
IMMUNE RESPONSE AGAINST MICROORGANISMS
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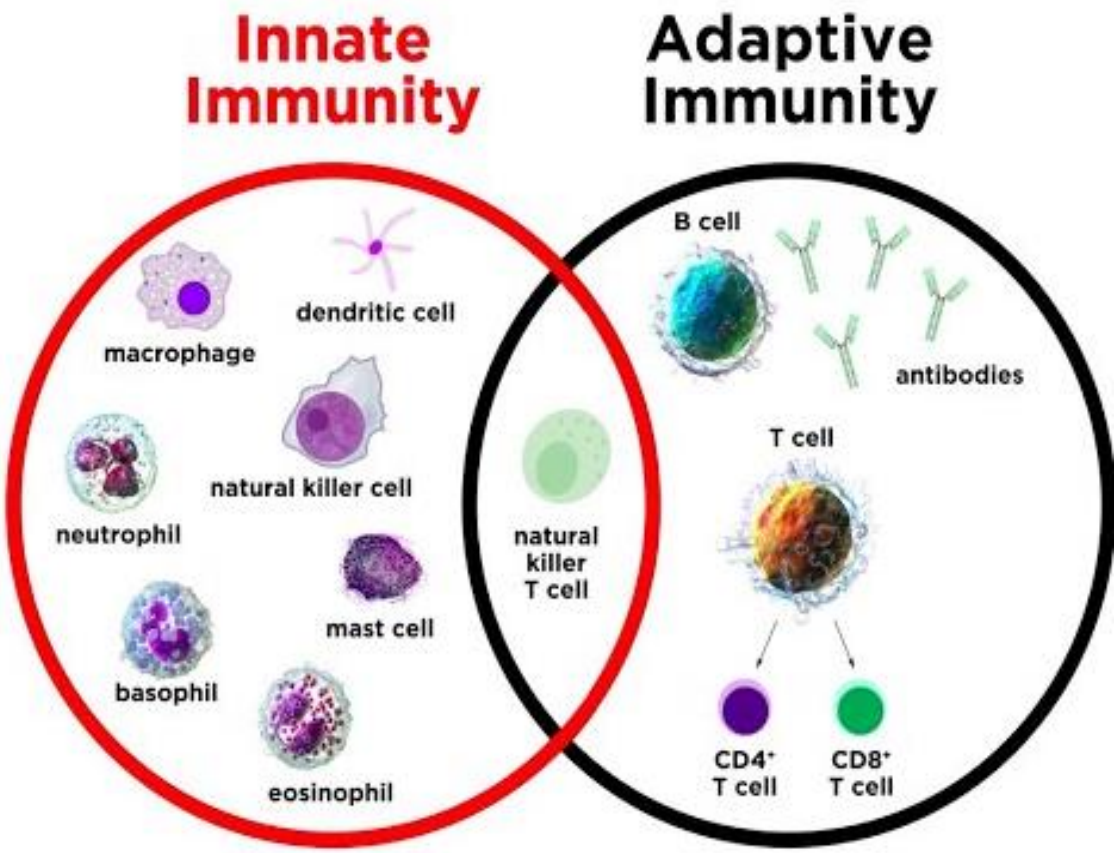
IMMUNE RESPONSE

Introduction

- The **immune response** against microorganisms is a complex, highly coordinated defense mechanism designed to protect the body from harmful invaders, such as bacteria, viruses, fungi, and parasites.
- This response is the result of the immune system's ability to recognize and eliminate foreign substances, ensuring that the body can maintain homeostasis and fight off infections.

The immune response against microorganisms involves both the innate and adaptive immune systems:

- **Innate Immune Response**
  - Physical and Chemical Barriers
  - Recognition of Pathogens
  - Phagocytosis
  - Inflammatory Response
  - Natural Killer (NK) Cells
- **Adaptive Immune Response**
  - Antigen Presentation
  - T-Cell Activation
  - B-Cell Activation
- **Memory Response**



Innate Immune Response

- This is the body's first line of defense. When a microorganism enters the body, it is recognized by **pattern recognition receptors (PRRs)** on immune cells such as macrophages, dendritic cells, and neutrophils.
- These cells engulf and destroy the pathogen through **phagocytosis**.
- The release of cytokines triggers inflammation, recruits other immune cells to the infection site, and activates the adaptive immune system.

Adaptive Immune Response

- If the innate response is insufficient, the adaptive immune system activates the **Antigen-presenting cells (APCs)** like dendritic cells which present microbial antigens to **T-cells**. Helper T-cells stimulate **B-cells** to produce **antibodies** that neutralize pathogens, while **cytotoxic T-cells** kill infected cells. Memory cells are also generated for faster responses in future infections.

Memory Response:

- After the infection is cleared, some T and B cells become memory cells, which provide a quicker and stronger immune response upon future exposure to the same pathogen.
- This combination of innate and adaptive immune responses ensures that the body can effectively identify, target, and eliminate pathogens while also creating long-term immunity against future infections.

IMMUNITY TO EXTRACELLULAR BACTERIA

- Extracellular bacteria are capable of replicating outside host cells, for example, in the blood, in connective tissues, and in tissue spaces such as the lumens of the airways and gastrointestinal tract.
- Disease is caused by two principal mechanisms.
- 1. First, these bacteria induce inflammation, which results in tissue destruction at the site of infection.
- 2. Second, bacteria produce toxins, which have diverse pathologic effects. The toxins may be endotoxins, which are components of bacterial cell walls, or exotoxins, which are secreted by the bacteria. The endotoxin of gram-negative bacteria, also called lipopolysaccharide (LPS) is a potent activator of macrophages, dendritic cells, and endothelial cells.

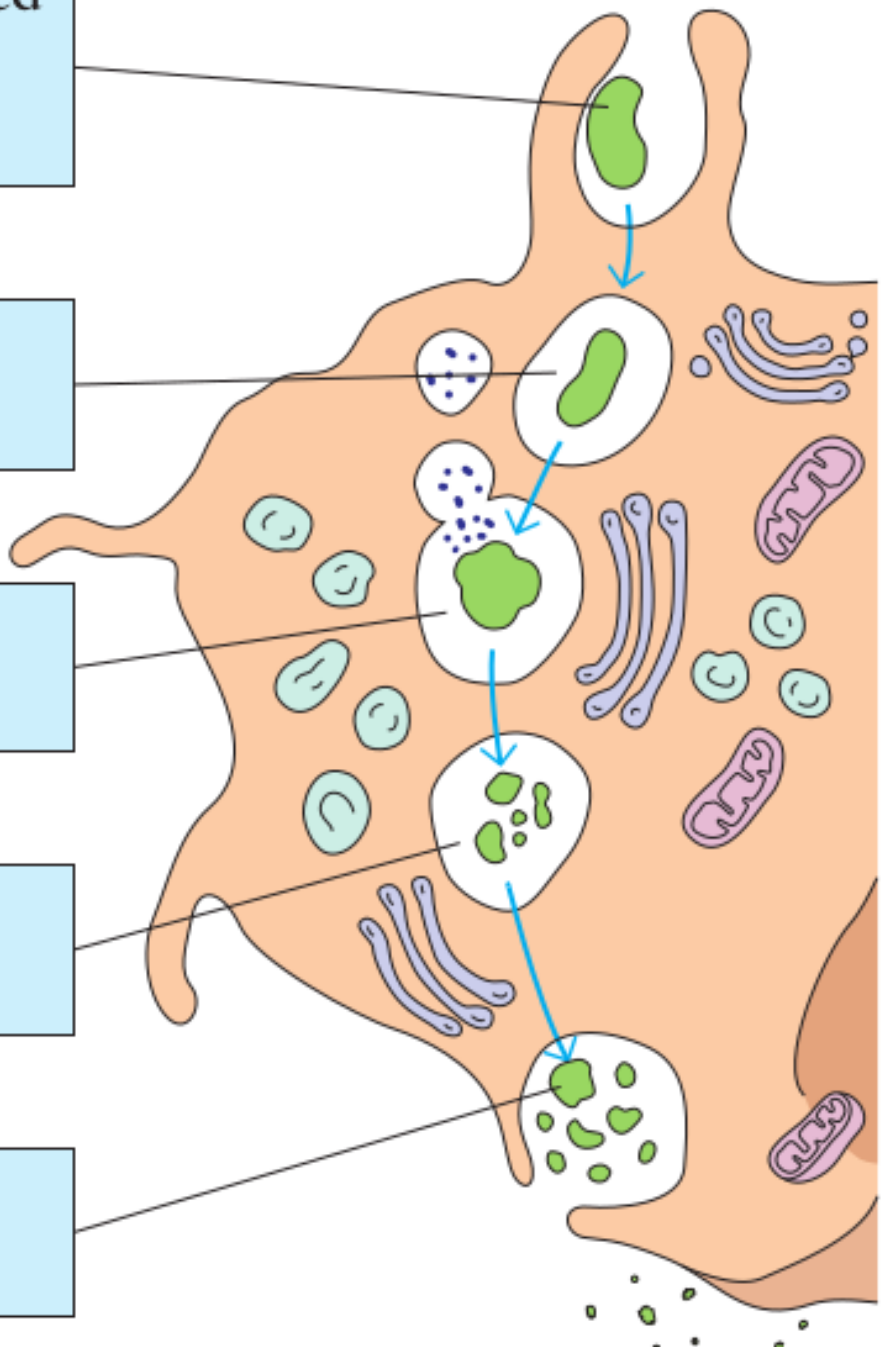
Innate Immunity to Extracellular Bacteria

- Innate Immunity to Extracellular Bacteria.
- The principal mechanisms of innate immunity to extracellular bacteria are complement activation, phagocytosis, and the inflammatory response.

Immune cells to identify and engulf pathogens like bacteria

- **1-Opsonization**:
- The process where immune molecules (**opsonins**) coat pathogens, such as bacteria, to signal phagocytes for ingestion and destruction.
- Opsonins are molecules that bind to pathogens, making them more recognizable to phagocytic cells (e.g., **macrophages and neutrophils**).
- **Examples of Opsonins**:
  - **C3b** (a component of the complement system).
  - **Antibodies** (like **IgG** and **IgM**).
- **2-Phagocytosis:**
- The process by which specialized immune cells (**phagocytes**) engulf and digest pathogens or cellular debris. This is one of the major mechanisms of eliminating bacteria.

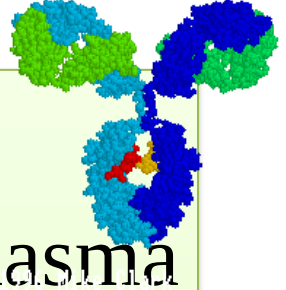
1. Bacterium becomes attached to membrane evaginations called pseudopodia
2. Bacterium is ingested, forming phagosome
3. Phagosome fuses with lysosome
4. Lysosomal enzymes digest captured material
5. Digestion products are released from cell



- **3-Complement System**:
- A series of proteins circulating in the blood that, when activated, enhance the ability of antibodies and phagocytic cells to clear pathogens.
- **C3b** is an important component of the complement system and serves as an opsonin, aiding in bacterial clearance.

4-Antigen:

- A molecule (often from a pathogen) that triggers an immune response. In bacteria, antigens can be proteins, lipids, or polysaccharides that are recognized by antibodies or immune cells.

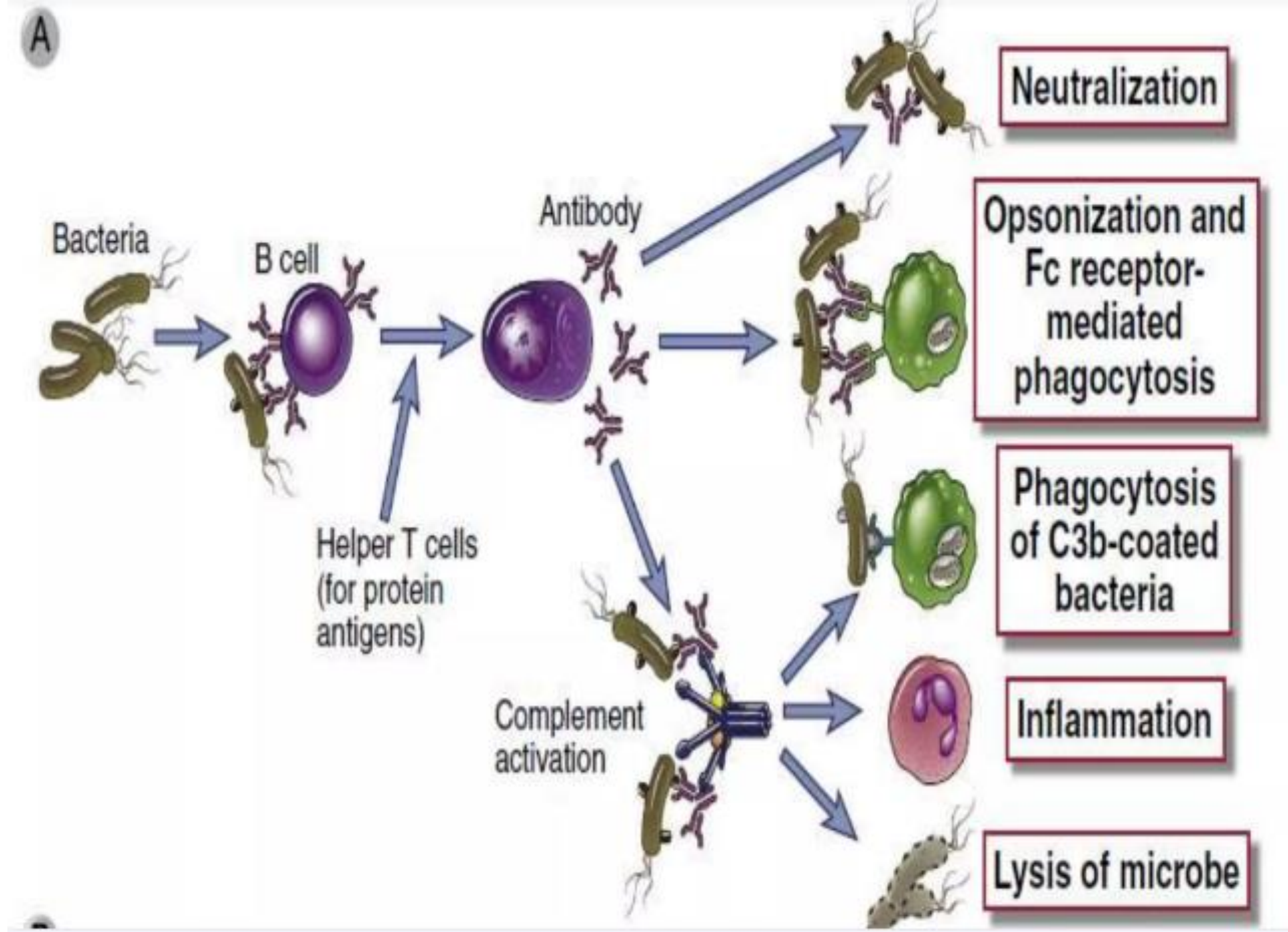


- **5-Antibodies (Immunoglobulins):**
- Y-shaped proteins produced by **B cells** (plasma cells) that recognize specific antigens.
- They can neutralize bacteria, trigger complement activation, or mark them for phagocytosis (opsonization).
- **Classes of Antibodies**:
  - **IgG:** Major opsonizing antibody in the blood stream.
  - **IgM:** Also participates in opsonization, especially early in immune responses.

- **6- Cytokines**:
- Small proteins secreted by immune cells that modulate the immune response. Examples include **IL-1**, **TNF-α**, and **IL-6**, which are involved in inflammation and recruitment of immune cells to the site of infection.
- **7- Pattern Recognition Receptors (PRRs)**:
- Receptors on immune cells (like *Toll-like receptors* or TLRs) that recognize general features of pathogens (known as pathogen-associated molecular patterns or PAMPs). This helps the immune system distinguish bacteria from host cells.

- **8-PAMPs(Pathogen-Associated Molecular Patterns)**:
- Molecules present on pathogens like bacteria, which are recognized by immune receptors (PRRs). For bacteria, PAMPs can include components like **lipopolysaccharides (LPS)** or **peptidoglycan**.
- **9-Major Histocompatibility Complex (MHC)**:
- Molecules on the surface of cells that present antigens to **T cells**.
- ***MHC class I**: Presents antigens to cytotoxic T cells.
- ***MHC class II**: Presents antigens to helper T cells, especially during bacterial infections.

- **10-Helper T Cells (CD4+)**:
- A subset of T cells that activate other immune cells (e.g., macrophages, B cells) by releasing cytokines. They play a key role in coordinating the immune response to bacteria.
- **Immunity to Intracellular Bacteria**
- **11-Cytotoxic T Cells (CD8+)**:
- T cells that can directly kill infected cells, particularly cells infected with intracellular pathogens (viruses and some bacteria).
- **12-Neutrophils**:
- A type of phagocyte and the most abundant white blood cell. Neutrophils are among the first responders to bacterial infections and are highly effective in phagocytizing and killing bacteria.


A
Bacteria
B cell
Antibody
Helper T cells
(for protein
antigens)
Complement
activation
Neutralization
Opsonization and
Fc receptor-
mediated
phagocytosis
Phagocytosis
of C3b-coated
bacteria
Inflammation
Lysis of microbe

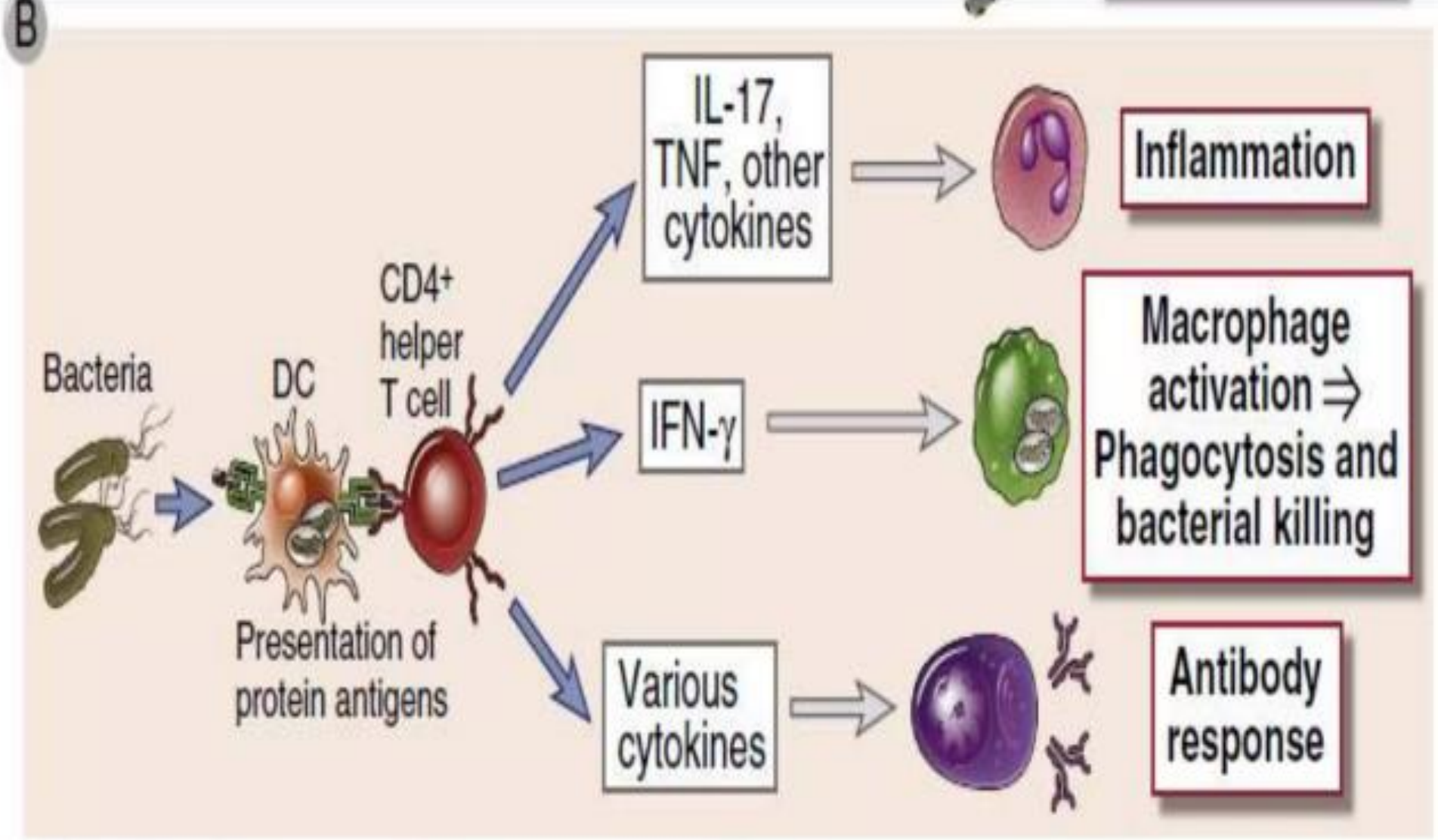


FIGURE 16-1 Adaptive immune responses to extracellular microbes. Adaptive immune responses to extracellular microbes such as bacteria and their toxins consist of antibody production **(A)** and the activation of CD4+ helper T cells **(B)**. Antibodies neutralize and eliminate microbes and toxins by several mechanisms. Helper T cells produce cytokines that stimulate inflammation, macrophage activation, and B cell responses. *DC*, dendritic cell.

Immune cells against to viruses

- **1. Recognition of Viruses**
- **Pattern Recognition Receptors (PRRs):** Innate immune cells, such as **macrophages**, **dendritic cells**, and **natural killer (NK) cells**, recognize viruses through PRRs, such as *Toll-like receptors (TLRs)*, which detect viral *Pathogen-Associated Molecular Patterns (PAMPs)*.
  - **PAMPs** in viruses include viral RNA, DNA, and viral proteins (e.g., double-stranded RNA in some viruses).
- **Interferons (IFNs):** When viral infection is detected, infected cells release **Type I interferons (IFN-α, IFN-β)**. These interferons serve two purpuses:
  - Alert neighboring cells to the presence of a virus.
  - Activate **NK cells** and boost the antiviral response.

- **2. Innate Immune Response to Viruses**
- **Phagocytosis**: While viruses are much smaller than bacteria, phagocytic cells like macrophages and dendritic cells can engulf virus particles, especially when viruses are coated with opsonins (such as **antibodies** or **complement proteins**). After engulfment, the virus is degraded in the **phagolysosome**.
- **Natural Killer (NK) Cells**: These cells play a critical role in targeting virus-infected cells. NK cells:

I. Recognize infected cells by detecting changes in **MHC class I** molecules or other stress signals on the infected cell's surface.

II. Release **perforin** and **granzymes**, which induce apoptosis (programmed cell death) in virus-infected cells, stopping viral replication.

3- Adaptive Immune Response

- Once the virus has by passed the innate immune system, the **adaptive immune response** is activated.
- **Antigen Presentation and T Cell Activation**
- **Antigen Presentation**: After phagocytosis or infection of antigen-presenting cells (APCs), viral antigens are processed and displayed on **MHC molecules**.
  - **MHC Class I** presents viral antigens to **cytotoxic T cells (CD8+ T cells)**.
  - **MHC Class II** presents viral antigens to **helper T cells (CD4+ T cells)**.
- **Cytotoxic T Cells (CD8+)**:
  - Once activated by viral antigens presented on **MHC class I** molecules, **cytotoxic T cells** (also called **killer T cells**) can directly attack and kill virus-infected cells.
  - They release perforin and granzymes to induce apoptosis in the infected cells, halting viral replication.
- **Helper T Cells (CD4+)**:
  - Helper T cells assist in the immune response by releasing cytokines that activate **B cells** and enhance the activity of **cytotoxic T cells**.

B Cells and Antibody Production

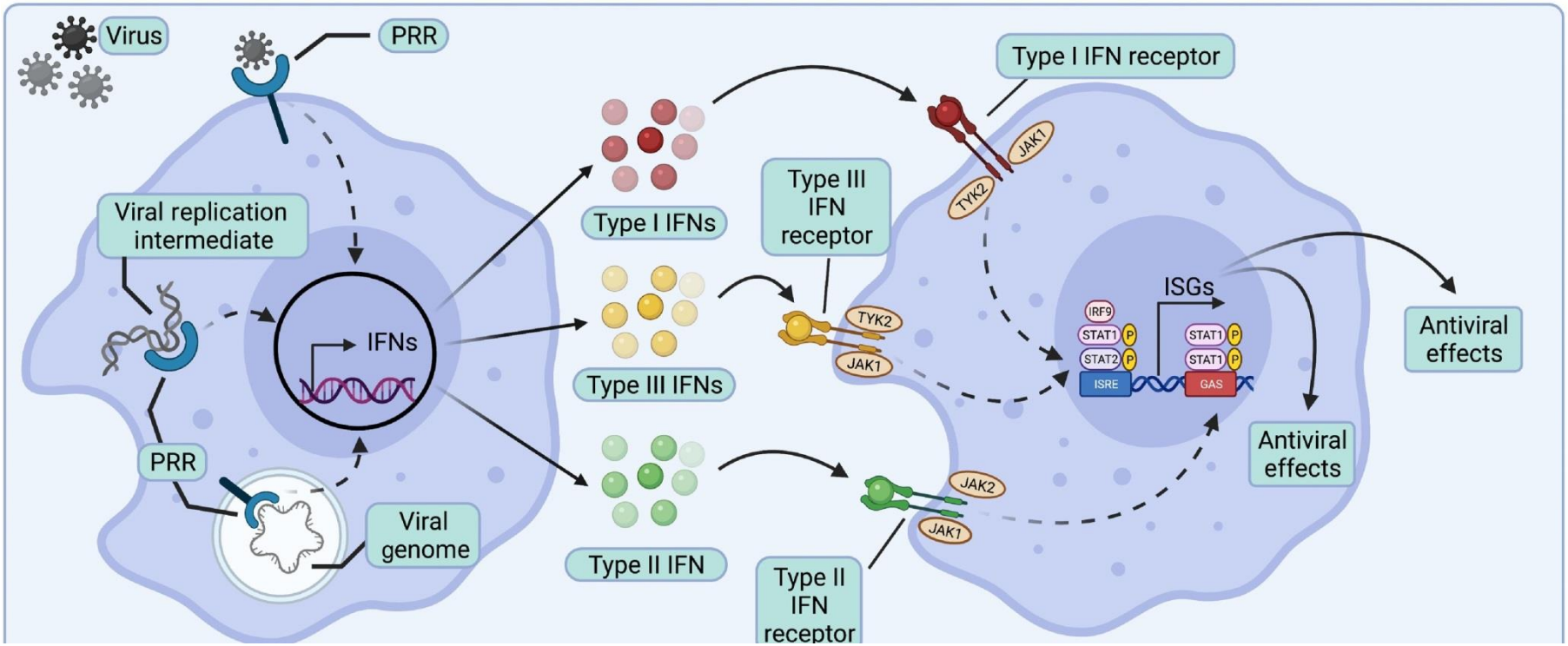
- **B Cells** produce **antibodies** (immunoglobulins) that specifically bind to viral antigens, neutralizing the virus and preventing it from infecting host cells.
- **Antibodies** can:
  1. **Neutralize** the virus by binding to viral surface proteins, blocking its ability to enter host cells.
  2. **Opsonize** the virus, tagging it for phagocytosis by macrophages and neutrophils.
  3. **Activate the complement system**, leading to viral particle destruction.

4. Destruction of Virus-Infected Cells

- **Apoptosis of Infected Cells**: Once cytotoxic T cells and NK cells recognize virus-infected cells, they induce apoptosis. This programmed cell death helps eliminate the infected cells while minimizing the release of new viral particles.
- **Memory Cells**: After the infection is cleared, memory T cells and B cells remain in the body, providing a rapid and effective response if the same virus is encountered again.

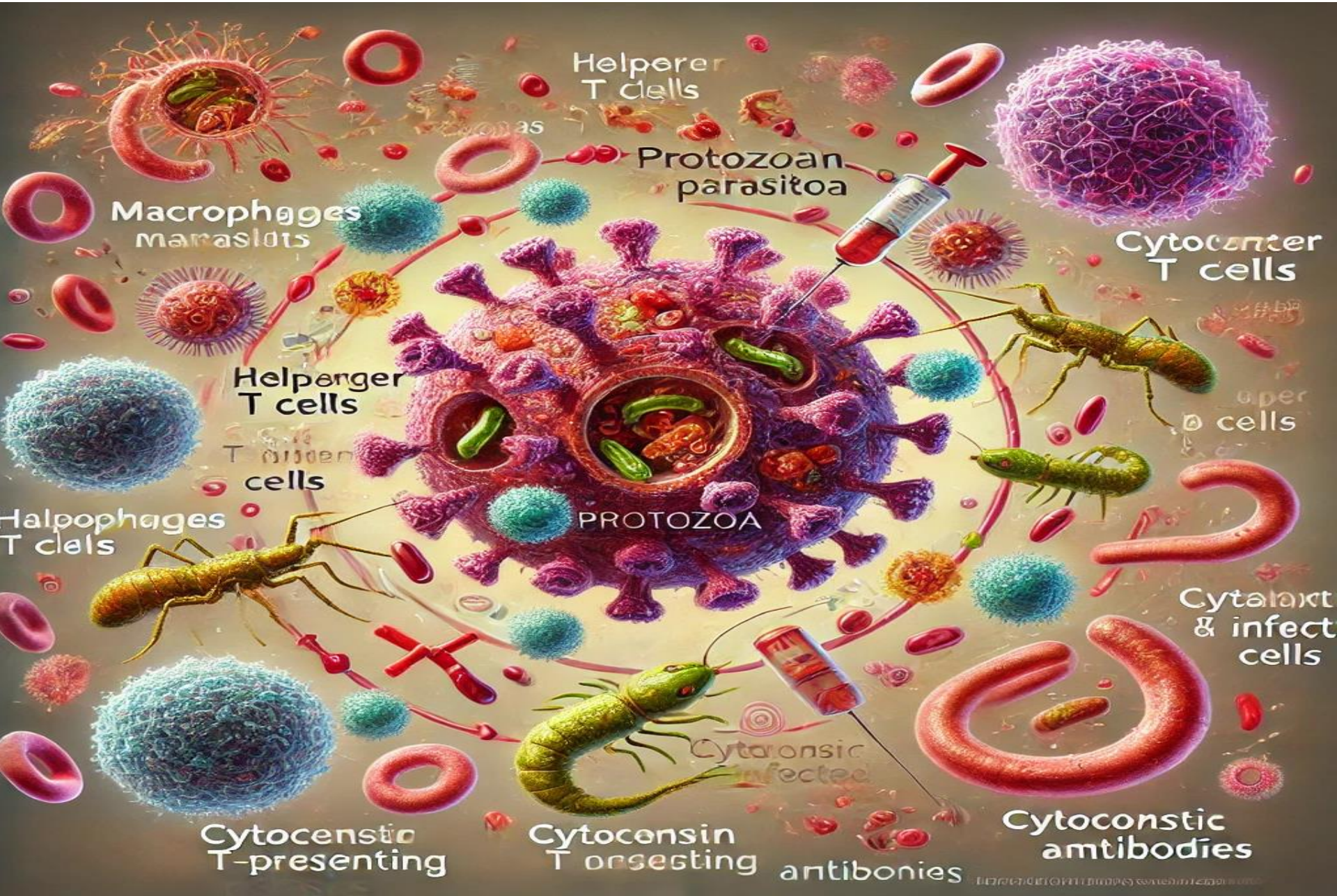
5. Interferon Response (IFN)

- ***Type I Interferons*** are crucial in the early antiviral response. They trigger an antiviral state in neighboring cells, helping limit viral replication and spread.
- These interferons enhance the activity of **NK cells** and stimulate the adaptive immune response.



Initially named after their function in 'interfering' with viral replication [1], IFNs are a class of cytokines responsible for initiating a cascade of immune responses against pathogens [2]. Subsequently grouped into three families (type I, II, and III; or IFN-I, -II, and -III), IFNs work together in a synergistic manner to induce antiviral activities in mammalian host cells such as epithelial cells and macrophages. In general, **pathogen-associated molecular patterns** (PAMPs) are sensed by **pattern recognition receptors** (PRRs), leading to induction and secretion of IFNs by infected immune or epithelial cells. IFNs bind IFN receptors on the surface of neighboring and/or immune cells, triggering a signaling cascade to induce a suite of IFN-stimulated genes (ISGs) that directly mediate the antipathogenic effects of IFNs (Figure 1) [3]. There are specificities to each IFN type, such as different receptor utilization, expression patterns, and distinct downstream genes, which are key for their divergent role2

Immune response against parasites

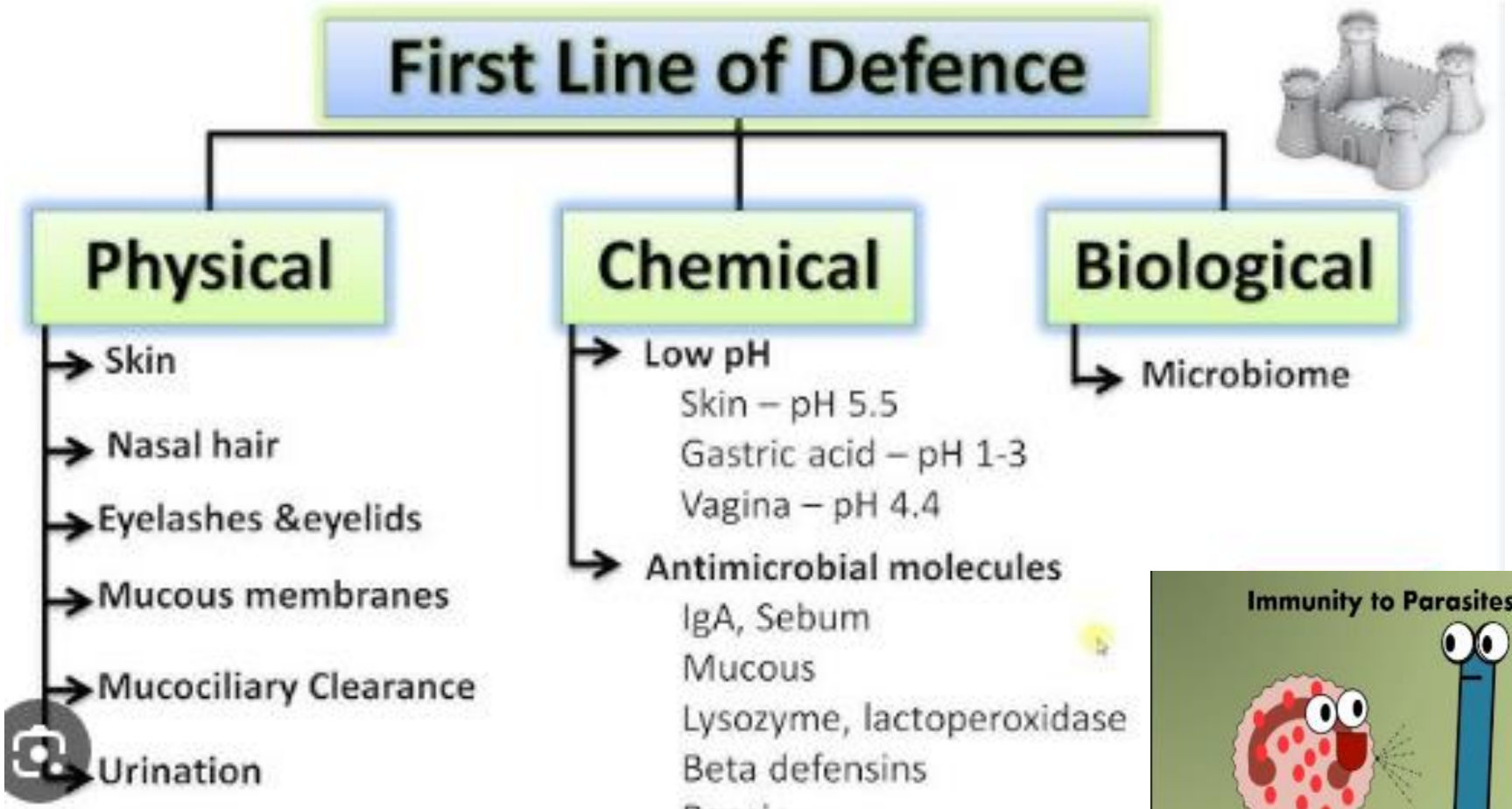


Immune Response Against Parasites

- The immune response against parasites involves a complex interplay between the innate and adaptive immune systems.
- Parasites, such as protozoa and helminths, often have mechanisms to evade immune detection, necessitating a robust immune response.

1. Innate Immune Response

a. Physical ,Chemical and biological Barriers



- **Skin and Mucous Membranes**: Act as the first line of defense to prevent parasite entry.
- **Secretions**: Mucus, enzymes (like lysozyme), and antimicrobial peptides can inhibit parasite growth.

Cellular Responses

- **Phagocytic Cells**: Macrophages and neutrophils can engulf and digest some parasites through **phagocytosis**.
- **Eosinophils**: These cells are particularly important in combating helminths (worms). They release toxic granules containing enzymes and proteins that damage or kill parasites.
- **Mast Cells**: Release histamine and other mediators in response to parasitic infections, contributing to inflammation and recruiting other immune cells.

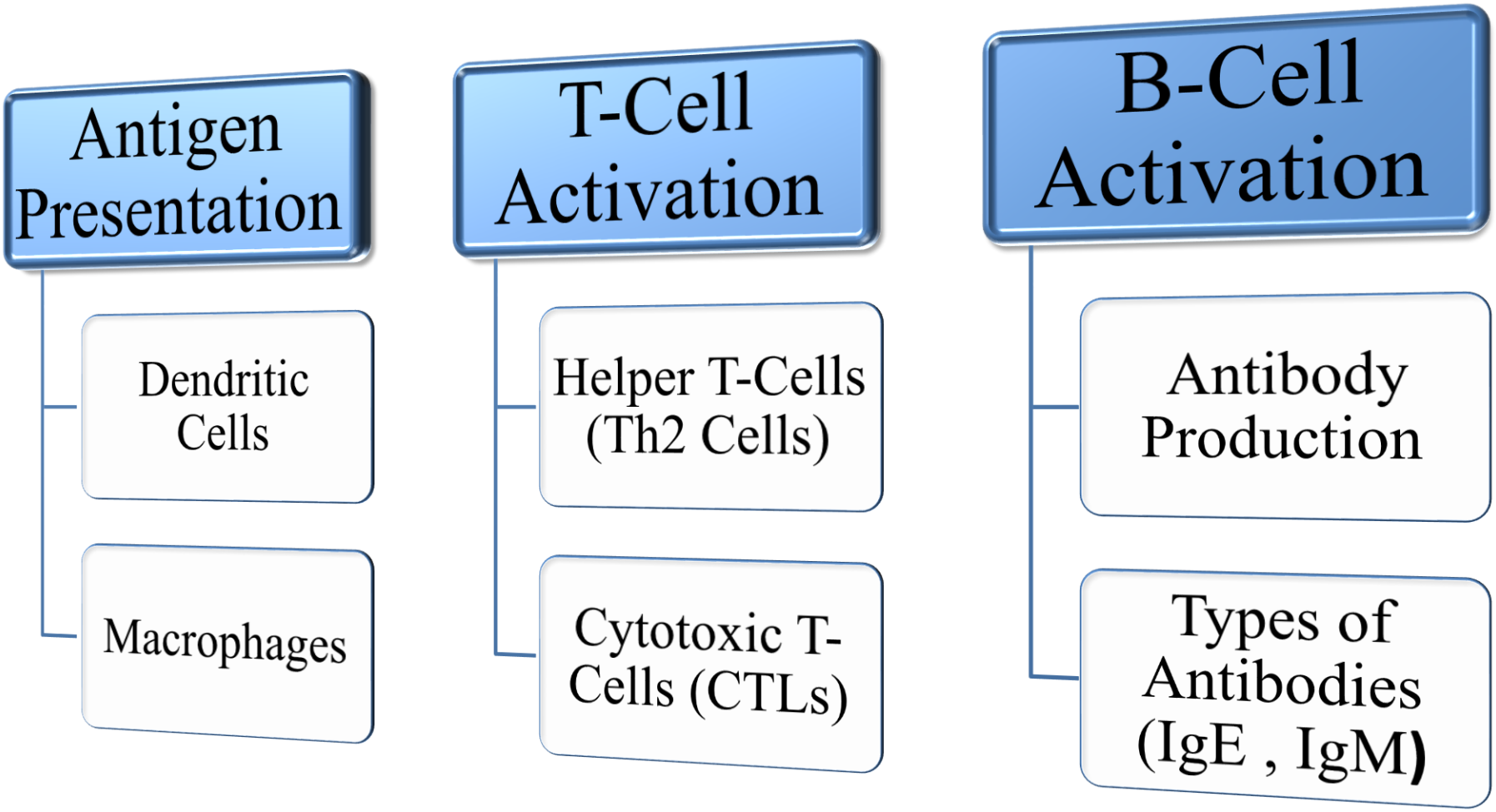
Inflammatory Response

- **Cytokine Release**: Infected tissues release cytokines (like IL-1, IL5, IL-6, and TNF-α) to recruit immune cells to the site of infection.
- **Inflammation**: This response increases blood flow and permeability, allowing more immune cells to access the infection site.

Natural Killer (NK) Cells

- NK cells can identify and kill infected host cells harboring intracellular parasites (like certain protozoa) through the release of cytotoxic granules.

2. Adaptive Immune Response



Antigen Presentation

Dendritic Cells and Macrophages

Engulfment:

- **Dendritic Cells**: These cells capture parasites through a process called phagocytosis. They extend their cell membranes to engulf the pathogen.
- **Macrophages**: Similar to dendritic cells, macrophages also ingest parasites and other pathogens.

T-Cell Activation

*** Helper T-Cells (Th2 Cells):**

- Secrete cytokines such as **IL-4**, **IL-5**, and **IL-13**, which promote the immune response against helminths.
- Encourage the production of immunoglobulin E (IgE) and enhance the activity of eosinophils and mast cells.

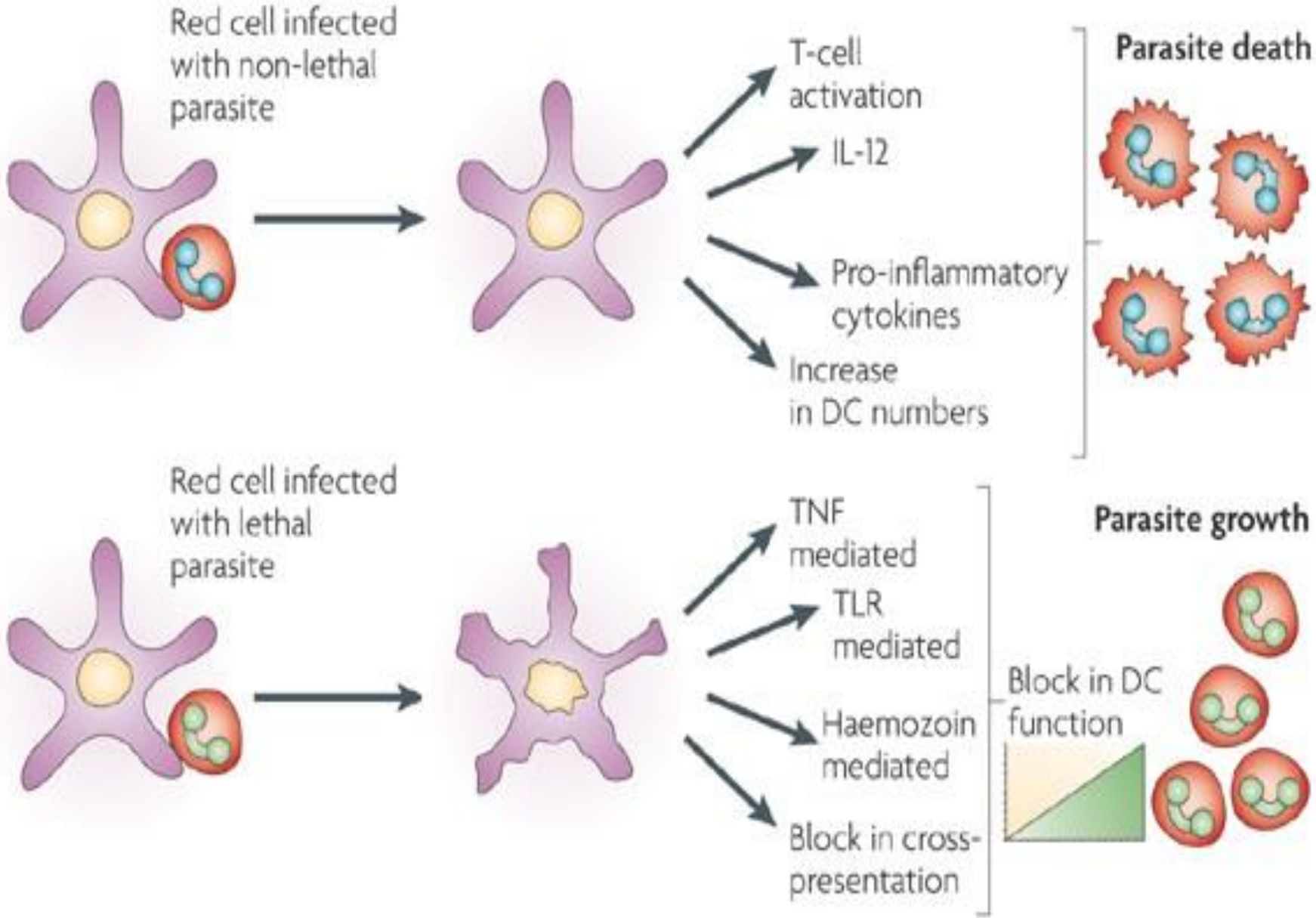
*** Cytotoxic T-Cells (CTLs):**

-Recognize and kill infected cells that contain intracellular parasites, particularly in protozoan infections.

Antigen Processing:

Once inside the cell, the parasite is broken down into smaller pieces (antigens) within phagolysosomes.

- **Antigen Presentation**:
- The processed antigens are then loaded onto Major Histocompatibility Complex (MHC) molecules.
- Dendritic cells primarily present antigens on MHC class II molecules, which activate CD4+ T-helper cells.
- Macrophages can present antigens on both MHC class I and class II, facilitating the activation of CD8+ cytotoxic T-cells and CD4+ T-helper cells.


Red cell infected with non-lethal parasite
T-cell activation
IL-12
Pro-inflammatory cytokines
Increase in DC numbers
Parasite death
Red cell infected with lethal parasite
TNF mediated
TLR mediated
Haemozoin mediated
Block in cross-presentation
Block in DC function
Parasite growth

- **B-Cell Activation**
- **Antibody Production**: Upon activation by T-helper cells, B-cells differentiate into plasma cells that produce specific antibodies against the parasite.
- **Types of Antibodies**:
  - **IgE**: Important for defense against helminths, it binds to parasites and activates mast cells and eosinophils.
  - **IgG and IgM**: These can opsonize parasites, enhancing their recognition and destruction by phagocytic cells.

3. Eosinophilic Response

- **Eosinophils**: Key effector cells in the response to helminths. They release cytotoxic granules containing:
  - **Major Basic Protein (MBP)**: Damages the outer membranes of helminths.
  - **Eosinophil Cationic Protein (ECP)**: Has direct antiparasitic effects.

4. Memory Response

- **Memory T and B Cells**: After an initial infection, some T and B cells become memory cells, enabling a quicker and more robust response upon re-exposure to the same parasite.

Immune response against fungi

- The **immune response against fungal infections** involves both **innate** and **adaptive immune systems** to protect the body from fungal pathogens like **Candida**, **Aspergillus**, and **Cryptococcus**.

Innate Immune Response

- Physical Barriers
- Pattern Recognition Receptors (PRRs)
- Phagocytosis
- CytokinesPro-inflammatory cytokines
- Complement Activation

Adaptive Immune Response

- T-helper Cells (Th Cells)
- Antibodies

1. Innate Immune Response:

- **Physical Barriers**: The skin and mucosal surfaces act as the first line of defense against fungal entry.
- **Pattern Recognition Receptors (PRRs)**: Cells like macrophages, neutrophils, and dendritic cells recognize fungal components (e.g., β-glucans, mannans) through receptors such as **Toll-like receptors (TLRs)** and **C-type lectin receptors (CLRs)**.
- **Phagocytosis**: Neutrophils and macrophages engulf and destroy fungi via **phagocytosis** and the production of **reactive oxygen species (ROS)**.
- **Cytokines**: **Pro-inflammatory cytokines** like TNF-α, IL-1β, and IL-6 are released to recruit immune cells to the infection site.
- **Complement Activation**: The complement system helps in opsonizing fungi for easier recognition and destruction by phagocytic cells.

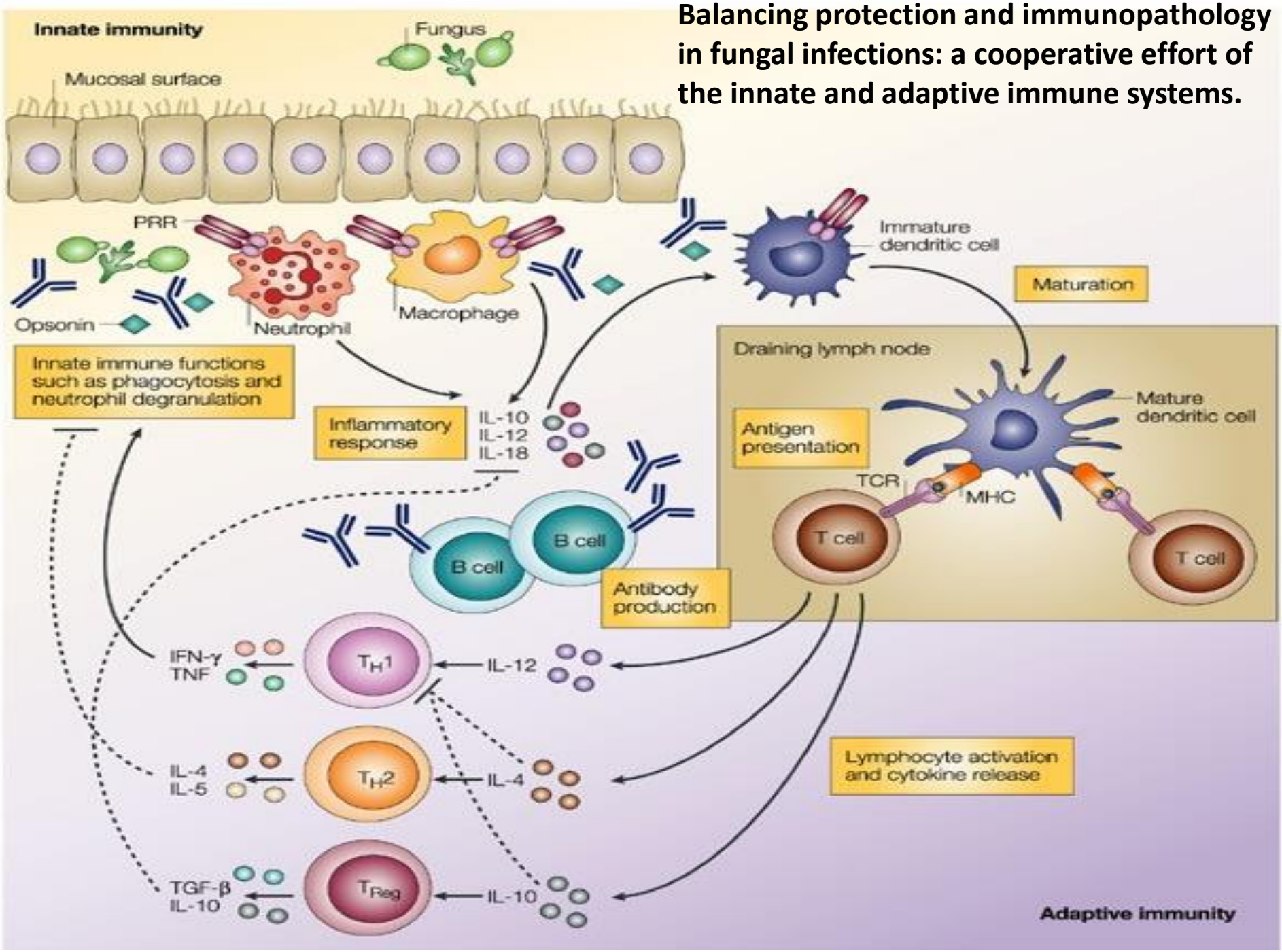
2. Adaptive Immune Response:

- **T-helper Cells (Th Cells)**:
  - **Th1 Response**: Promotes cell-mediated immunity by activating macrophages and producing **IFN-γ**, which enhances the killing of intracellular fungi.
  - **Th17 Response**: Produces **IL-17** and **IL-22**, crucial for neutrophil recruitment and maintaining mucosal barriers against fungal infections.
- **Antibodies**: Although antibodies play a less dominant role in fungal immunity, **IgG** and **IgA** can help neutralize fungal antigens and assist in fungal clearance.
- **Memory Cells**: Upon a second encounter with the same fungus, memory T cells and B cells provide faster and more effective immune responses.

Key Fungal Defense Mechanisms:

- **Neutrophils** are crucial for fighting systemic fungal infections.
- **Dendritic cells** present fungal antigens to activate T cells, linking innate and adaptive immunity.
- The **balance of Th1 and Th17 responses** is critical for effective fungal immunity.
- Failure in these immune mechanisms, especially in immunocompromised individuals, can lead to severe fungal infections.

Balancing protection and immunopathology in fungal infections: a cooperative effort of the innate and adaptive immune systems.



Comparing the **immune response** against **bacteria**, **parasites**, **viruses**, and **fungi**:

Feature	Bacteria	Viruses	Parasites	Fungal
Innate Immune Cells Involved	Neutrophils, Macrophages, Dendritic Cells	Eosinophils, Macrophages, Neutrophils	Natural Killer (NK) Cells, Dendritic Cells	Neutrophils, Macrophages, Dendritic Cells
Pattern Recognition Receptors (PRRs)	Toll-Like Receptors (TLRs), NOD-Like Receptors (NLRs)	TLRs, RIG-I-like Receptors (RLRs)	TLRs, C-type Lectin Receptors (CLRs), others	CLRs, TLRs, NLRs, Dectin-1
Phagocytosis	Neutrophils and Macrophage	Limited (Viruses are intracellular)	Limited, for some parasite stages	phagocytosis by Neutrophils
Antibodies	IgM, IgG, IgA (Opsonization, neutralization, complement activation)	IgG, IgM, IgA (Neutralization, blocking entry)	IgE (against helminths), IgG, IgA	IgG, IgA (Assist in fungal clearance)
Cytokines Involved	TNF-α, IL-1β, IL-6, IFN-γ	IFN-α, IFN-β, IFN-γ, IL-12	IL-4, IL-5, IL-13, IL-10	TNF-α, IL-6, IFN-γ, IL-17
Adaptive Immune Cells Involved	$CD4^+$ Th1 and Th17, $CD8^+$ T cells	$CD8^+$ cytotoxic T cells, $CD4^+$ Th1 and Th2 cells	$CD4^+$ Th2 cells (Helminths), Th1 and Th17 (Protozoa	$CD4^+$ Th1, Th17 cells
Role of T-helper Cells	**Th1/Th17** responses: activate phagocytes and produce IFN-γ	**Th1** response: $CD8^+$ T cells and NK cells activated	**Th2** response for helminths (IL-4, IL-5), **Th1/Th17** for protozoa	**Th1/Th17**: Stimulate phagocytes, recruit neutrophils

Comparing the **immune response** against **bacteria**, **parasites**, **viruses**, and **fungi**:

Feature	Bacteria	Viruses	Parasites	Fungal
Cytotoxicity	Indirect, through phagocytosis	Direct killing by $CD8^+$ cytotoxic T cells, NK cells	Limited, more relevant for intracellular parasites	Limited, fungi are usually extracellular
Eosinophils Role	Minor	None	Major for **helminths** (parasites)	Limited, possible role in some fungal infections
Natural Killer (NK) Cells	Minor	Major role in killing virus-infected cells	Limited	Limited
Complement Activation	Significant: Opsonization, Membrane Attack Complex (MAC)	Minor, for opsonization	Limited	Minor
Immunopathology	Excessive inflammation, septic shock	Autoimmunity, chronic inflammation	Tissue damage due to chronic infections	Granuloma formation, chronic inflammation
Evasion Mechanisms by Pathogens	Capsules, toxins, biofilm formation	Antigenic variation, latency, inhibition of MHC I	Antigenic variation, cyst formation (protozoa), immune modulation	Cell wall shielding, morphogenesis, immune evasion

Each immune response is tailored to the pathogen's characteristics, like whether it is intracellular (viruses, some parasites) or extracellular (bacteria, fungi, helminths).

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