## ii. Biophysics of Immune System

ii. Biophysics of Immune System, Structure of antigen and antibody molecules, Antigen recognition by T cell and B cells, B-cell receptors, TCR gene rearrangement, antigen presentation and MHC/HLA complex

The immune system hinges on molecular recognition between specialized receptors (on T cells, B cells) and foreign antigens presented or in free form. This involves biophysical principles of binding affinity, specificity, and signal transduction, which underlie how antibodies neutralize pathogens, how T cells parse antigenic peptides, and how Major Histocompatibility Complex (MHC/HLA) orchestrates antigen presentation. Below is a comprehensive explanation of each facet, from biophysics to gene rearrangements.

# **Biophysics of the Immune System**

### 1. Molecular Recognition

- Immune receptors (antibodies, T-cell receptors) use non-covalent interactions (hydrogen bonds, Van der Waals forces, electrostatics) to bind epitopes with high specificity.
- **Affinity** (strength of one binding site to an antigen) and **avidity** (combined strength of multiple binding sites, e.g., IgM pentamer) shape functional potency.

## 2. Thermodynamics

- $\circ$   $\Delta G$  (Gibbs free energy) correlates with receptor-ligand binding stability; favorable enthalpy (forming hydrogen bonds) and sometimes favorable entropy (releasing water from surfaces).
- o Conformational changes upon binding may alter receptor architecture, affecting downstream signaling.

#### 3. Kinetics of Immune Responses

- Receptor-ligand on-rate and off-rate define how quickly complexes form and dissociate.
- o T-cell activation demands sustained TCR-MHC-peptide interaction above a threshold dwell time.

# Structure of Antigen and Antibody Molecules

## **Antigens**

### 1. **Definition**

- Antigens are **substances** (proteins, polysaccharides, lipids, or nucleic acids) recognized by the immune system, specifically by B or T lymphocytes.
- Epitopes (antigenic determinants) are discrete parts binding to an antibody or T-cell receptor.

# 2. Types of Epitopes

- Linear: Consecutive amino acid sequences recognized primarily by T cells after processing.
- **Conformational**: Three-dimensional shape recognized by B cells (antibody binding) in native protein folding.

## 3. Immunogenicity

- Influenced by foreignness, molecular size, chemical complexity, and dosage/route of exposure.
- Certain molecules (haptens) require a carrier to elicit an immune response.

# **Antibodies (Immunoglobulins)**

## 1. Basic Structure

- Y-shaped glycoproteins made of two heavy (H) and two light (L) chains, each chain containing constant (C) and variable (V) regions.
- The **antigen-binding site** (Fab region) is formed by the variable domains of heavy and light chains, providing specificity. The **Fc region** interacts with immune effectors (e.g., complement, Fc receptors).

### 2. Domains

- Ig heavy chain: VH + CH1 + hinge + CH2 + CH3 (IgM also has CH4).
- Ig light chain: VL + CL.
- **Hypervariable regions** or complementarity-determining regions (CDRs) in the V regions contact the antigen.

### 3. Isotypes and Functions

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#### WHERE CLASSICAL WISDOM MEETS INTELLIGENT LEARNING

- IgG: Most abundant, crosses placenta, opsonization, neutralization, complement activation.
- **IgM**: First antibody produced, pentameric, potent agglutination.
- **IgA**: Mucosal immunity (in secretions).
- **IgE**: Parasitic/allergic responses, binds mast cells/basophils.
- o IgD: B-cell receptor on naive B cells (less understood effector role).

# Antigen Recognition by T Cells and B Cells

## **B-Cell Receptors (BCR)**

## 1. Membrane-Bound Antibody

- $\circ$  BCR is essentially a monomeric immunoglobulin (IgM or IgD in naive cells) embedded in the plasma membrane with associated signaling molecules (Ig $\alpha$ /Ig $\beta$ ).
- o Recognizes native or unprocessed antigens (proteins, polysaccharides, lipids) in solution or on surfaces.

### 2. Activation

 Cross-linking of BCRs by repeated epitopes triggers intracellular signaling (via ITAMs on Igα/Igβ), leading to B-cell proliferation and differentiation into antibody-secreting plasma cells.

## **T-Cell Receptors (TCR)**

## 1. Structure

- Heterodimeric protein ( $\alpha\beta$  or  $\gamma\delta$ ) with variable (V) and constant (C) domains.
- o Each chain has three hypervariable CDR loops determining antigenic specificity.

### 2. MHC-Restricted Recognition

- TCR binds **peptide** antigens only when presented on host MHC molecules.
- o CD4+ T cells recognize MHC Class II, CD8+ T cells recognize MHC Class I.

# **TCR Gene Rearrangement**

### Mechanism

### 1. Somatic Recombination

- $\circ$  TCR  $\alpha$  and  $\beta$  chains undergo **VDJ** (Variable–Diversity–Joining) recombination, akin to immunoglobulin genes in R cells
- **RAG-1/RAG-2** enzymes mediate this process, generating the vast TCR repertoire crucial for recognizing diverse peptides.

## 2. Diversity Generation

- Combinatorial: Random pairing of V, (D), and J segments.
- Junctional: Additions or deletions of nucleotides at gene segment joints (N-region additions by TdT).
- Yields an immense repertoire enabling T cells to detect myriad potential antigens.

### 3. Thymic Selection

- **Positive selection** retains T cells with moderate affinity for self-MHC.
- Negative selection deletes T cells with high affinity for self-peptides (autoimmune risk).
- Ensures TCR specificity to foreign peptides but tolerance to self.

# Antigen Presentation and MHC/HLA Complex

## MHC/HLA Basics

# 1. Major Histocompatibility Complex (MHC)

- o Cell-surface glycoproteins essential for presenting peptide antigens to T cells.
- $\circ$  In humans, called **Human Leukocyte Antigen (HLA)**.
- o Polymorphic genes—no two individuals (except identical twins) share the same MHC profile.

## 2. Classes

MHC Class I: On nearly all nucleated cells. Presents endogenous peptides (viral or cytosolic) to CD8+ T

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 MHC Class II: On professional APCs (dendritic cells, macrophages, B cells). Presents exogenous peptides (from phagocytosed microbes) to CD4+ T cells.

## **Antigen Processing Pathways**

#### 1. Endogenous Pathway

 Proteins in cytosol (e.g., viral) are degraded by the proteasome → peptides enter ER via TAP → loaded onto MHC I.

### 2. Exogenous Pathway

 Antigens phagocytosed, degraded in phagolysosomes → peptides fuse with MHC II compartments → MHC IIpeptide displayed on cell surface.

### **T-Cell Activation and Immune Outcomes**

### 1. CD8+ Cytotoxic T Cells

o Interact with MHC I-peptide, kill infected or abnormal cells.

### 2. CD4+ Helper T Cells

• Recognize MHC II-peptide, secrete cytokines, coordinate B-cell help, macrophage activation, or tolerance.

# **Integrative Summary and Clinical Relevance**

### 1. Biophysical Interactions

• Receptor-ligand specificity shaped by **TCR** and **MHC** or **antibody-antigen** complexes; TCR gene rearrangement fosters enormous repertoire for pathogen recognition.

## 2. Healthcare Implications

- Understanding TCR and BCR rearrangements underpins **precision immunotherapies** (CAR T-cells) and **monoclonal antibody** development.
- MHC polymorphism influences organ transplant acceptance/rejection and predisposition to autoimmune diseases.

### 3. Ayurvedic Parallel

- Although classical Ayurveda doesn't detail "TCR rearrangement," it conceptually addresses how the body discerns "self" vs. "non-self" under *doșic* or *ojas* frameworks.
- Rasāyana therapies might bolster host defense akin to optimizing T/B cell function, synergy with conventional immunobiology.

## **Future Directions**

## 1. Next-Generation Sequencing

 High-throughput TCR/BCR repertoire profiling clarifies immune responses in infections, vaccines, or autoimmune states.

## 2. Biophysics and Structural Immunology

• **Cryo-EM** or **X-ray crystallography** of TCR-peptide-MHC complexes refining vaccine design, e.g., structure-based antigen engineering.

## 3. Immunotherapies

- o Checkpoint inhibitors, adoptive T-cell therapies guided by TCR specificity.
- o Potential synergy with immuno-nutritional approaches bridging Western and Eastern concepts.

Conclusion: The immune system exemplifies intricate molecular and cellular synergy—antigen-antibody bonding, T-cell recognition of MHC-presented peptides, and TCR gene rearrangement fueling an immense repertoire. The biophysics of these interactions ensures specificity and robust host defense. Understanding these fundamentals drives modern immunotherapeutics, underscores antigen presentation protocols, and opens translational frontiers for vaccine design, autoimmune control, and integrative health solutions bridging classical and contemporary immunological frameworks.

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