

## 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

- $\Delta G$  (Gibbs free energy) correlates with receptor–ligand binding stability; favorable enthalpy (forming hydrogen bonds) and sometimes favorable entropy (releasing water from surfaces).
- 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.
- 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



- **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.
- **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

- BCR is essentially a monomeric immunoglobulin (IgM or IgD in naive cells) embedded in the plasma membrane with associated signaling molecules (Ig $\alpha$ /Ig $\beta$ ).
- 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 Ig $\alpha$ /Ig $\beta$ ), 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.
- 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.
- CD4+ T cells recognize MHC Class II, CD8+ T cells recognize MHC Class I.

## TCR Gene Rearrangement

### Mechanism

#### 1. Somatic Recombination

- TCR  $\alpha$  and  $\beta$  chains undergo **VDJ** (Variable-Diversity-Joining) recombination, akin to immunoglobulin genes in B 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)

- Cell-surface glycoproteins essential for presenting peptide antigens to T cells.
- In humans, called **Human Leukocyte Antigen (HLA)**.
- 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 cells.



- **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 II-peptide displayed on cell surface.

## T-Cell Activation and Immune Outcomes

### 1. CD8+ Cytotoxic T Cells

- 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 *doṣic* 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

- *Checkpoint inhibitors, adoptive T-cell therapies* guided by TCR specificity.
- 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.