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**
   - ΔG (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 (Igα/Igβ).
   - 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.
   - 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 α and β 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.