BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Code: BM35C6
Course Title: Immunology

Unit-II

Hematopoiesis

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Unit II:

Hematopoiesis– T and B lymphocytes ontogeny and development, Activation and Effector mechanism of innate immune system – Phagocytosis - Respiratory burst - inflammation, T lymphocyte activation and downstream signaling following activation. Granzyme and perforin pathways, Fas-FasL pathway, T cell and B cell interaction - B cell activation and downstream signaling following activation and Immunoglobulin class switching. Complement mediated cytotoxicity and Antibody dependent cytotoxicity (ADCC).

PRESENTATION: 3

IMMUNOGLOBULIN CLASS SWITCHING

- Immunoglobulin class switching, also known as isotype switching, is a central process that allows B cells to produce different classes (or isotypes) of antibodies while maintaining specificity for the same antigen.
- This process is essential for tailoring the immune response to different types of pathogens and ensuring effective immune protection.

Overview:

1.Initial Antibody Production (IgM):

1. When a B cell first encounters an antigen, it typically produces immunoglobulin M (IgM) antibodies. IgM is the first antibody produced in response to an infection and is effective in forming complexes and initiating the complement cascade.

2.Signals for Class Switching:

1. **T Cell Help**: Class switching is often induced by interactions with T helper cells. The interaction between CD40 ligand (CD40L) on T helper cells and CD40 on B cells is critical for initiating class switching.
2. **Cytokines**: Different cytokines secreted by T helper cells or other immune cells influence the type of immunoglobulin that B cells will switch to. For example, IL-4 promotes switching to IgE, while IL-5 and TGF-β can promote switching to IgA.

3. Class Switching Mechanism:

1. **Activation-Induced Cytidine Deaminase (AID)**: A key enzyme in the class switching process. AID introduces double-strand breaks in the switch regions (S regions) of the immunoglobulin heavy chain gene locus.
2. **DNA Recombination**: The double-strand breaks are repaired through a process called non-homologous end joining, which brings a new constant region gene segment into proximity with the variable region genes, resulting in the recombination of the heavy chain gene.

4. Switch Regions (S Regions):

1. Each class of antibody (IgG, IgA, IgE) has specific switch regions upstream of its constant region genes. During class switching, AID-mediated recombination occurs between these switch regions to replace the original constant region gene with a new one.

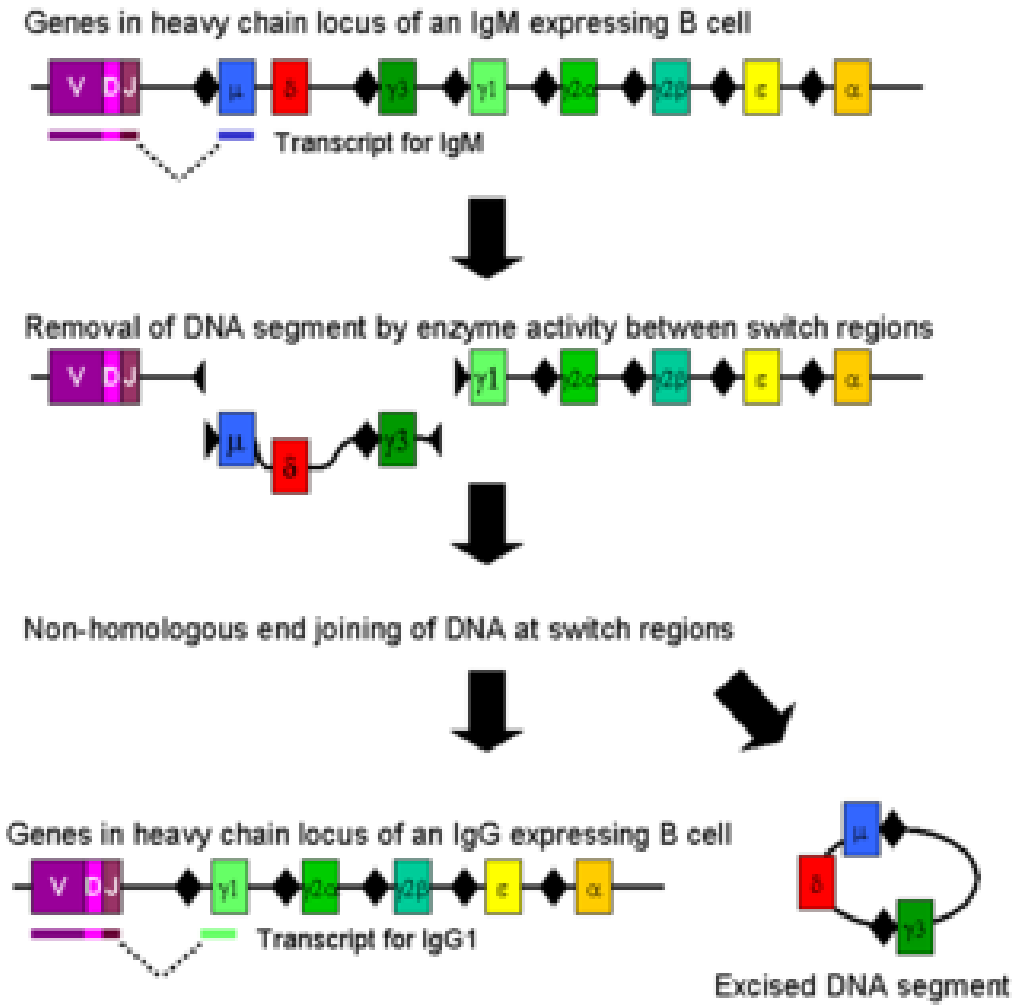
5. Production of New Antibody Class:

1. After class switching, the B cell starts producing antibodies of the new class (e.g., IgG, IgA, or IgE) with the same antigen specificity. The new antibody class is suited to different functions, such as:
    1. **IgG**: Provides long-term protection and can cross the placenta to protect the fetus.
    2. **IgA**: Found in mucosal areas, such as the gut and respiratory tract, where it helps protect against infections.
    3. **IgE**: Involved in allergic reactions and defense against parasitic infections.

6. Memory B Cells:

1. Class switching also affects memory B cells. Upon re-exposure to the same antigen, these cells can rapidly produce the appropriate antibody class, providing a more efficient and tailored immune response.

IMMUNOGLOBULIN CLASS SWITCHING



COMPLEMENT-MEDIATED CYTOTOXICITY (CMC)

- Complement-mediated cytotoxicity (CMC) is a process in which the complement system, a group of proteins in the blood that help the immune system, targets and destroys cells that are marked for destruction.
- This mechanism plays a significant role in immune defense against pathogens and abnormal cells, such as cancer cells.

Complement System Overview

- The complement system consists of a series of plasma proteins that are activated in a cascade-like manner. There are three main pathways for complement activation:

1. **Classical Pathway**: Activated by antigen-antibody complexes.
2. **Alternative Pathway**: Activated directly by pathogen surfaces or damaged cells.
3. **Lectin Pathway**: Activated by lectins binding to specific carbohydrates on pathogen surfaces

Mechanism

1. Activation of Complement:

1. **Recognition and Binding**: Complement proteins recognize and bind to pathogens, damaged cells, or cells tagged with antibodies (through the classical pathway).
2. **Complement Activation**: Binding initiates the complement cascade, leading to the sequential activation of complement proteins.

2. Formation of the Membrane Attack Complex (MAC):

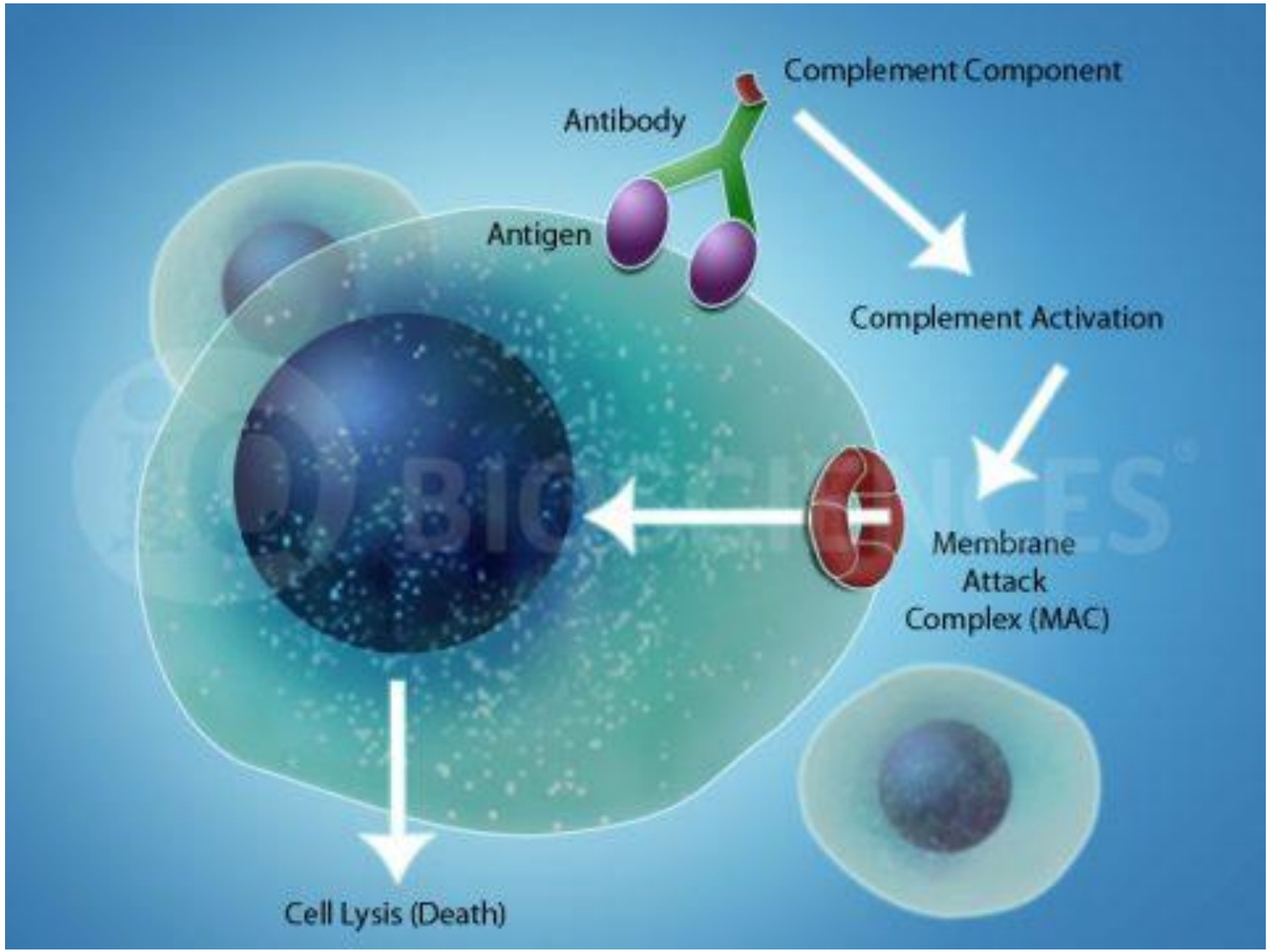
1. **Complement Cascade**: The activation of complement proteins results in the cleavage of C3 into C3a and C3b. C3b binds to the target cell surface.
2. **C5 Convertase Formation**: C3b binds to other complement components to form C5 convertase, which cleaves C5 into C5a and C5b.
3. **MAC Formation**: C5b binds to the cell membrane and recruits C6, C7, C8, and multiple C9 molecules to form the Membrane Attack Complex (MAC). The MAC forms a pore-like structure in the target cell membrane.

3. Cell Lysis:

1. **Pore Formation**: The MAC creates pores in the target cell membrane, disrupting its integrity.
2. **Increased Permeability**: The formation of pores leads to increased permeability of the cell membrane, causing loss of essential ions and molecules, and influx of water.
3. **Cell Death**: The disrupted membrane results in cell lysis and death of the target cell.

- **Regulation**
- **Complement Regulators**: The complement system is tightly regulated by various regulatory proteins (e.g., Factor H, C1 inhibitor, and CD55) to prevent damage to host cells and tissues. These regulators inhibit complement activation and MAC formation on normal cells.

Complement-mediated cytotoxicity



Antibody-dependent cellular cytotoxicity (ADCC)

ADCC

- Antibody-dependent cellular cytotoxicity (ADCC) is an immune mechanism in which antibodies bound to the surface of a target cell facilitate its destruction by immune cells.
- Unlike complement-mediated cytotoxicity, which relies on the complement system, ADCC involves the direct engagement of immune effector cells.

Mechanism of ADCC

1.Antibody Binding:

1. **Antigen Recognition**: Target cells, such as infected or cancerous cells, present specific antigens on their surface.
2. **Antibody Binding**: Antibodies (usually IgG) produced by B cells bind to these antigens on the target cell surface. The antibody's Fc (fragment crystallizable) region interacts with Fc receptors on immune effector cells.

2. Engagement of Effector Cells:

1. **Fc Receptors**: Immune effector cells, such as natural killer (NK) cells, macrophages, and neutrophils, express Fc receptors (e.g., FcγRIII on NK cells). These receptors specifically bind to the Fc region of antibodies.
2. **Cell Activation**: When antibodies bound to the target cell interact with the Fc receptors on the effector cells, this engagement activates the effector cells.

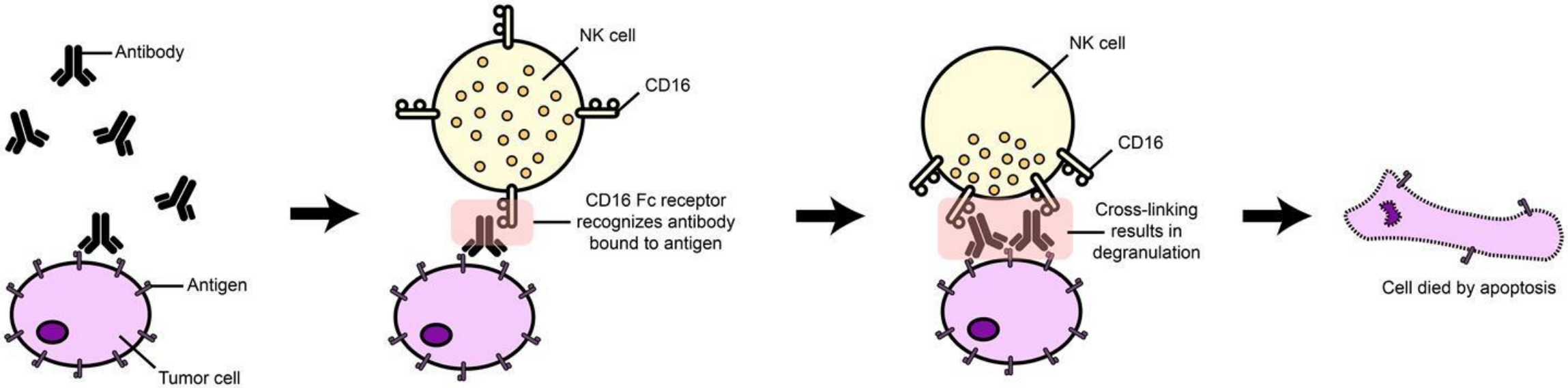
3. Effector Cell Activation and Cytotoxicity:

1. **Release of Cytotoxic Molecules**: Activated NK cells and other effector cells release cytotoxic molecules, such as perforin and granzymes, or other cytotoxic substances.
    1. **NK Cells**: Release perforin and granzymes to induce apoptosis in the target cell.
    2. **Macrophages and Neutrophils**: Release reactive oxygen species (ROS) and proteolytic enzymes to destroy the target cell.
2. **Phagocytosis**: Macrophages and neutrophils may also phagocytose (engulf and digest) the target cell.

4. Cell Death:

1. **Apoptosis**: The cytotoxic molecules and mechanisms induce apoptosis (programmed cell death) in the target cell.
2. **Destruction**: The target cell is effectively destroyed, and its remains are often cleared by phagocytes.

Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)



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