integrin composed of CD11b and CD18 subunits.
- **Expression**: Found on neutrophils, monocytes, macrophages, dendritic cells, and NK cells.
- **Functions**:
  - **Phagocytosis**: CR3 mediates the ingestion of iC3b-opsonized particles by phagocytes.
  - **Cell Adhesion and Migration**: CR3 facilitates leukocyte adhesion to endothelium and migration to sites of inflammation.
  - **Immune Regulation**: Involved in various immune regulatory functions, including cytokine production and suppression of inflammatory responses.

CR4 (Complement Receptor 4, CD11c/CD18)

- **Structure**: An integrin composed of CD11c and CD18 subunits.
- **Expression**: Found on monocytes, macrophages, dendritic cells, neutrophils, and some subsets of NK cells.
- **Functions**:
  - **Phagocytosis**: CR4 promotes the phagocytosis of iC3b-coated particles.
  - **Cell Adhesion and Migration**: Similar to CR3, CR4 aids in leukocyte adhesion and migration.

C1q Receptors

- **C1qRp**: Found on monocytes, macrophages, neutrophils, and endothelial cells. It binds C1q and enhances phagocytosis.
- **gC1qR/p33**: Found in various cells and has multiple functions, including binding to C1q and other ligands involved in inflammation and immune responses.

Functions of Complement Receptors:

1. **Enhancing Phagocytosis**: Complement receptors bind to complement-coated pathogens, facilitating their uptake and destruction by phagocytes.
2. **Immune Complex Clearance**: Receptors like CR1 help in the clearance of immune complexes from the circulation, reducing the risk of immune complex-mediated diseases.
3. **Modulating Immune Responses**: Complement receptors can influence the activation and regulation of various immune cells, contributing to both the amplification and resolution of immune responses.
4. **Promoting Inflammation**: By binding complement fragments, these receptors can promote inflammatory responses, recruiting additional immune cells to sites of infection or injury.
5. **Linking Innate and Adaptive Immunity**: Complement receptors, particularly CR2 on B cells, play a role in enhancing the adaptive immune response by providing co-stimulatory signals during antigen presentation.

RECOGNITION MOLECULES AND RECEPTORS OF ADAPTIVE IMMUNE SYSTEM

- **Major Histocompatibility Complex (MHC) molecules** are crucial components of the adaptive immune system, responsible for **presenting peptide antigens to T cells**.
- They play a central role in the recognition of antigens and the activation of T lymphocytes.
- There are two main classes of MHC molecules: **MHC class I** and **MHC class II**.
- Each class has distinct roles and is involved in different aspects of immune responses.

• MHC Class I:

Structure

- **Composition**: MHC class I molecules are composed of a large α chain and a smaller β2-microglobulin molecule. The α chain has three extracellular domains (α1, α2, and α3) and is anchored in the cell membrane.
- **Peptide Binding**: The peptide-binding groove is formed by the α1 and α2 domains and accommodates peptides of 8-10 amino acids in length.

Distribution:

MHC class I molecules are expressed on nearly all nucleated cells in the body. This widespread expression allows for the presentation of intracellular antigens to CD8+ cytotoxic T cells.

Function:

- **Antigen Presentation**:

MHC class I molecules present endogenous peptides (derived from proteins synthesized within the cell) to CD8+ T cells. These peptides can be from viral proteins or aberrant self-proteins in tumor cells.

- **Immune Response**:

The recognition of MHC class I-peptide complexes by CD8+ T cells leads to the activation and cytotoxic killing of infected or abnormal cells.

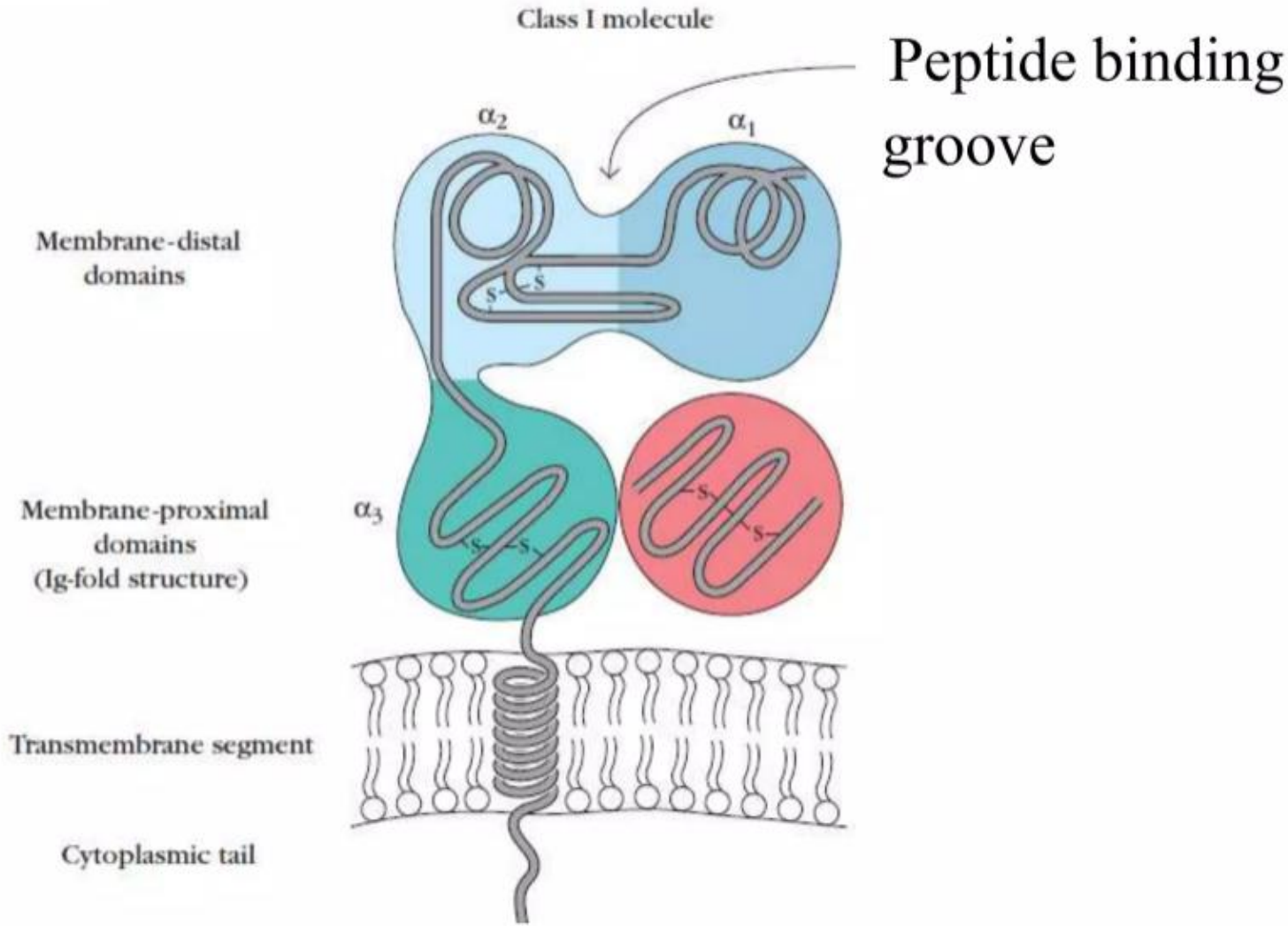


Fig:- Class I MHC antigen

Pathway:

1. **Antigen Processing**: Intracellular proteins are degraded into peptides by the proteasome.
2. **Peptide Transport**: Peptides are transported into the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP).
3. **Peptide Loading**: In the ER, peptides bind to MHC class I molecules.
4. **Surface Expression**: The MHC class I-peptide complex is transported to the cell surface for presentation to CD8+ T cells.

MHC Class II

- **Composition**: MHC class II molecules are composed of two different chains, α and β, each with two extracellular domains (α1, α2 and β1, β2). Both chains are membrane-bound.
- **Peptide Binding**: The peptide-binding groove is formed by the α1 and β1 domains and can accommodate longer peptides, typically 12-25 amino acids in length.
- **Distribution**: MHC class II molecules are primarily expressed on professional antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells.

Function:

- **Antigen Presentation**: MHC class II molecules present exogenous peptides (derived from proteins that have been taken up, processed, and presented by the APC) to CD4+ helper T cells.
- **Immune Response**: The recognition of MHC class II-peptide complexes by CD4+ T cells provides help to B cells and other immune cells, promoting antibody production, cell-mediated responses, and the activation of additional immune components.

Pathway:

1. **Antigen Uptake**: Antigens are taken up by APCs through endocytosis or phagocytosis.
2. **Antigen Processing**: The antigens are degraded into peptides within endosomes or lysosomes.
3. **Peptide Loading**: Peptides are loaded onto MHC class II molecules in the endosomal compartments.
4. **Surface Expression**: The MHC class II-peptide complex is transported to the cell surface for presentation to CD4+ T cells.

Peptide binding groove

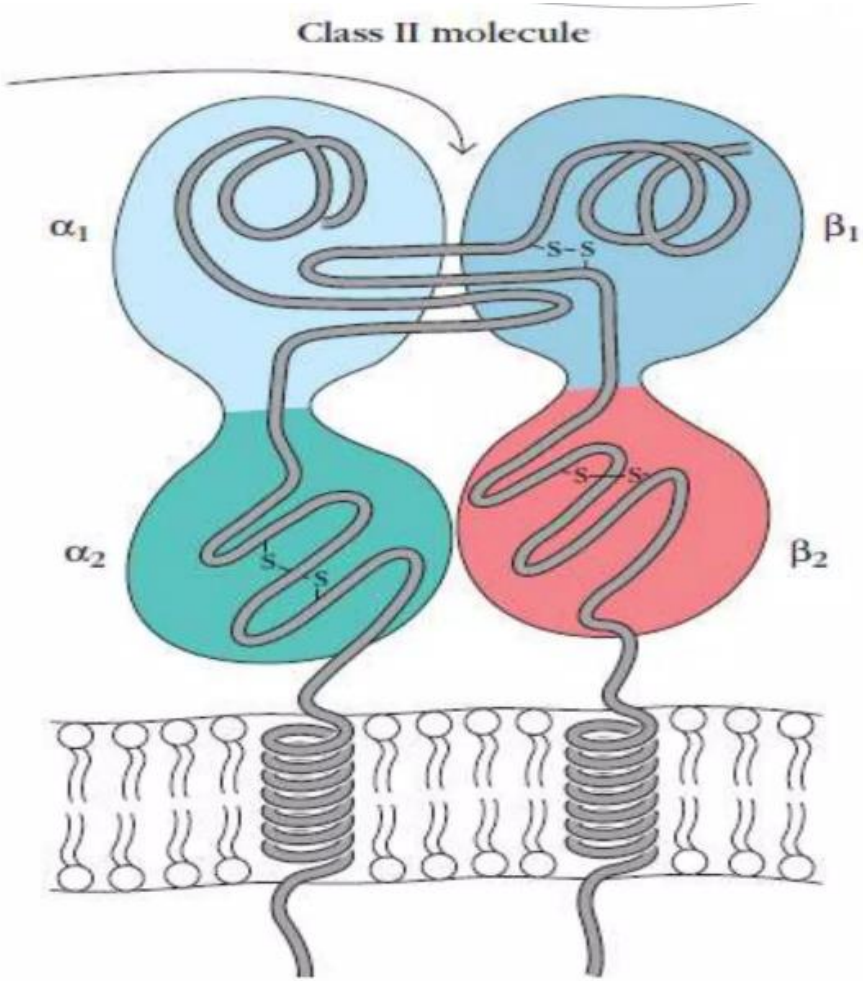


Fig:- Class II MHC molecule

Difference between MHC class I and MHC class II

MHC class I	MHC class II
1. Have 8-10 amino acids	Have 13-18 amino acids
2. Peptide binding domain alpha1, alpha2	Peptide binding domain alpha1, beta1
3. Present antigen to CD 8 T- cells	Present antigen to CD 4 T- cells
4. Found on all surfaces of nucleated cells	Found on surface of APCs and activated T cells
5. Composed of one peptide encoded in HLA locus and beta 2 microglobullin	Composed of two peptide encoded by HLA locus
6. Bind with endogenous antigen	Bind with exogenous antigen
7. Has no invariant chain	Has invariant chain

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