

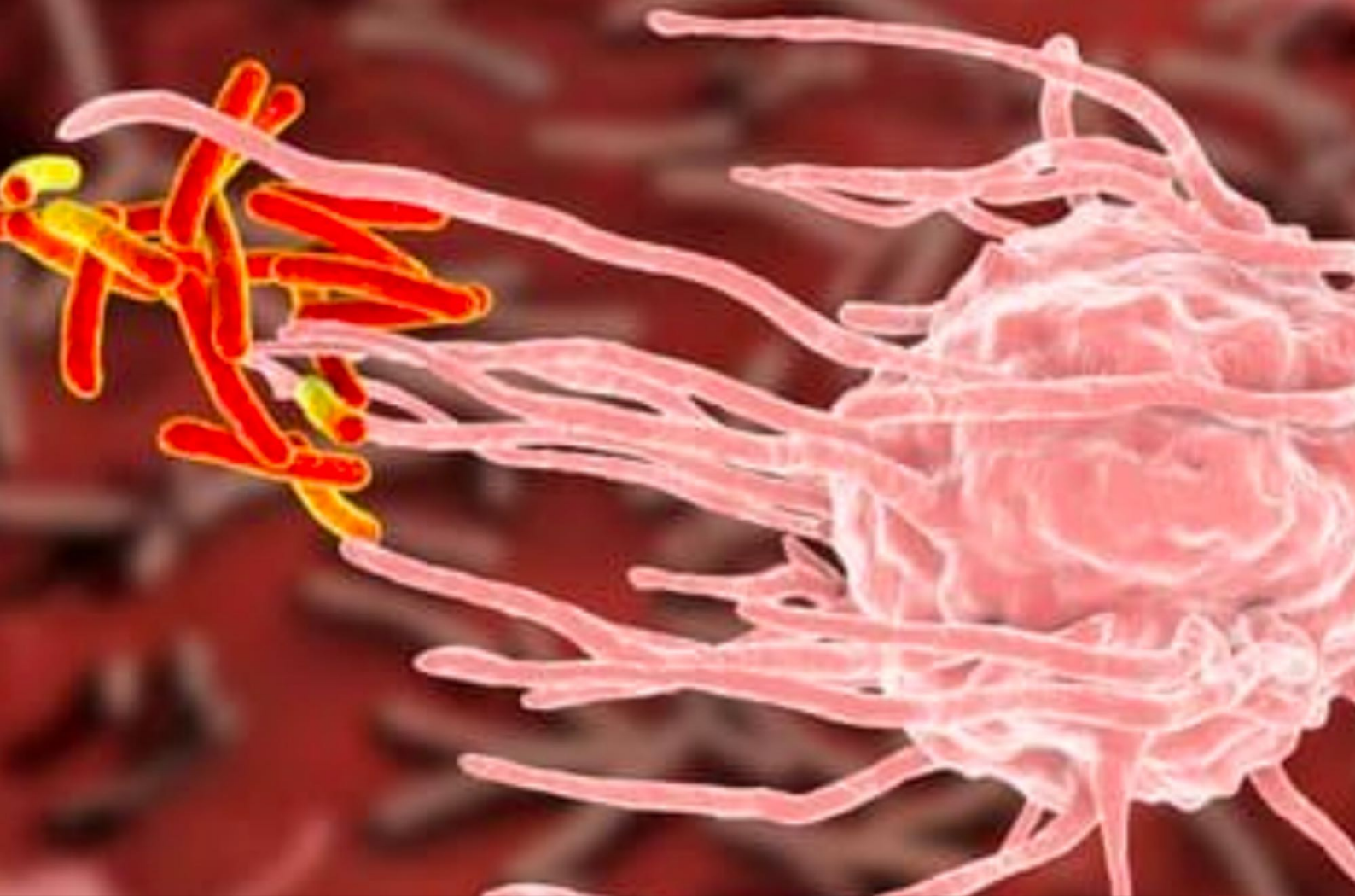
# IMMUNOLOGY & RHEUMATOLOGY

## NOTES

**FOURTH EDITION**

PRE-SUMMARIZED  
READY-TO-STUDY  
HIGH-YIELD NOTES

FOR THE TIME-POOR  
MEDICAL, PRE-MED,  
USMLE OR PA STUDENT



**149 PAGES**



## A Message From Our Team

Studying medicine or any health-related degree can be stressful; believe us, we know from experience! The human body is an incredibly complex organism, and finding a way to streamline your learning is crucial to succeeding in your exams and future profession. Our goal from the outset has been to create the greatest educational resource for the next generation of medical students, and to make them as affordable as possible.

In this fourth edition of our notes we have made a number of text corrections, formatting updates, and figure updates which we feel will enhance your study experience. We have also endeavoured to use only open-source images and/or provide attribution where possible.

**If you are new to us, here are a few things to help get the most out of your notes:**

- 1. Once saved, the notes are yours for life!** However, we strongly advise that you download and save the files immediately upon purchasing for permanent offline access.
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## Table Of Contents:

**What's included:** Ready-to-study summaries of the anatomy and physiology of the human immune system, as well as its related pathologies, presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

### Immunology & Rheumatology Topics:

- OVERVIEW OF THE IMMUNE SYSTEM
- ANTIGENS & ANTIBODIES
- MAJOR HISTOCOMPATIBILITY COMPLEXES
- CELLS OF THE IMMUNE SYSTEM
- FUNCTIONAL ANATOMY OF THE IMPORTANT SECONDARY LYMPHOID ORGANS
- INNATE VS ADAPTIVE IMMUNE RESPONSES
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- IMMUNITY AGAINST INFECTIOUS ORGANISMS & EVASION OF THE IMMUNE RESPONSE
- INFECTION IMMUNOLOGY
- AUTOIMMUNITY

## OVERVIEW OF THE IMMUNE SYSTEM

## OVERVIEW OF THE IMMUNE SYSTEM

### The Immune System:

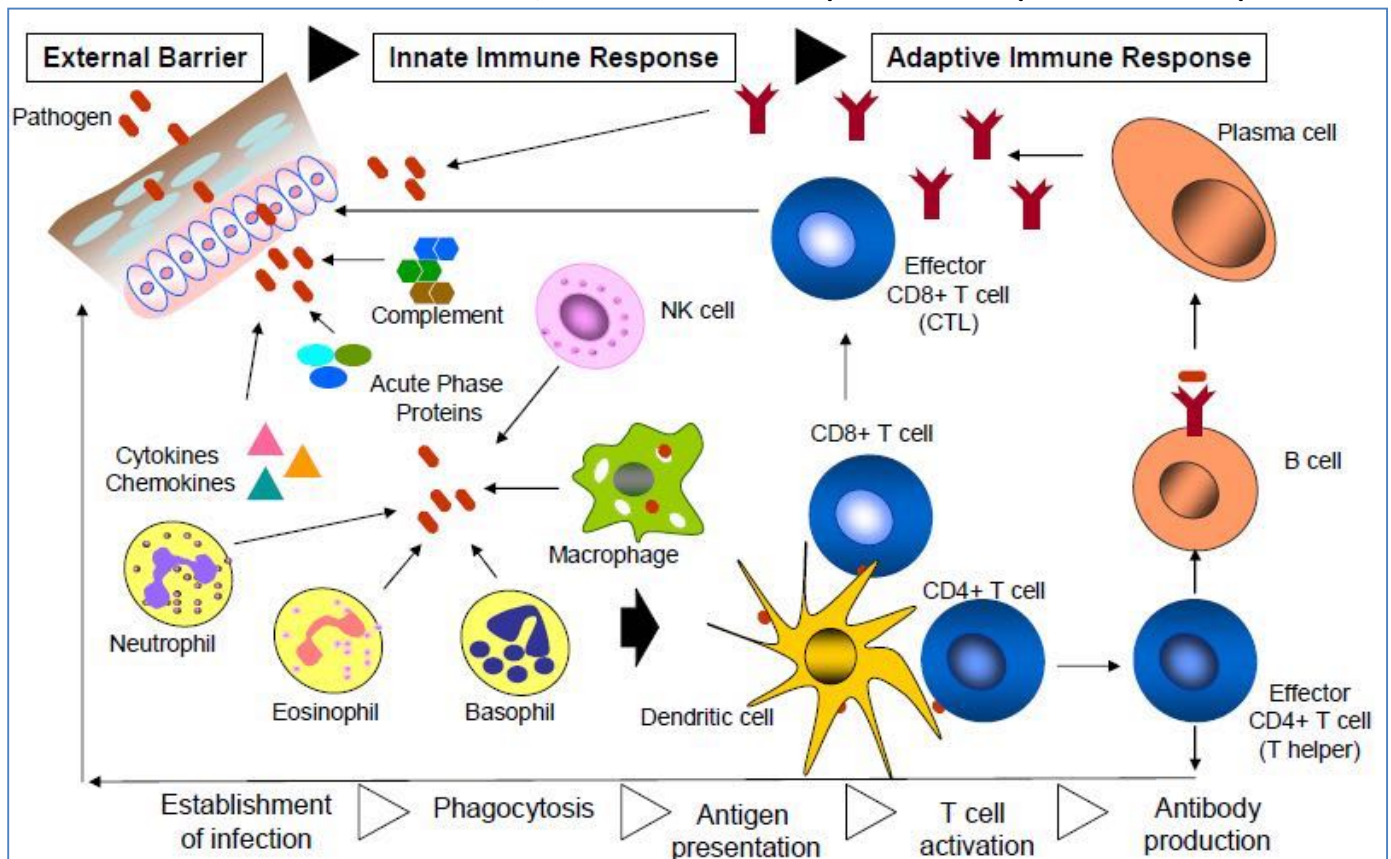
- The immune system is more a **functional system** rather than an **anatomical or organ-based** system.
- **Consists of:**
  - o a diverse array of molecules
  - o -and trillions of immune cells (especially lymphocytes).
  - o These molecules & immune cells inhabit lymphoid tissues & circulate in body fluids.
- **Functions to protect the body from:**
  - o Most infectious microorganisms
  - o Cancer cells
  - o Transplanted organs
  - o Grafts
  - o Any other foreign material
- **Can act directly** – by cell attack
- **Can act indirectly** – by releasing mobilising chemicals & antibody molecules.

### Terminology:

- **Pathogen:** microorganism that is able to cause disease
- **Pathogenicity:** the ability of a microorganism to cause disease.
- **Virulence:** the degree of pathogenicity.
- **Opportunistic pathogens:** bacteria which cause disease in a compromised host.
- **Normal flora:** harmless bacteria consistently associated with the host.
- **Infection:** when an organism (Incl: Normal flora) breaches a body surface.
  - o Note: Infection Doesn't necessarily lead to disease; Depends on:
    - Route of entry
    - Number of pathogens
    - Immune status of host

### Basic Diagram of the Immune System:

- Note that there is an **External Barrier**, An **Innate Immune Response** & an **Adaptive Immune Response**





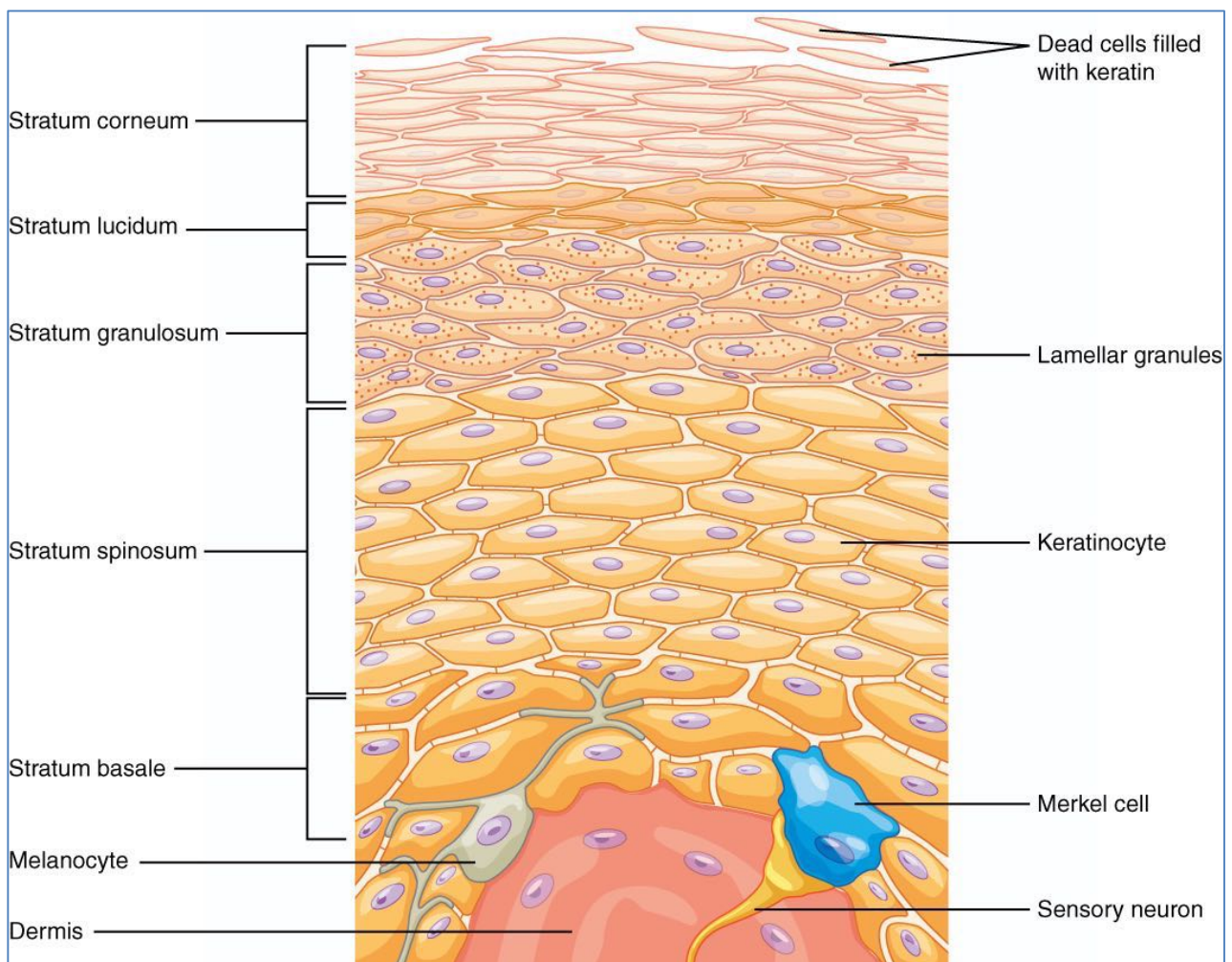
## INNATE VS ADAPTIVE IMMUNE SYSTEM

	<u>Protective Elements</u>			<u>Characteristics</u>		
	Barriers	Proteins	Cells	Specificity	Memory	Tolerance
<b><u>Innate</u></b>	Skin Epithelia Chemicals	Complement system Inflammation (Acute Phase Proteins)	Phagocytes and NK cells	PAMPs	No	Yes
<b><u>Adaptive</u></b>	Epithelial-Lymphocytes	Antibodies	Lymphocytes (T and B)	Specific Antigens on microbe surface	Yes	Yes

### **INNATE (NON-SPECIFIC) IMMUNE SYSTEM:**

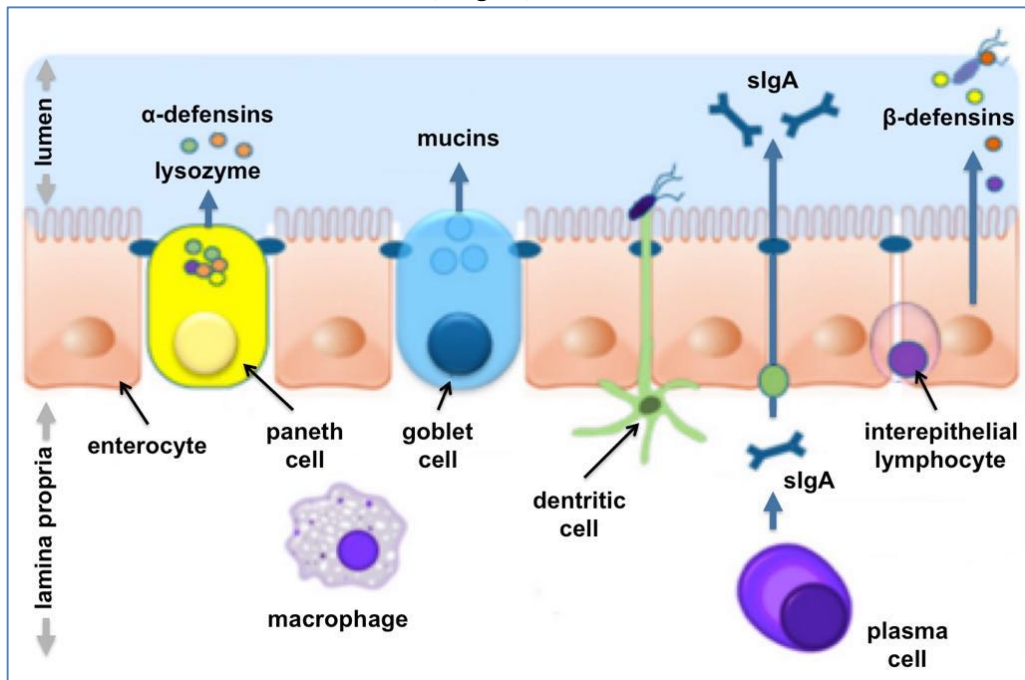
The Passive, Rapid and Non-Selective mechanisms of the immune system that defend the host from infection.

- **Features:**
  - Already in place at birth.
  - Is always prepared
  - Responds within minutes
- **Role:**
  - Protects the body from all foreign substances.
  - Are often sufficient to ward off invading pathogens single-handedly.
  - Essentially, it exists to **reduce the workload of the adaptive system.**
- **1<sup>st</sup> Line of Defence: Surface Barriers:**
  - **Role: Prevents Entry of Pathogen**
    - **Skin**
      - Stratified
      - Heavily keratinised



- **Mucous membranes**

- Lysozyme: enzyme found in saliva & tears →destroy bacteria.
- Sticky Mucus: in digestive & respiratory tracts →traps bacteria.
- Cilia – nasal & respiratory →sweep bacteria into mouth→swallowed.
- Acid secretion: skin, vagina, stomach →kills microbes.

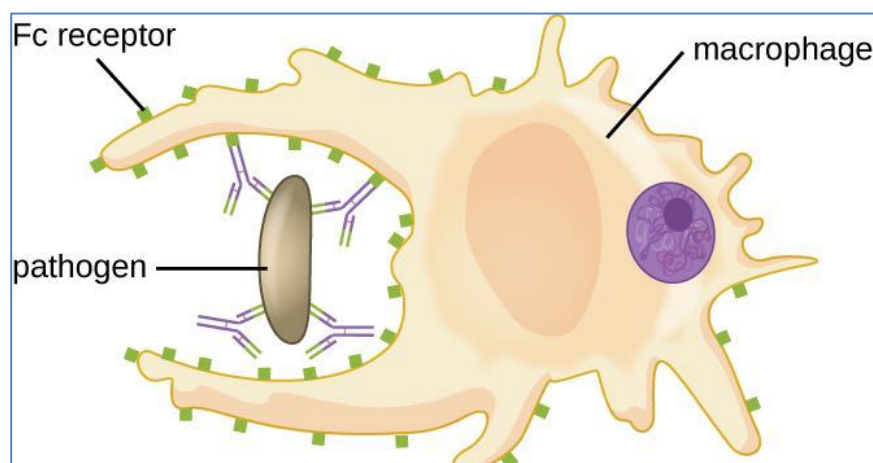


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- **2<sup>nd</sup> Line of Defence: Internal Defences:**

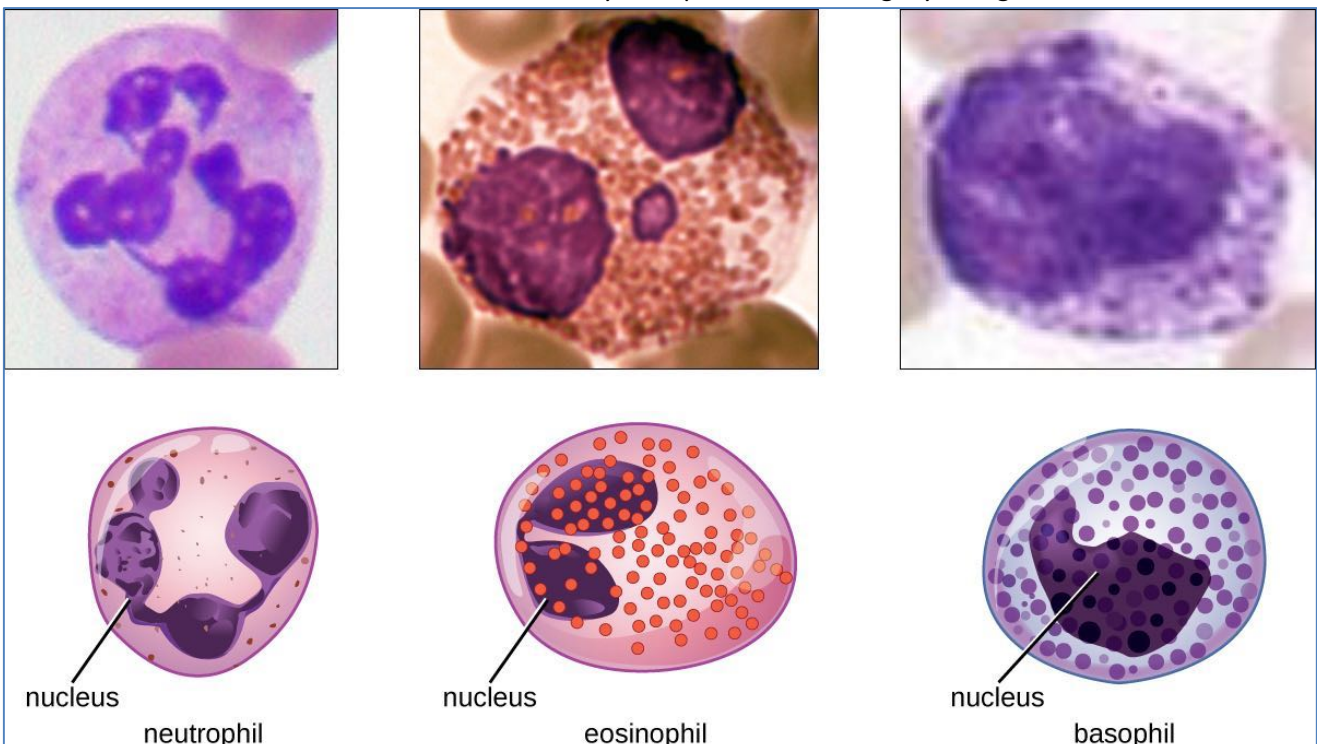
- **Role: Prevents Spread of Pathogen If Surface Barriers are Breached**

- **Macrophages** – Large phagocytic cells derived from bone-marrow precursors & found in Tissues throughout the body. They are involved in all phases of the immune system;
  - Engulf and Kill invading Microorganisms – Innately
  - Engulf and Kill Microbes 'marked' by an Adaptive Immune Response.
    - Eg: Agglutinated Ag:Ab complexes
  - Scavenge dead cells & general debris.
  - Help induce Inflammation (Required for an effective immune response), secreting Pro-Inflammatory Cytokines (specifically those that induce the Acute Phase Response) & Chemokines.
  - Antigen-Presentation to T-Helper Cells



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- **Granulocytes** – possess cytoplasmic granules. named according to the stain-ability of the cytoplasmic granules. They are ‘Polymorphonuclear’ – (Multi-shaped lobed nucleus)
  - **Neutrophils** –they release toxic chemicals into the extracellular fluid, killing both the target and themselves. (kamikaze)
    - Most Numerous in blood samples 40-75%.
    - Most Important Granulocyte.
    - **Phagocytic** – Engulf invaders coated with Antibodies & Complement, damaged cells & debris.
    - Life-span = 5 days (Note: Neutrophils don’t return to the blood; they turn into Pus.)
  - **Eosinophils** – Red-Staining Granules with **Eosin** Dye → Anti-Parasite & Anti-Fungal Roles.
    - Weakly Phagocytic
    - Life-Span = 12 Days in Tissues - OR - 30min in Blood
    - Kills extracellular organisms (Eg: Parasites) by excreting toxic chemicals onto their prey.
    - Involved in Antigen Presentation & Destroy Tumour Cells.
  - **Basophils** – Granules stain with **Basic** Dyes → Hypersensitivity & Allergic Reactions.
    - Least Numerous
    - Non-Phagocytic
    - Granules contain Histamine, Serotonin & Prostaglandins → ↑Inflammation, ↑Permeability of Capillaries → ↑Phagocyte migration to site of infection.

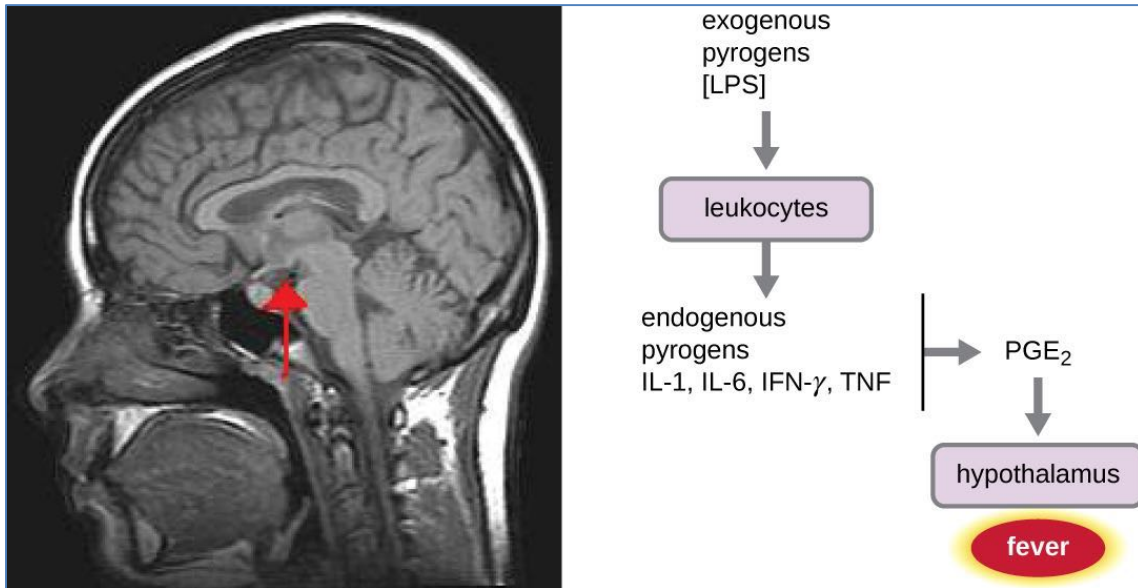


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▪ **Fever**

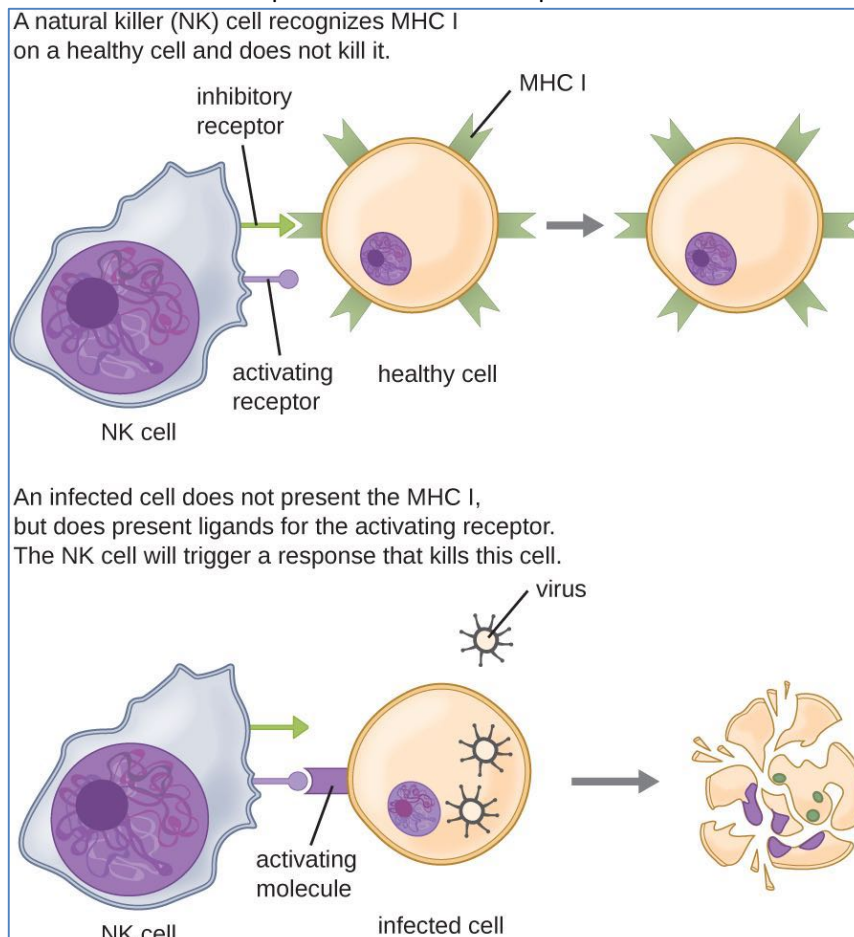
- When exposed to foreigners, leukocytes & macrophages secrete pyrogens → increases the body's thermostat.
- Increases metabolic rate, kills microbes, speeds up repair.



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▪ **Natural Killer cells** - Large, Granular, **Lymphoid-Derived** cells, which kill malignant cells, and cells infected by Intracellular pathogens (viruses/bacteria).

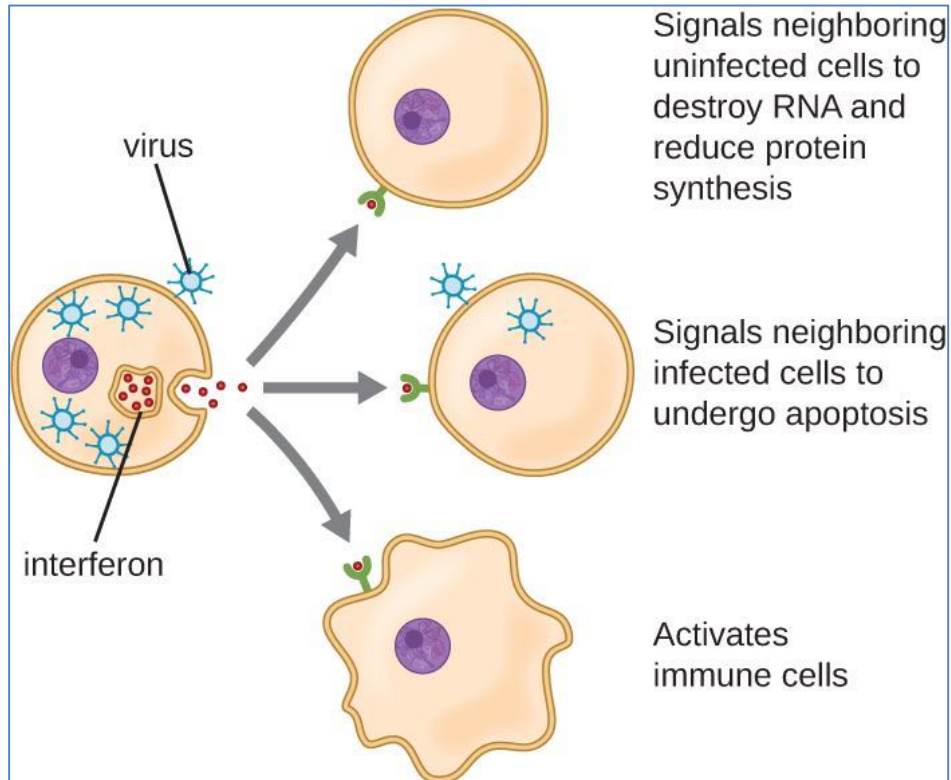
- Police the body in blood & lymph
- Can lyse & kill cancer cells & virus-infected cells
- Target all cells that lack 'self' surface receptors (non-specific)
- Kill by latching onto invaders and inducing apoptosis.
- Also secrete potent chemicals that promote inflammation



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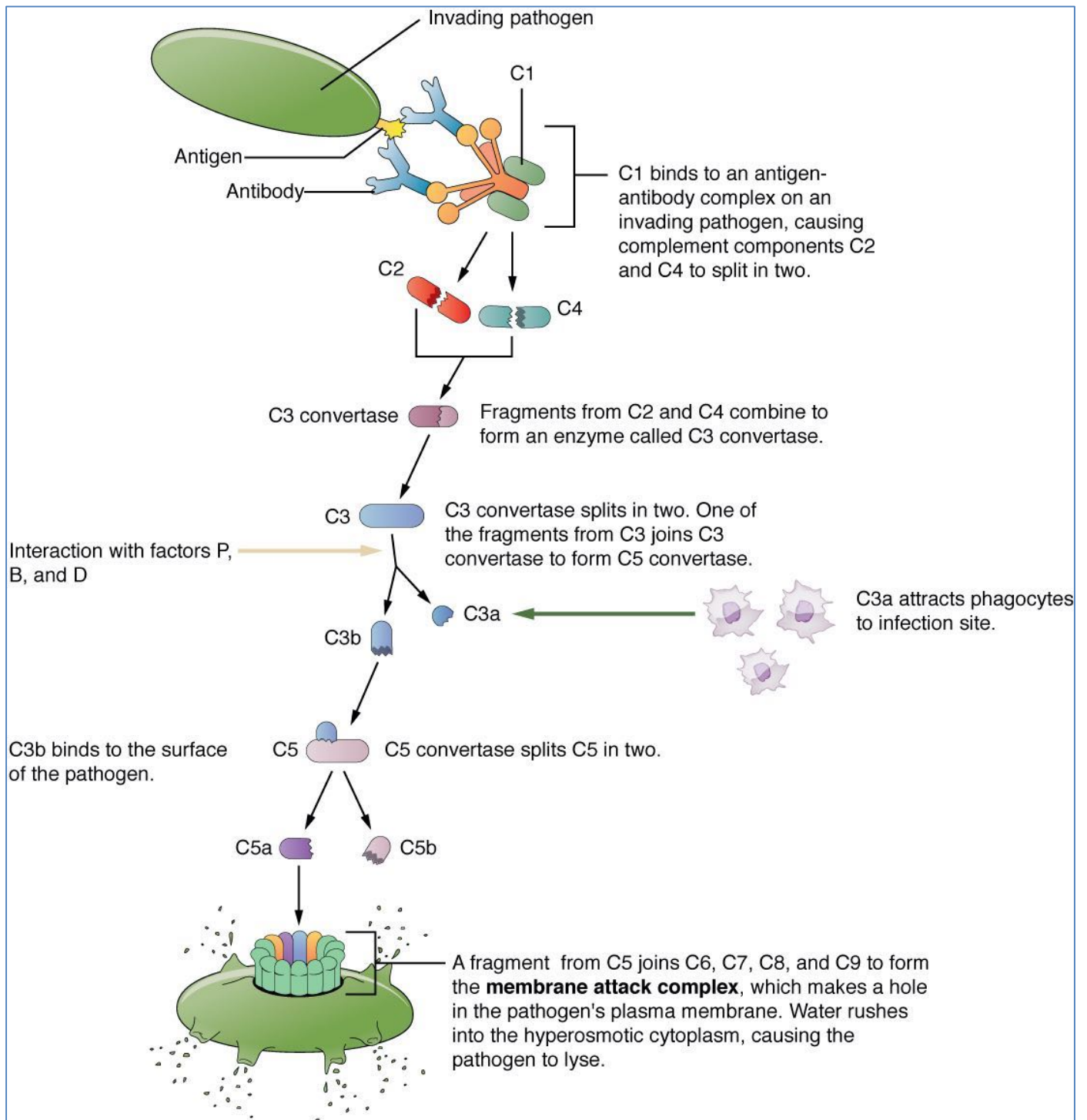
▪ **Antimicrobial proteins (Eg: Interferon & Complement):**

- Either attack microbes directly or reduce their reproductive ability.
- **Interferon Proteins** – Virally Infected cells secrete Interferons (IFNs) to protect cells that haven't yet been infected. Interferons stimulate nearby cells to synthesize proteins which "interfere" with viral replication by blocking protein synthesis & degrading viral RNA. IFNs also attract Macrophages & NK Cells to destroy the infected cells.



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- **Complement Proteins** – A group of over 30 small Pro-Enzymes (Zymogens) produced by the liver, which are widely distributed through blood & tissues. When stimulated via one of 3 pathways (Classical, Alternative & MB-Lectin), self-amplifying proteolytic cascades are initiated leading to:
  - **1- Opsonisation of pathogens by C3b** → Targets foreign particles for Phagocytosis.
  - **2- Lysis of antibody-coated cells by the Membrane Attack Complex** → Creates a pore in the PM of bacteria.
  - **3- Chemotaxis by C5a** → Attracts Phagocytic cells to the area.
- **Note:** Although the complement system is part of the Innate Immune System, it has an important role in activating the Adaptive Immune System. It does this by:
  1. Enhancing the uptake of complement-coated antigens by Antigen-Presenting Cells (as APCs have receptors for complement). &
  2. Enhancing the response of B-Cells to complement-coated antigens (as B-Cells also have receptors for complement – act as co-stimulators)

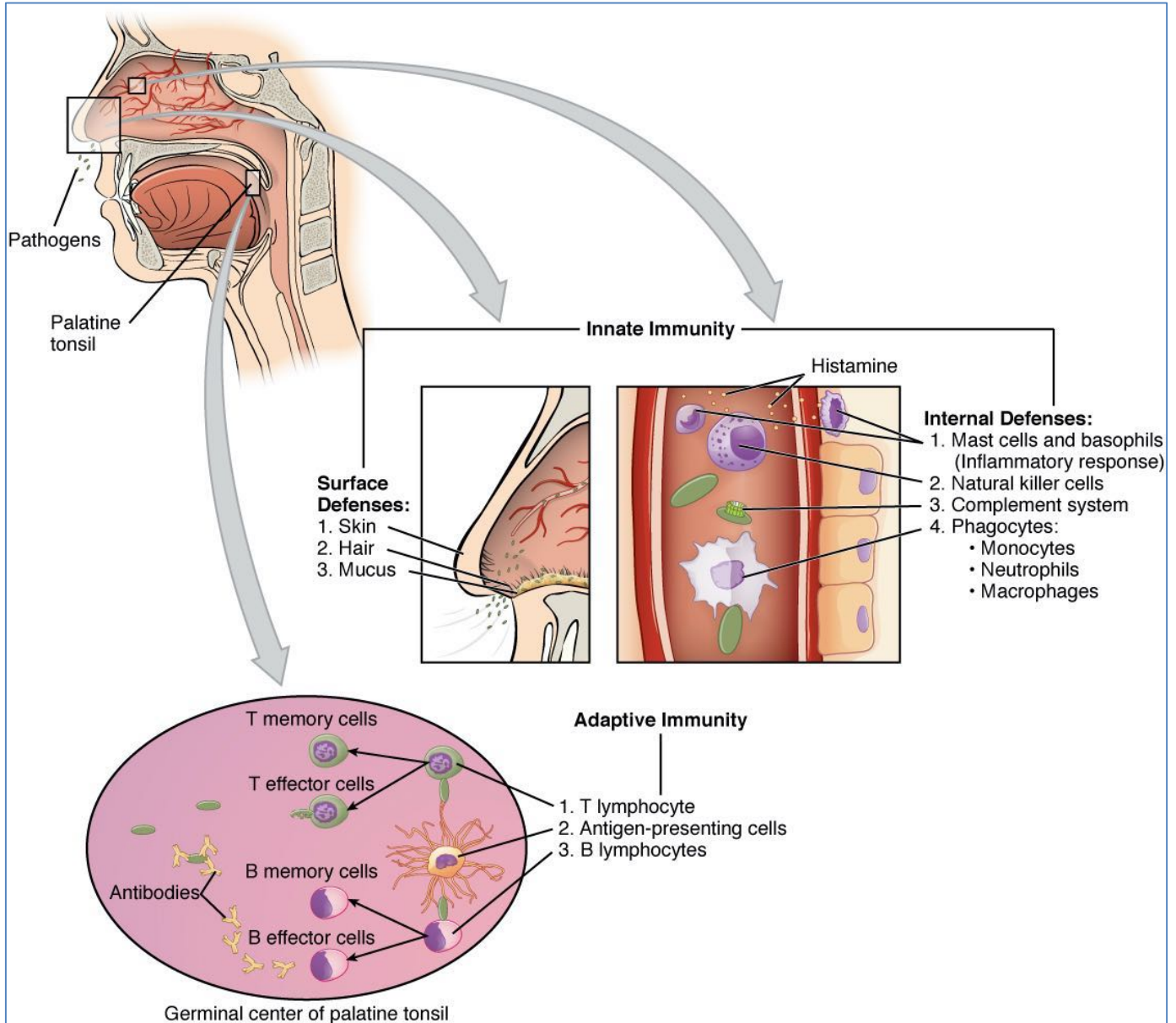


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**Complement Cascade and Function** The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

- **Inflammation**
  - In response to physical trauma/intense heat/bad chemicals/infection.
  - Injured cells secrete Cytokines
  - Attracts Macrophages, Neutrophils & Lymphocytes to the Injured/Infected Area.
  - Prevents spread of damaging agents to nearby tissue
  - Disposes of cell debris & pathogens
  - Sets stage for repair.
  - Characterised by **heat, redness, pain & swelling**
  
- **Cytokines are Important Mediators:**
  - **IL-6:**
    - Pyrogenic action on Hypothalamus → Fever
    - Stimulates the Acute Phase Response (in liver).
    - Activates Lymphocytes during Antigen-Presentation.
  - **TNF- $\alpha$ :**
    - Pyrogenic action on Hypothalamus → Fever
    - Induces *Local Inflammatory Response* → Helps Contain Infection.
      - ↑Blood Flow
      - ↑Vascular Permeability
      - ↑Endothelial Adhesiveness (For Leukocytes & Platelets)
      - Note: This can be maladaptive in Sepsis → Septic Shock.
    - Induces the Acute Phase Response (in liver).
    - Stimulates Dendritic-Cell Migration to Lymph Nodes.
  - **Note: Septic Shock** – Systemic Release of pro-inflammatory cytokines (**TNF, IL-1, IL-6, IL-8, IFN**) from Neutrophils/Macrophages/Endothelial cells, plus pro-inflammatory Complement → Systemic Vasodilation (blood-pooling) (amongst other things) → ↓↓BP → **Septic Shock**.
  
- **Acute Phase Proteins:** A class of proteins produced by the liver in response to Inflammatory Cytokines (IL-1, **IL-6** & TNF $\alpha$ ). **Relevant Examples include:**
  - **CRP – (C-Reactive Protein) →**
    - An Opsonising Agent for microbes → Phagocytosis (Similar action to Antibodies – except have broad specificity for PAMPs)
    - Also Activates the ***Classical Pathway of the Complement Cascade***.
  - **MBL – (Mannose-binding Lectin) →**
    - Also an Opsonising Agent for microbes → Phagocytosis.
    - Also Activates the ***Lectin Pathway in the Complement Cascade***.
  - **SP-A & SP-D:**
    - Found in Alveolar Fluid & Also have Opsonizing Properties.
  - **Note:** Measurement of acute-phase proteins, especially CRP, is a useful marker of Inflammation.



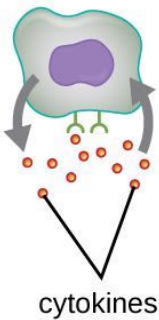
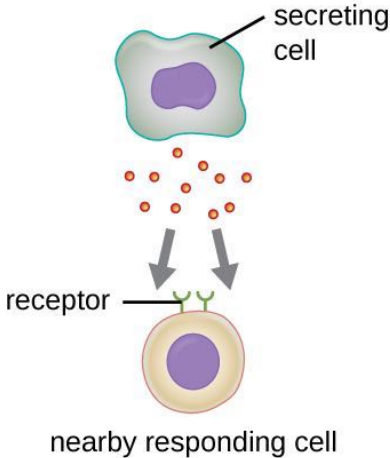
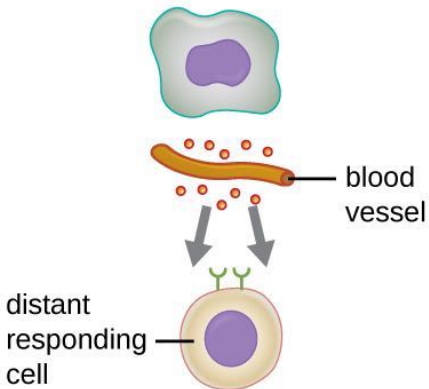


## LINKS BETWEEN THE INNATE AND ADAPTIVE IMMUNE SYSTEMS:

### Cytokines:

**Literally:** proteins made by cells that affect the behaviour of other cells. They act via specific cytokine receptors on the cells that they affect.

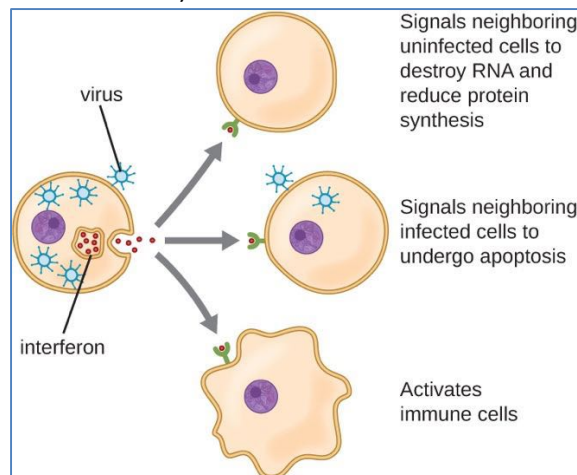
- **Regarding the Immune System:** The collective group of chemical messengers involved in the Adaptive Immune Response, released following the activation of Toll-Like Receptors (TLR's)→ Ie: Hormones that promote inflammation and attract WBC's to the site of infection, by stimulating Immune-Cell Development, Differentiation & Responses. **They include:**
  - **Interleukins:** ("Between Leukocytes") Group of over 35 cytokines first seen to be produced by Leukocytes (WBC's) and act on Leukocytes. However, it has since been found that Interleukins are also produced by a variety of other body cells, the majority of which from Helper-(CD4)-T-Lymphocytes, as well as monocytes, macrophages and endothelial cells. They Promote Development & Differentiation of T, B, & Haematopoietic Cells.
  - **Chemokines:** 4 Groups of Cytokines named by their ability to induce Chemotaxis (Migration) in nearby cells; hence they are **Chemotactic Cytokines**. Receptive cells detect the concentration of Chemokine, & then move up the concentration gradient to where the cell is required.
  - **Lymphokines:** Group of Cytokines named due to their production by Lymphocytes (Typically T-Cells). They attract other immune cells (Chemotaxis), like macrophages & other lymphocytes, to an infected site and prepare them to attack the invaders.
- **How do they Act on Cells?**
  - They induce cellular responses by binding with specific cytokine receptors.
  - They can act in an –
    - **Autocrine** manner (affecting the cell that released them – Eg: Chemokines),
    - a **Paracrine** manner (affecting the adjacent cells – Eg: Chemokines),
    - or, if stable enough, an **Endocrine** manner (affecting distant cells – Eg: Acute Phase Cytokines & Pyrogens.)
  - Note:the above depends on their ability to enter Circulation & also their Half-Life in blood.

CYTOKINES: Molecular Messengers		
Autocrine	Paracrine	Endocrine
Same cell secretes and receives cytokine signal.	Cytokine signal secreted to a nearby cell.	Cytokine signal secreted to circulatory system; travels to distant cells.
 <p>cytokines</p>	 <p>secreting cell</p> <p>receptor</p> <p>nearby responding cell</p>	 <p>blood vessel</p> <p>distant responding cell</p>

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- **Important Cytokines:**

- **IL-1, IL-6 & TNF<sub>α</sub>** –
  - Critical to the **Acute Phase Response** (or Synthesis of Acute Phase Proteins) Some **Acute Phase Proteins** mimic the action of Antibodies, but have broad specificity for PAMPs and depend only on the Cytokines for their production.
  - Mobilise Neutrophils from bone marrow.
  - Pyrogenic effects on the Hypothalamus
  - Stimulate Dendritic Cells to mobilise → Initiate Adaptive Response.
- **IL-8** – A Chemokine secreted by Monocytes, Macrophages & Injured Epithelium. Attracts Granulocytes, Monocytes (Macrophages) & CD8-(Cytotoxic)-T-Cells
- **IFN<sub>γ</sub> (Interferon-Gamma)** – the major cytokine-activator of Macrophages. (Produced by T-Helper cells, T-Cytotoxic Cells & NK-Cells).

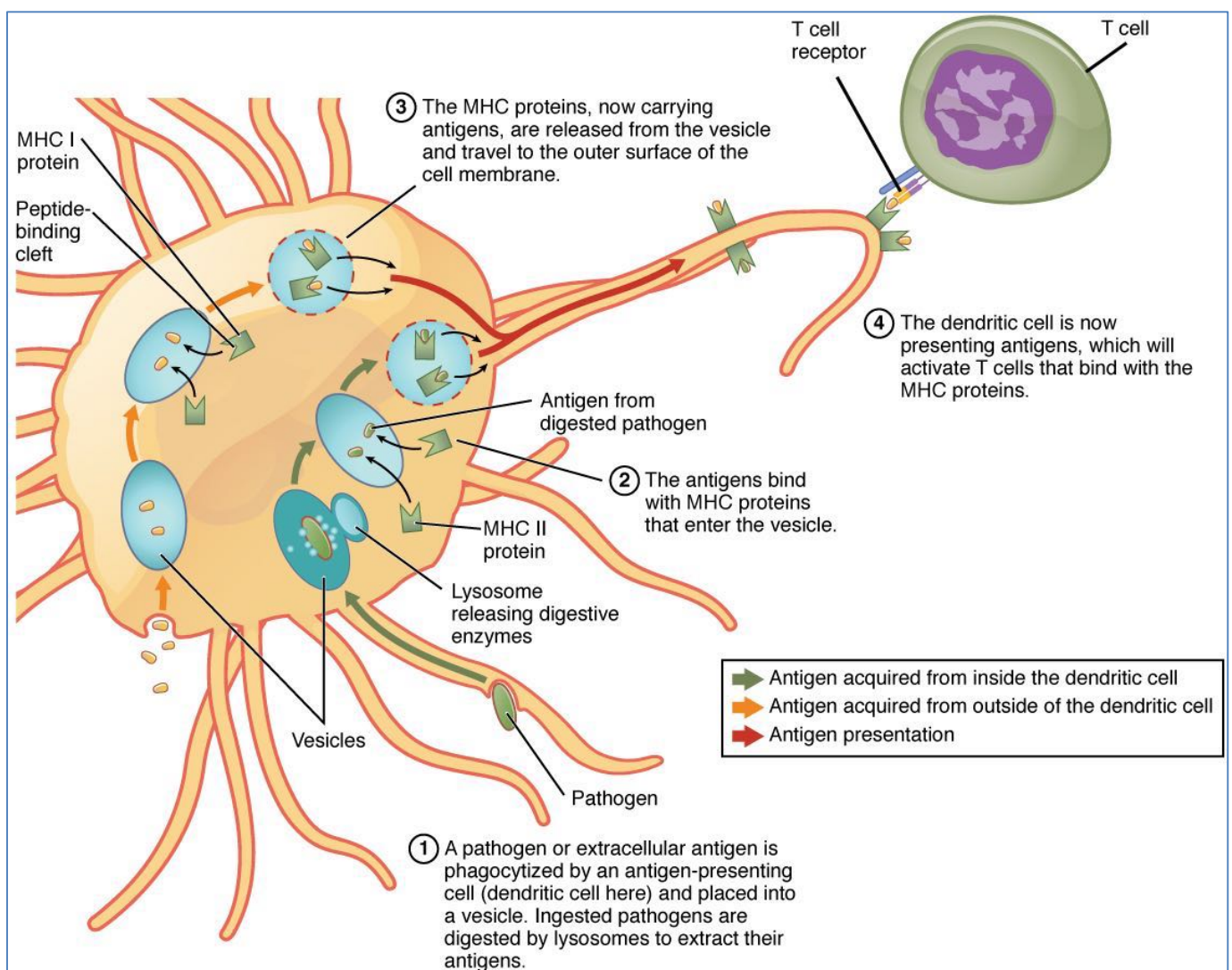


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Cytokine	Cell source	Target	Actions
<b>Proinflammatory Cytokines</b>			
IL-1	Macrophage Dendritic cell	Lymphocytes Endothelial cell CNS Liver	Enhances responses Activates Fever, sickness behavior Synthesis and release of acute-phase proteins
IL-6	Macrophage Dendritic cell Endothelium Th2 cell	Liver  B cell	Synthesis and release of acute-phase proteins  Proliferation
TNF-alpha	Macrophage Dendritic cell Th1 cell	Endothelial cell  Neutrophil Hypothalamus Liver	Activates vascular endothelium – increased permeability and stimulates adhesion molecules Activates Fever Synthesis and release of acute-phase proteins
<b>Anti-inflammatory Cytokines</b>			
IL-10	Macrophage Th2	Macrophage Dendritic cell	Inhibits IL-12 production Inhibits pro-inflammatory cytokine synthesis
IL-12	Macrophage Dendritic cell	CD4+T helper cell NK cell	Th1 differentiation IFN-gamma synthesis
<b>Cytokines Involved in the Acquired Immune Response</b>			
IL-2	T cell	T cell NK Cell B cell	Proliferation Activation and proliferation Proliferation
IL-4	Th2 cell Mast cell	T cell  B cell Macrophage	Th2 cell development/proliferation Isotype switch to IgE Inhibit IFN-gamma activation
IFN-gamma	Th1 cell Cytotoxic T cell NK cell	T cell B cell Macrophage	Th1 cell development Isotype switch to IgG Activation

**Antigen-Presenting Cells: (The link between the Innate & the Adaptive Immune Systems)** - Cells that engulf & process antigens, and then present fragments of them, like signal flags, on their own surfaces where they are recognised by T-Cells (Helper & Cytotoxic). Note: T-Cells are unable to independently recognise Antigens, & hence require Antigen Presentation). **Such APCs include:**

- **#1 Dendritic Cell:** The most efficient APC. Upon recognition of an infectious particle, it ingests & processes the antigen, and displays it on its cell surface, bound to either **MHC-I or MHC-II**. (Note: because Dendritic Cells present via MHC-I & -II, they can present antigens to **both Helper-T-Cells AND Cytotoxic-T-Cells**.) The Dendritic Cell then migrates to the nearest Lymph Node and activates 'Naive' T-Cells, which then leave the lymph nodes & travel to the site of infection.
- **Macrophages:** Part of the Innate Response. They possess various TLRs (Toll-like Receptors) that recognise patterns (PAMPs) on foreign organisms, which when activated, causes processing & presentation of the antigen via **MHC-II**, as well as **Cytokine Secretion**. **pMHC-II** then allows **T-helper-Cells** to bind to & further activate the Macrophage → More Phagocytic.
- **B-Lymphocytes:** The least efficient APC. Each recognises a specific antigen via its immunoglobulin-based surface receptors. Once ingested, the antigen is presented via **MHC-II** to **T-Helper-Cells**. The T-Helper Cell then *Activates the B-Cell* → Differentiates into a Plasma Cell → Secretes Antibodies.



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### ADAPTIVE (SPECIFIC) IMMUNE SYSTEM:

- Think of the Adaptive Immune System as "The body's elite special forces" – with high-tech weapons.

- **5 Characteristics:**

- **>It is Specific:** recognises *particular* pathogens/antigens
- **>It is Systemic:** immunity isn't restricted to initial infection site
- **>It has Memory:** mounts stronger attacks on previously encountered pathogens.
- **>Self-Limitation:** Immune response wanes off following elimination of antigens.
- **>Self-Tolerance:** Immune system non-reactive to self-antigens.

- **Roles:**

- Tremendously amplifies the inflammatory response.
- Attack specific foreign substances – Incl: Antigens and abnormal body cells
- mounts stronger attacks on previously encountered pathogens.

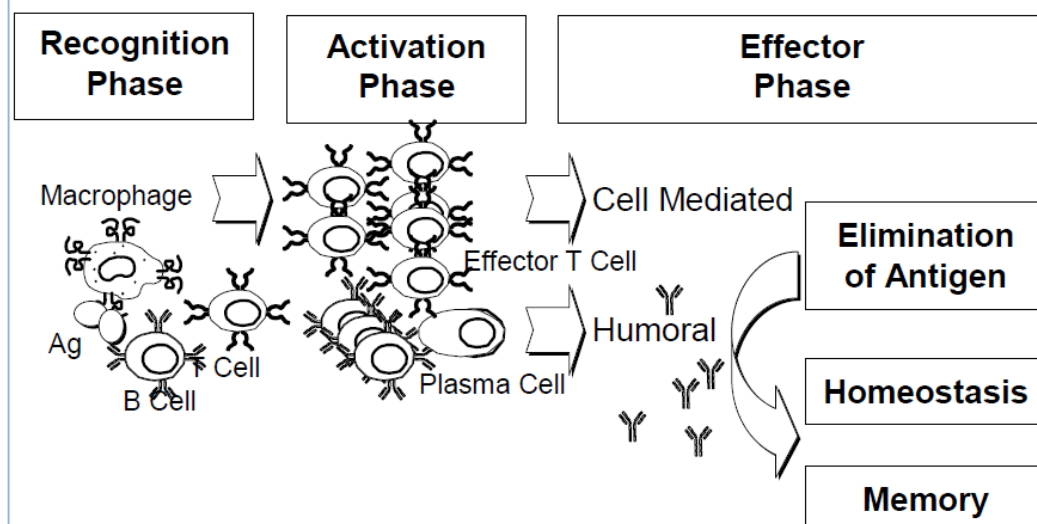
**May be either Humoral OR Cell-Mediated depending on the Microbe.**

Humoral Immunity	Cell-mediated Immunity
The immunity can be transferred from one individual to another via serum	The immunity can be transferred from one individual to another via effector cells
The immunity is due to the formation of antibodies	The immunity is due to the formation of activated cells
An important function of antibodies is to neutralise toxins and infectious organisms	An important function of the activated cells is to destroy infected or foreign cells

- **3 Phases:**

- **Recognition Phase:** TLRs & PRRs on **Macrophages & Dendritic Cells** recognise **PAMPs** on the **Antigens**, & engulf them via **Phagocytosis**. The Antigen is processed, and bits of it are displayed on their cell surfaces to be 'presented' to T-Lymphocytes. Activated Macrophages & damaged epithelia secrete pro-inflammatory cytokines to attract more immune cells.
- **Activation Phase:** Activated Dendritic Cells migrate to Lymph Nodes, where they activate Naive T-Cells, → Which activate Naive B-Cells → secrete Antibodies.
- **Effector Phase:** Active T-Cells, as well as the secreted Antibodies, leave the Lymph Node and head back to fight the infection via the Lymph→Blood.

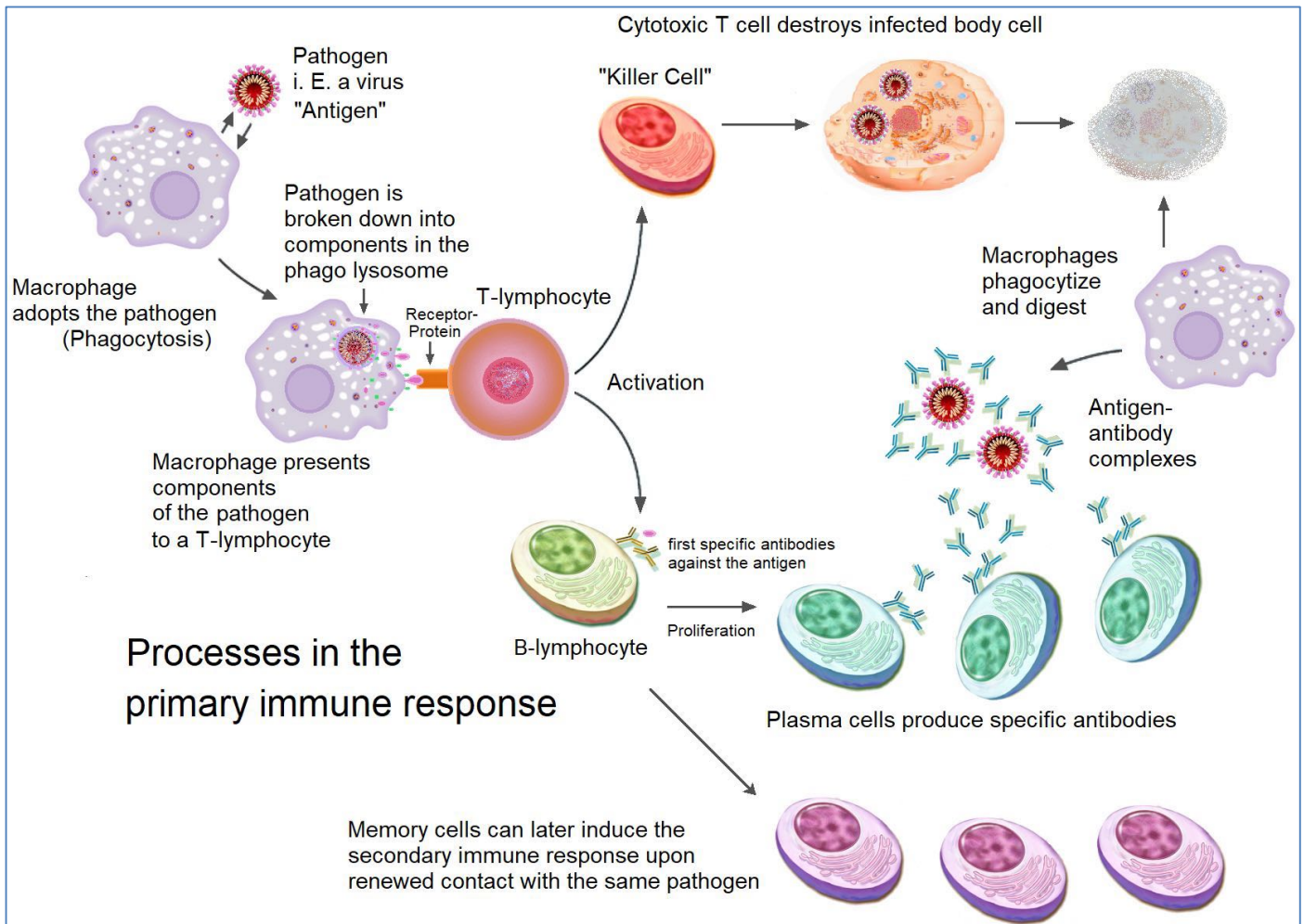
### **PHASES OF ADAPTIVE IMMUNE RESPONSES**



- **The body's 3<sup>rd</sup> line of defence (Humoral & Cellular Immunity):**

○ **a) CELLULAR IMMUNITY:**

- Antigen **causes activation** of macrophages, NK-cells, T-lymphocytes & cytokines
  - Macrophages & NK-Cells – destroy intracellular pathogens
  - **T Cells (T-Lymphocytes)** – induce apoptosis of body cells with viruses/intracellular bacteria/cancerous traits.
  - Cytokines are secreted – enhance inflammatory response and/or activate other lymphocytes/macrophages.
- Activated cells **destroy** infected/foreign cells.

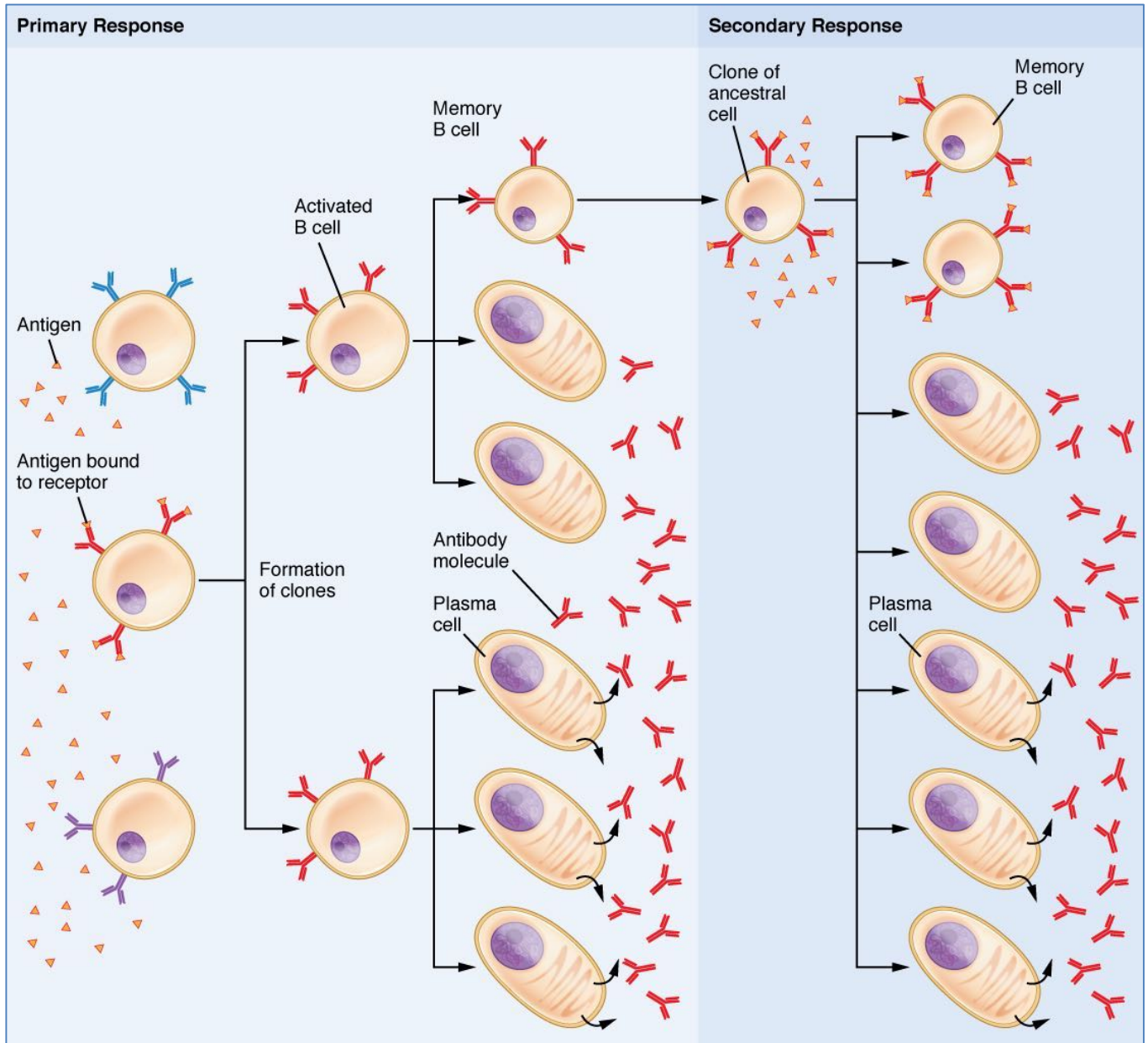


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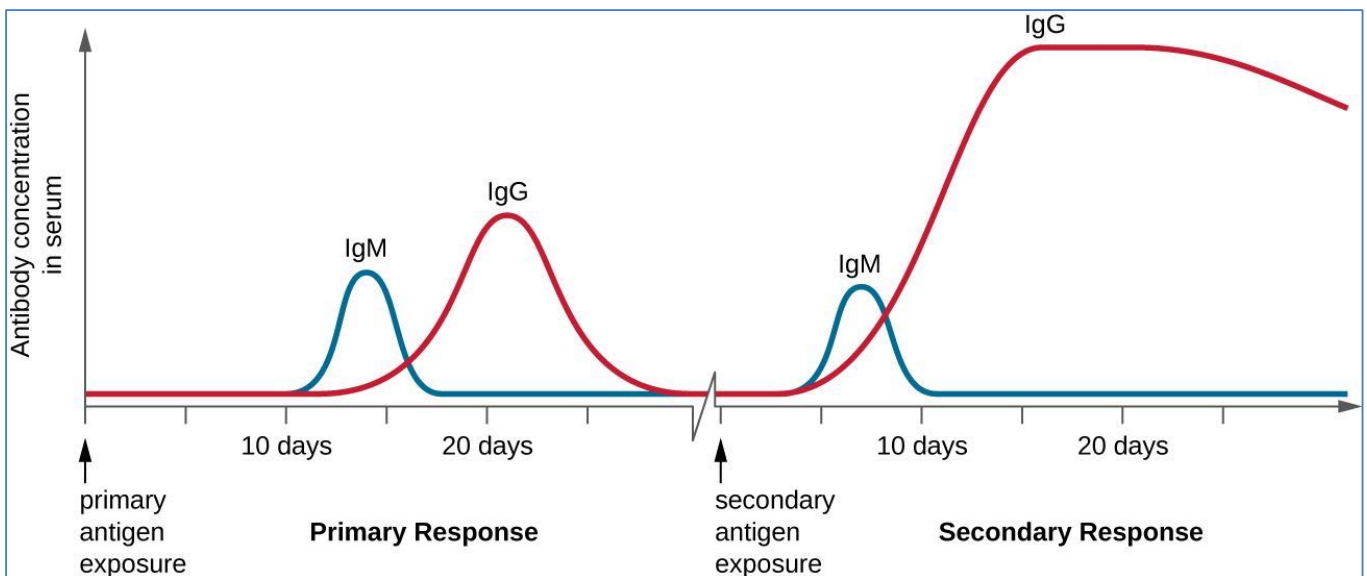
○ **b) HUMORAL IMMUNITY** (aka. Antibody-mediated immunity) -Immunity can be **transferred** from

person-person **via serum**

- **B Cells (B-Lymphocytes)**
  - **Make antibodies** against soluble antigens.
- **Antibodies (Immunoglobulins):**
  - Circulate freely in blood & lymph
  - **Neutralises** bacteria/toxins/& viruses →marks for destruction by phagocytes or compliment.



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**(Note: Once the body has Memory B-Cells from the first immune response, the immune reaction to the second exposure is much quicker and has a higher antibody yield. Is the primary mechanism behind vaccines)**

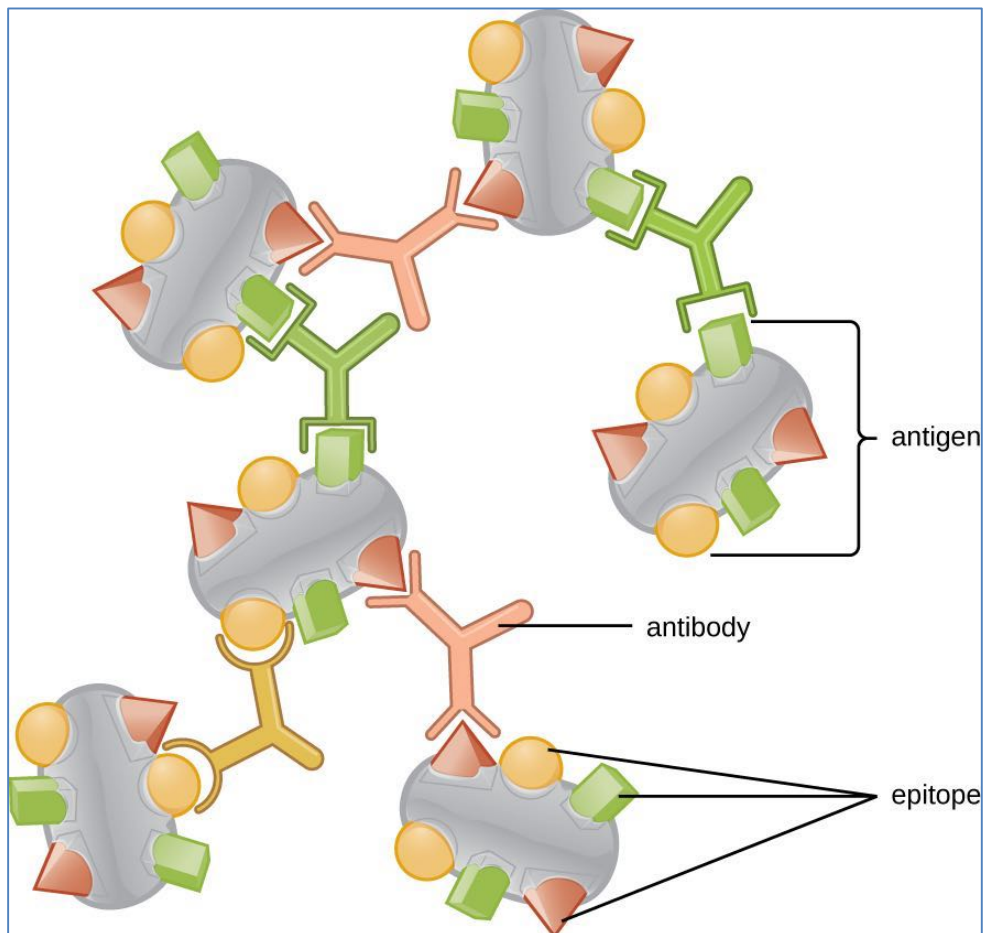
## **ANTIGENS & ANTIBODIES**



## ANTIGENS & ANTIBODIES

### Antigens:

- = Any molecule that can bind specifically to an Antibody (Incl: BCRs) OR T-Cell Receptor.
- Their name arises from their **Antibody-Generating** ability.
  - o However some antigens don't cause antibody production; i.e: Self-Antigens
  - o Antigens that DO induce antibody production are called **Immunogens**.
- **Antigenicity:** The degree to which an Antigen binds to Antibodies (Incl: BCRs) &/or TCRs.
  - o **Antigenicity Increases with:**
    - ↑Ag. Size
    - ↑Ag. Complexity
    - ↑Ag. Foreignness
    - ↑Route of Ag. Administration (→ dealt with by different 2° Lymphoid Organs)
    - ↑Ag. Dose
- **"Epitopes":** A single Antigen can have multiple *Sites* (or Epitopes) which are Immunogenic.

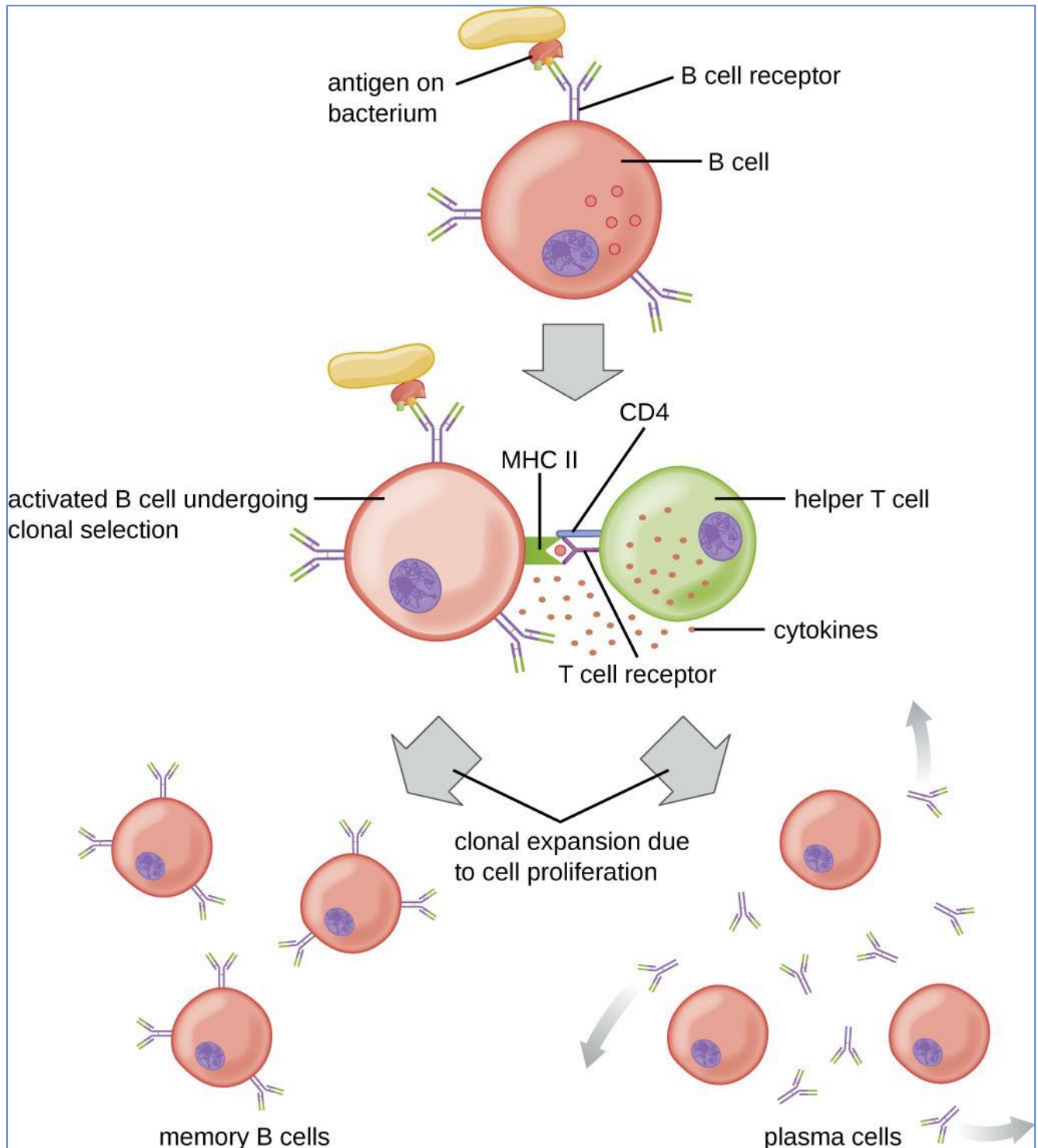


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- **"Thymus-Dependent Antigens":**

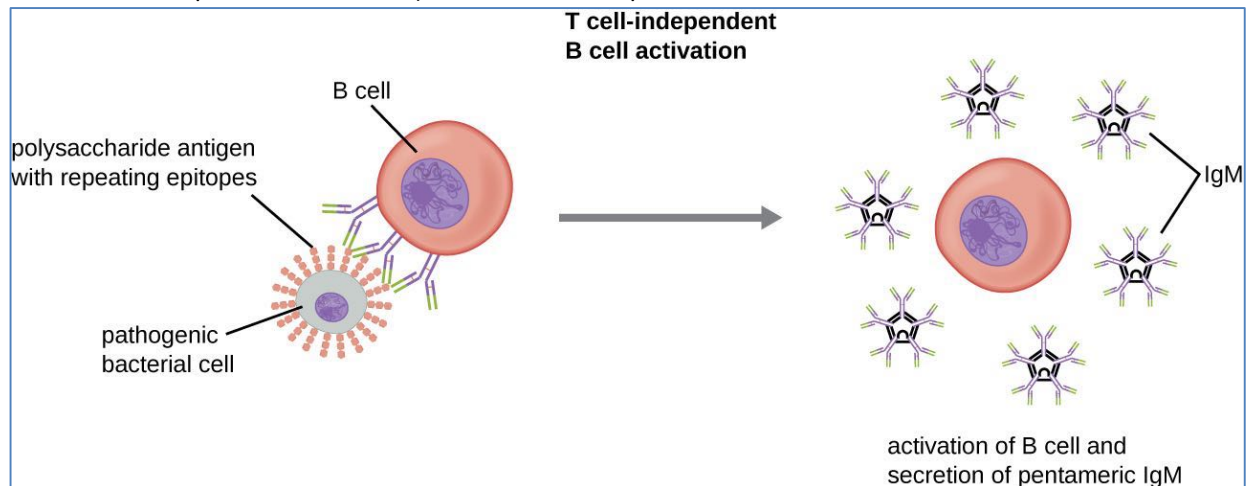
- Antigens recognised by **B-Cells** which require Ag-Specific CD4-Helper-T-Cell help in order to Activate the B-Cell → Plasma Cell → Secrete Antibodies.

In T cell-dependent activation of B cells, the B cell recognizes and internalizes an antigen and presents it to a helper T cell that is specific to the same antigen. The helper T cell interacts with the antigen presented by the B cell, which activates the T cell and stimulates the release of cytokines that then activate the B cell. Activation of the B cell triggers proliferation and differentiation into B cells and plasma cells.



- **"Thymus-Independent Antigens":**

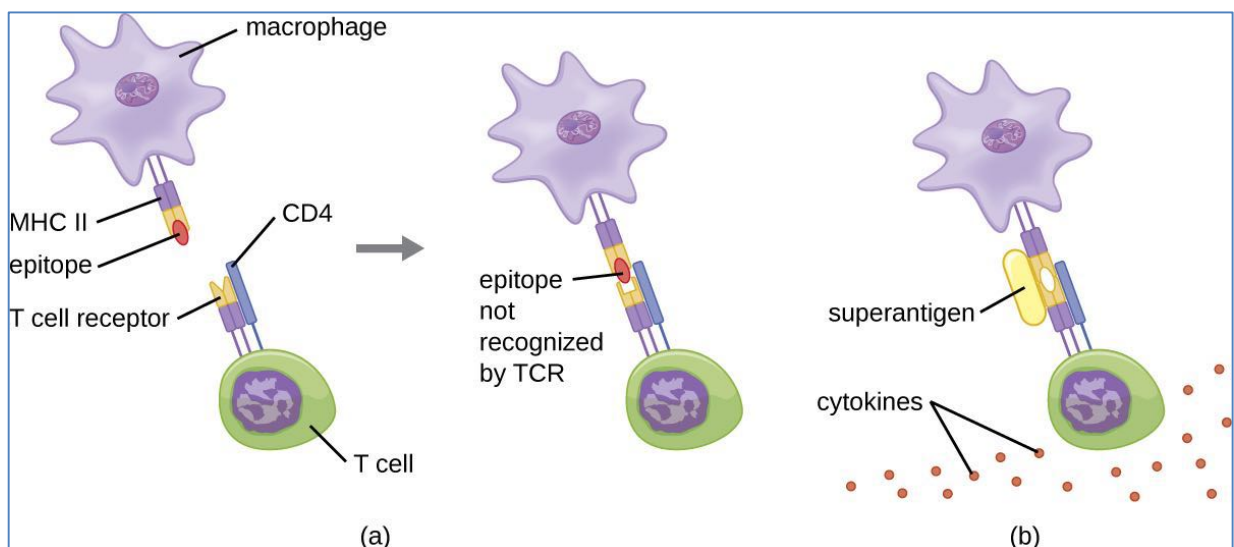
- Antigens recognised by **B-Cells** which, *by themselves*, are enough to cause B-Cell Activation (& subsequent Ab-secretion) *Without CD4-Helper-T-Cell Assistance*.



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- **"Superantigens":**

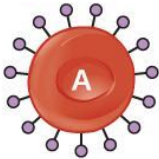

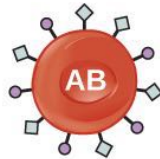
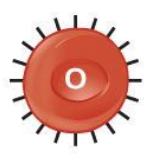






- Bacterial or Viral Antigens that *Non-Specifically* activate T-Cells *Without being Processed by APCs*.
- T-Cell responses are therefore *also Non-Specific* & hence are *Maladaptive* for host & helpful to pathogen. (See section on MHC for details)



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- **Common Antigens:**

- **Bacterial Antigens:**
  - (See Pathogen-Associated Molecular Patterns - PAMPs)
  - Flagellin
  - Capsule
  - Cell Wall
  - Bacterial Toxins (Endotoxins & Exotoxins)
- **Viral Antigens:**
  - (See Pathogen-Associated Molecular Patterns - PAMPs)
  - Capsid Proteins
  - Nucleoproteins
  - Envelope Glycoproteins
- **Self-Cell Surface Antigens:**
  - Red Blood Cell Antigens (A, B, Rhesus-D)
  - Major-Histocompatibility Complex Antigens (MHC-I & -II)
  - Clusters of Differentiation (CD) – Cell surface antigens. (Eg: CD40/CD28 etc)

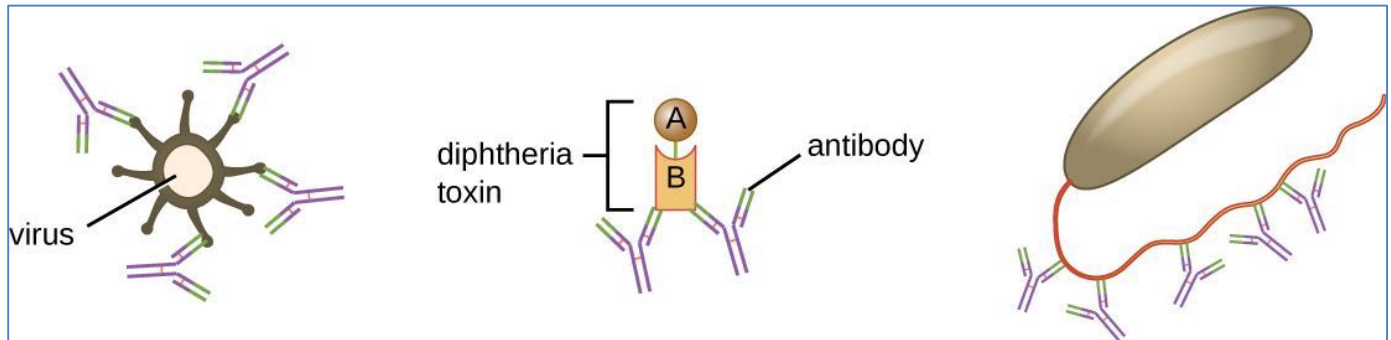
	Blood Type			
	A	B	AB	O
Red blood cell type				
Isohemagglutinins	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens on red blood cell	 A antigen	 B antigen	 A and B antigens	None

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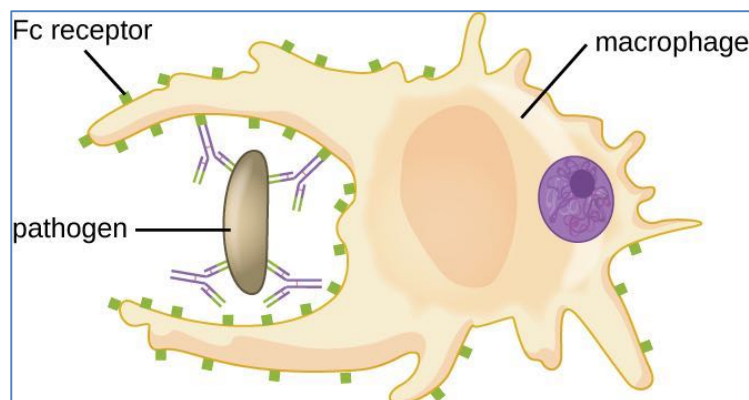
### **Antibody:**

- = Class of proteins called Immunoglobulins that Directly Bind to Specific Antigen.
- They are produced by Plasma Cells (Activated B-Cells) in response to infection/immunisation.
- **4 Functions:** They bind specifically to their corresponding antigens, leading to:
  - **1- Neutralisation** of Pathogens/Toxins → Phagocytosed.



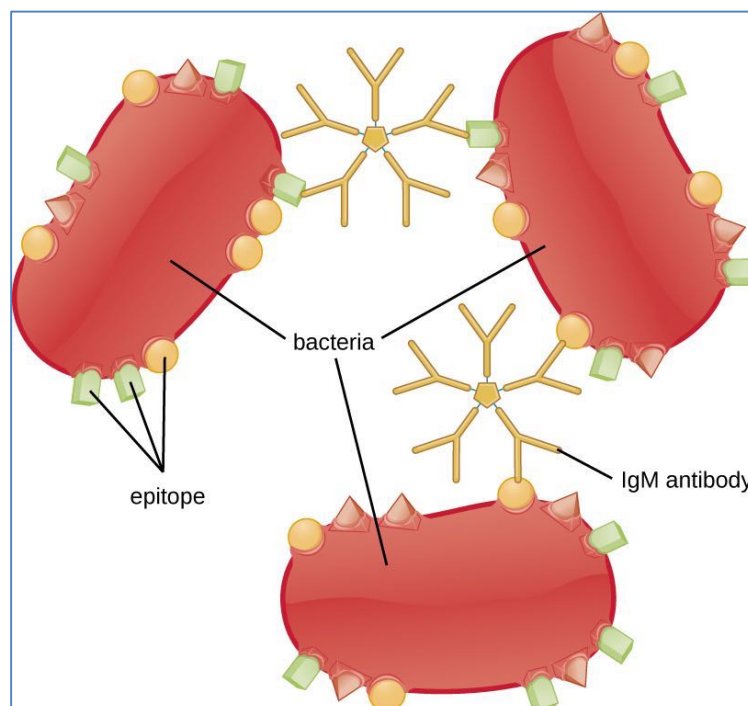
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- **2- Opsonisation** of Pathogen → Marks them for destruction by Phagocytes.



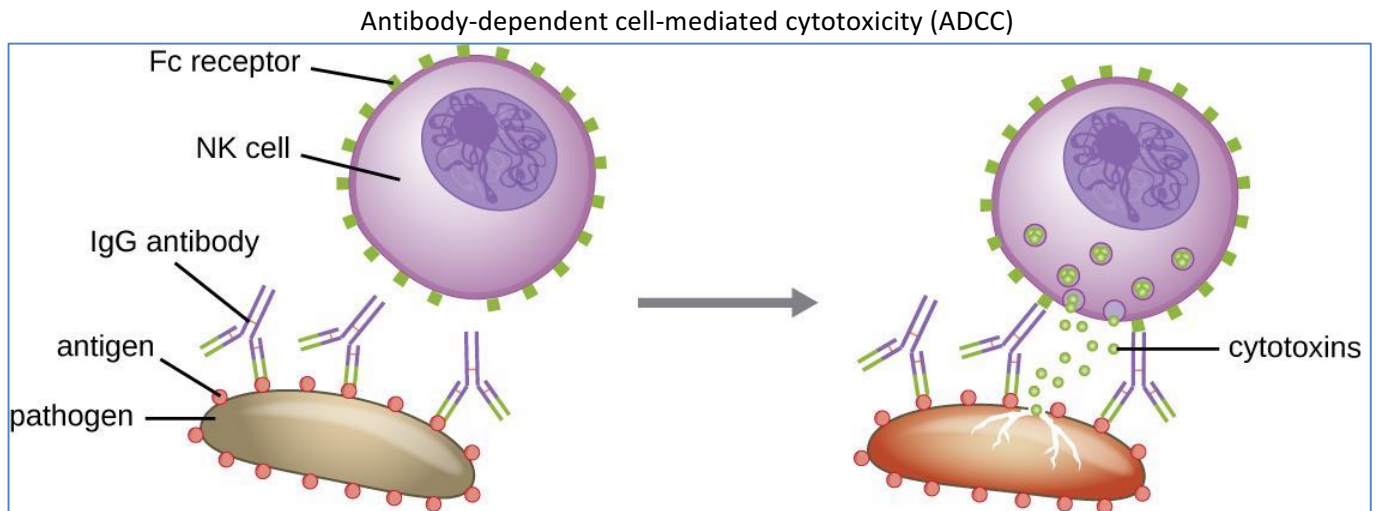
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- **3- Activation of Complement** → Lysis of Extracellular Bacteria → Phagocytosed.
- **4- Agglutination** by binding to epitopes of two or more bacteria simultaneously → Forms aggregates of inactivated crosslinked bacteria.



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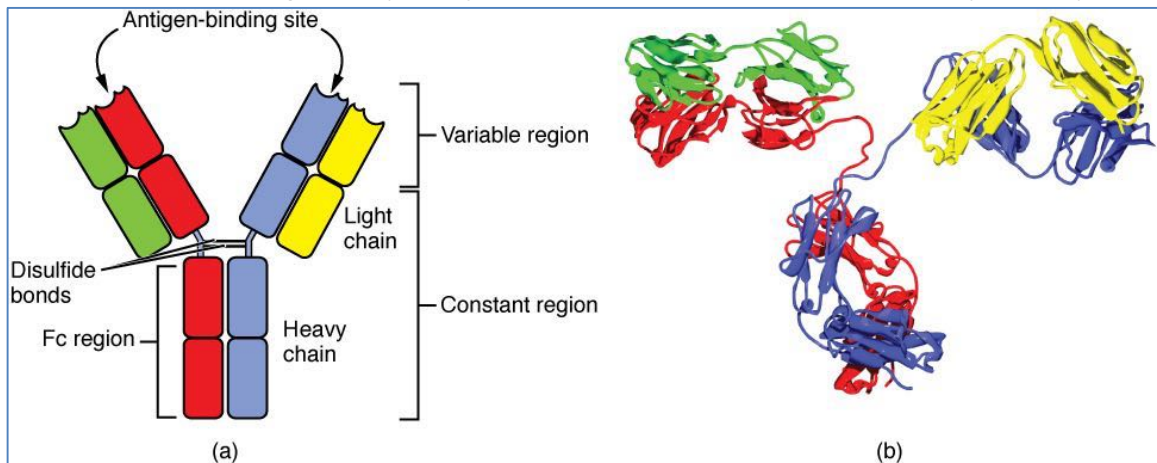
- **5- Ab-Dependent Cellular Cytotoxicity (ADCC)** → Lysis of a Target Cell that has been bound by Specific Antibodies:
  - **Eg: NK-Cells** → Lysis of a Pathogen-Infected Cell.
  - **Eg: Eosinophils (Via IgE)** → Kills Parasites that are too big for phagocytosis.



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- **Where Are They Found?**
  - On their own (in plasma)
  - As Antigen-Receptors on B-Cells (BCRs).
- **Structure:**
  - **Y-Shaped molecule:**
    - Arms = Antigen Binding Sites
    - Tail = Constant Region
  - **2x Heavy (Long) Chains & 2x Light (Short) Chains:**
    - Each chain has a **Constant Region** & a **Variable Region**.
    - **Constant Region:**
      - Interacts with Effector Cells, Fc-Receptors (On NK-Cells; in ADCC – Antigen-dependent cellular toxicity) & Complement.
      - Constant Regions of BCRs & TCRs are involved in Signal Transduction into B/T-Cell.
    - **Variable Region:**
      - Binds to the Ag
      - Highly Variable
  - **Antigen Binding Sites** (Same for BCRs):
    - = the Variable Regions of partnered Heavy & Light Chains ( $V_H$  &  $V_L$ ).
    - Within these Variable Regions are Ag-Specific **Complementarity-Determining Regions (CDRs)**.
      - These CDRs allow binding of **Intact Antigen** by adhering to epitopes on the outside of folded antigenic proteins. (See diagram)
    - **Note: Typically, Ag's bind to Ab's via Non-Covalent Forces**, rather than chemically binding:
      - Ie: Electrostatic Forces,
      - Hydrogen Bonding,
      - Van-der-Waal's Forces,
      - Hydrophobic Forces.
  - **Nomenclature:**
    - $F_{ab}$  = Antigen Binding Site
    - $F_c$  = Constant Region
    - $V_H$  = Variable Region of a Heavy Chain
    - $V_L$  = Variable Region of a Light Chain
    - $C_H$  = Constant Region of a Heavy Chain
    - $C_L$  = Constant Region of a Light Chain
    - CDR = Complementarity Determining Region

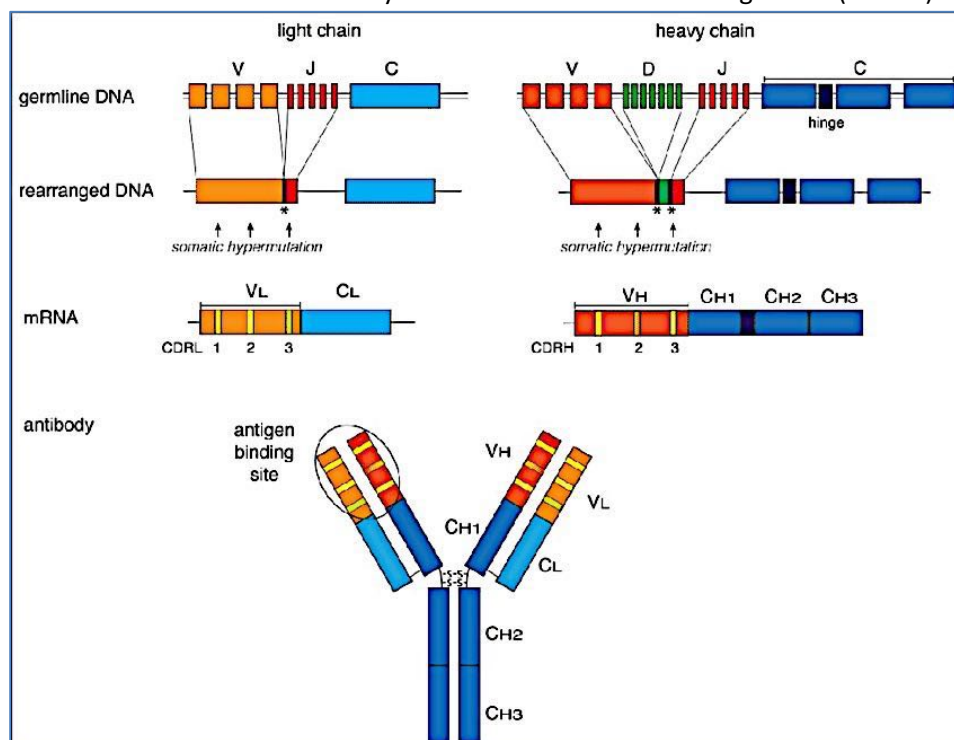
- **Hinge Region:**
  - Formed by the Heavy Chains
  - Allows flexible binding of Antigen & Enables Cross-Linking between Multiple Ab's & Ag's.
  - Is Held together by **Disulphide Bonds** – Hence can be dissociated by Proteolytic Cleavage.



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## - Generating Diversity of Antibody-Repertoire:

- **Why is it important?**
  - Since Antibodies & Ab-based receptors (in this case BCRs & also the  $F_{ab}$  on TCRs) are the only *Activators & Effectors* of the Adaptive Immune System, they have to be able to *Evolue* to keep up with *Evolving Pathogens*.
- **How does it happen?**
  - **Primary Diversification Mechanisms (During B/T-Cell Maturation In 1<sup>o</sup> Lymphoid Organs):**
    - **Ig-Gene Rearrangement (B-Cells):**
      - **1- Heavy Chain Rearrangement:**
        - Random selection of 1xGene from Each of the **V, D & J**–Gene Loci, Then Recombination of these to make a functional gene.
      - **2- Light Chain Rearrangement:**
        - Random selection of 1xGene from Each of the **V & J**–Gene Loci, Then Recombination of these to make a functional gene.
      - Note: Very similar to TCR-Gene Rearrangement (T-Cells).

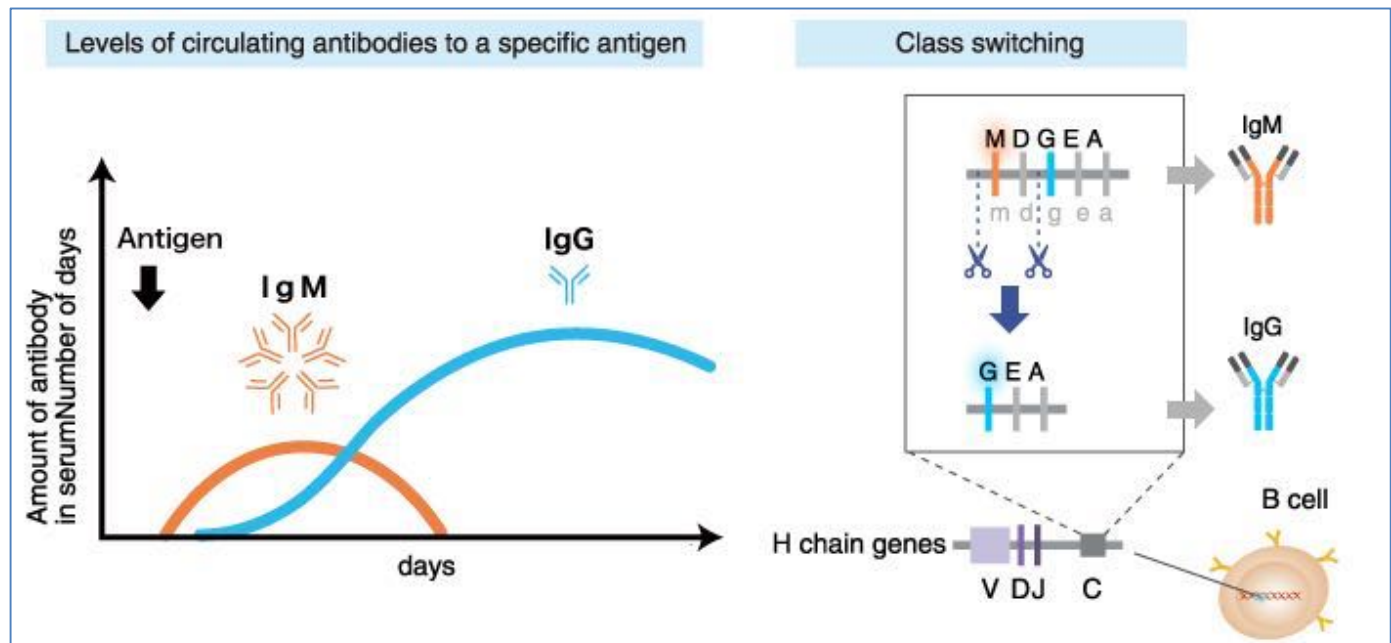


Antibodies specific for nucleic acid modifications: [https://www.researchgate.net/figure/Schematic-overview-of-the-organization-and-expression-of-immunoglobulin-Ig-genes\\_fig1\\_315756763](https://www.researchgate.net/figure/Schematic-overview-of-the-organization-and-expression-of-immunoglobulin-Ig-genes_fig1_315756763)

- **Secondary Diversification Mechanisms [B-Cells Only] (In 2° Lymphoid Organs):**
  - **Somatic Hypermutation:**
    - Occurs in Activated B-Cells in Germinal Centres.
    - – Single Amino-Acid Mutations are introduced into Variable-Region-Genes.
    - Result = Activated B-Cells with Increased *AND* Decreased Ag-Affinity.
    - **New Ag-Receptors (BCRs) are tested for Increased Affinity:**
      - Cells with Receptor Mutations that Decrease Ag-Affinity → Die:
      - Cells with Receptor Mutations that Increase Ag-Affinity → Survive.
    - →→Proliferation of High-Affinity B-Cells.
    - →→↑Ab Affinity
  - **Isotype Switching:**
    - Occurs in Activated B-Cells in Germinal Centres.
    - – F<sub>C</sub> Region-Genes of IgM are Replaced with F<sub>C</sub> Region-Genes for IgG/IgA/IgE.
    - **Requires T<sub>H1/2</sub>-Cell Help:**
      - **Note:** Cytokines from CD4-T<sub>H</sub>-Cells determine which Ab-Class is made.
      - **Note:** It is triggered at the time of B-Cell Activation & hence also Requires CD40<sub>(B-Cell)</sub>:CD40L<sub>(T-Cell)</sub> Interaction
    - This change in Ab Constant-Regions → Change in Ab Effector Function.
    - See Below For Details:

- **'Isotype Switching':**

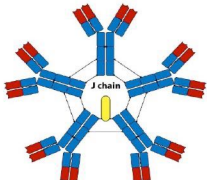
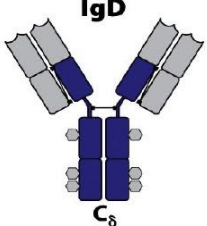
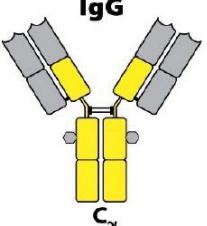
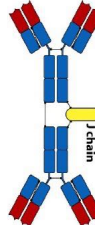
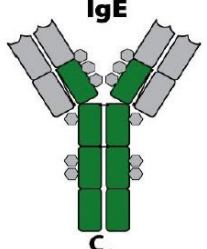
- **IgM & IgD are the *Default Abs*** Expressed on Naive B-Cells (as BCRs)
- **IgM** is the 1<sup>st</sup> Ab-Isotype to be secreted by B-Cells (Plasma Cells)
- However, IgM has limited versatility & therefore the body requires different Isotypes of that same Antibody for different effector functions.
- **Activated B-Cells (Plasma Cells) Undergo Class-Switching → Secrete:**
  - **IgG<sub>1/2/3/4</sub>**
  - **IgA**
  - **IgE**
- **Trigger – Isotype Switching Requires CD4-T-Cell Help:**
  - Activated (Ag-Specific) CD4-Helper-T-Cells, (Pre-differentiated due to Ag-Presentation), Recognise & Bind to Ag:MHC-II Complexes on Activated B-Cells → Secrete **Cytokines**:
  - **Note:**T<sub>H</sub>-Cell Binding Requires CD40<sub>(B-Cell)</sub>:CD40L<sub>(T-Cell)</sub> Interaction
    - **If the Ag was a *Thymus Dependent Antigen* →**
      - T<sub>H</sub>-Cell → Activates the B-Cell → Differentiate/Proliferate → Plasma Cells → Secrete Antibodies (Ab Isotypes depend on Cytokine Combination).
    - **If the Ag was a *Thymus Independent Antigen* →**
      - B-Cell is already activated; **T-Cell Cytokines cause B-Cell to → Isotype Switching** from the IgM (default) to other classes. (IgG/IgA/IgE)
  - **Note:** Cytokines from CD4-T<sub>H</sub>-Cells determine which Ab-Class is made.
  - **Note:**Ab Specificity doesn't change.
- **Mechanism Behind Isotype Switching:**
  - Genes encoding the *Constant Regions* of the IgM *Heavy Chains* undergo Recombination → Replaced with Heavy-Chain Constant-Region Genes for IgG/IgA/IgE.
  - This change in Ab Constant-Regions → Change in Functional Specialisation of the Ab.



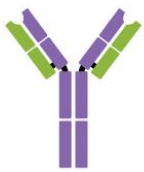

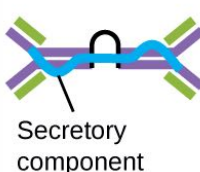
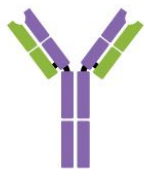
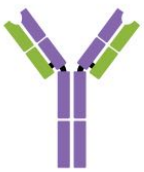
Source: <https://ruo.mbl.co.jp/bio/e/support/method/antibody-isotype.html>



- The 5 Isotypes:

Isotype	Functional Specialisation	Morphology	Picture
IgM	<b>- 1<sup>st</sup> Ab Produced</b> in a Primary Humoral Response. - Neutralisation - Opsonisation of Bacteria - Activates Complement Cascade <b>- Act as B-Cell Ag-Receptors (BCRs).</b> - (Serum $T_{1/2}$ = 10 Days)	- Pentamer (5 Monomers) (Massive Molecule → Relatively Cumbersome) - (Note: Monomeric on B-Cells)	
IgD	<b>- Act as B-Cell Ag-Receptors (BCRs).</b> - (Serum $T_{1/2}$ = 3 Days)	- Monomer	
IgG	<b>- The Major Serum Ab-Isotype.</b> <b>- The 2<sup>nd</sup> Ab produced</b> in Humoral Response. <b>- Responsible for most Ab Reactions.</b> - Neutralisation <b>- #1 - Opsonisation of Bacteria</b> - Activates Complement Cascade <b>- The ONLY Isotype in PLACENTAL TRANSFER.</b> <b>- Also DIFFUSES into EXTRAVASCULAR SITES.</b> - 4 Sub-Classes (IgG1, IgG2, IgG3, IgG4) - (Serum $T_{1/2}$ = 7-21 Days; depending on Sub-Classes)	- Monomer	
IgA	<b>- The Major Ab in Mucosal Immunity (Secretions)</b> - Saliva - Tears - GIT - Bile - Colostrum/Breast Milk - Respiratory Tract - Urinary Tract <b>Functions:</b> - Neutralisation - Opsonisation of Bacteria <b>- Transported Across Epithelium</b> <b>- Also DIFFUSES into EXTRAVASCULAR SITES.</b> - Very Little Found in Plasma. - ( $T_{1/2}$ = 6 Days)	- Dimer (In Secretions) - Monomer OR Dimer (In Serum)	
IgE	<b>- Major Ab in Allergic Reactions &amp; Inflammation.</b> <b>- Major Ab in Parasitic Infection.</b> - Very Little Found in Plasma. - F <sub>C</sub> -Region binds to Mast Cells → Allergy: - Histamine Release - Serotonin Release - Other Vasoactive Amines - (Serum $T_{1/2}$ = 2 Days)	- Monomer	

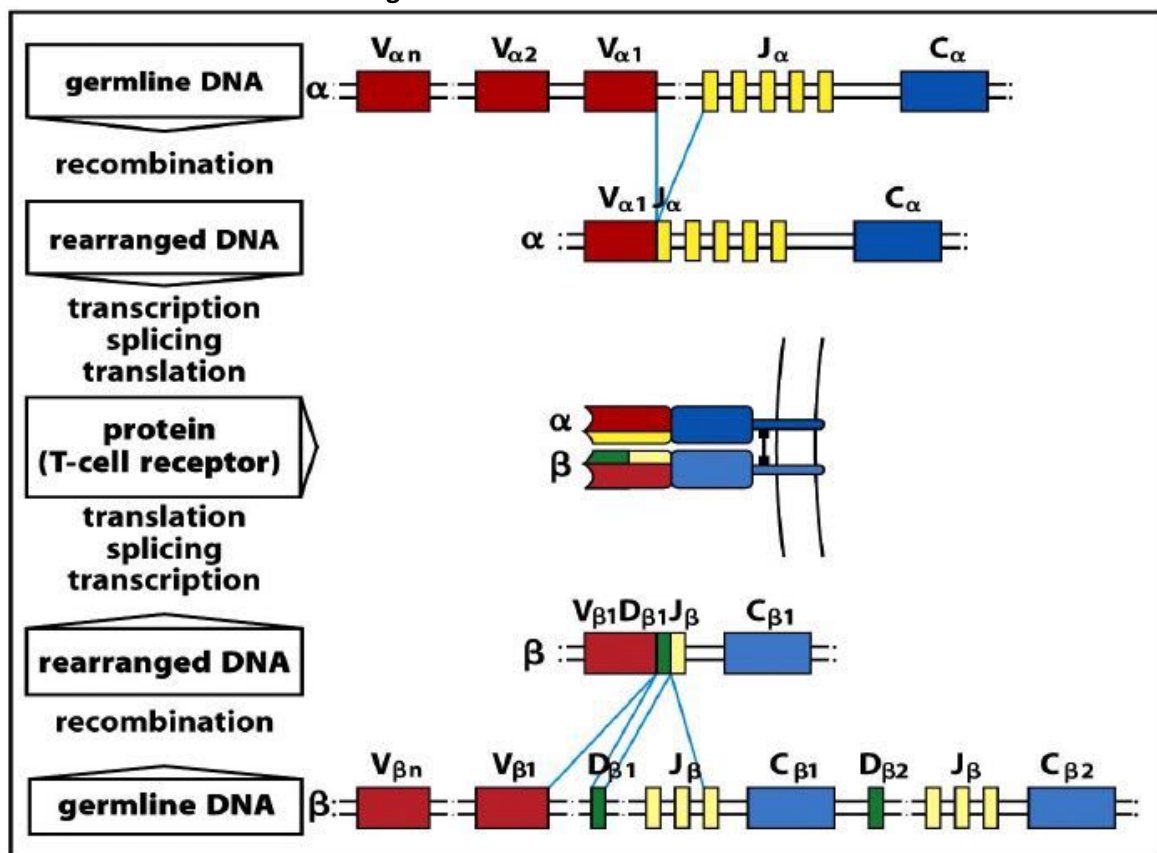
**Note:** IgM & IgE both have 1x Extra Constant Domain (3 instead of 2)

The Five Immunoglobulin (Ig) Classes					
Properties	IgG monomer	IgM pentamer	Secretory IgA dimer	IgD monomer	IgE monomer
Structure					
Heavy chains	$\gamma$	$\mu$	$\alpha$	$\delta$	$\epsilon$
Number of antigen-binding sites	2	10	4	2	2
Molecular weight (Daltons)	150,000	900,000	385,000	180,000	200,000
Percentage of total antibody in serum	80%	6%	13% (monomer)	<1%	<1%
Crosses placenta	yes	no	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to	phagocytes				mast cells and basophils
Function	Neutralization, agglutination, complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity.	Neutralization, agglutination, and complement activation. The monomer form serves as the B-cell receptor.	Neutralization and trapping of pathogens in mucus.	B-cell receptor.	Activation of basophils and mast cells against parasites and allergens.

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### Antigen Receptors (on B & T-Lymphocytes):

- Lymphocytes become *Immunocompetent* BEFORE meeting their antigens. (I.e: They are equipped with their specific Antigen-Receptors before leaving the Primary Lymphoid Organs – Thymus/Bone-Marrow)
- **Hence, Antigen Receptors on Lymphocytes are pre-determined by Genetics, not antigens.**
  - o The Presence of an Antigen just determines which existing T- or B-Cells will proliferate in Periphery.  
(Note:TCRs = T-Cell<sub>Antigen</sub> Receptors; BCRs = B-Cell<sub>Antigen</sub> Receptors)
- **Function:**
  - o To sense presence of Antigens in the Environment.
- **Ag-Receptor Specificity:**
  - o Ag-Receptors only respond to their Specific Antigen.
  - o Ag-Specificity is determined by the Amino-Acid Sequence at the Ag-Binding Site.
- **Generation of Ag-Receptor Diversity:**
  - o Enormous Diversity of Receptors is needed for a Huge Range of Constantly-Evolving Antigens.
  - o During B- & T-Cell Development; (In 1<sup>o</sup> Lymphoid Organs – BM & Thymus):
    - **Ag-Receptor Gene Rearrangement (Ig-Gene (B-Cells); TCR-Gene (T-Cells)):**
      - **1<sup>st</sup>: Heavy Chain Rearrangement:**
        - o Random selection of 1xGene from Each of the V, D & J –Gene Loci, Then Recombination of these to make a functional gene.
        - o Note: this is the  $\beta$ -Chain in TCRs.
      - **2<sup>nd</sup>: Light Chain Rearrangement:**
        - o Random selection of 1xGene from Each of the V & J –Gene Loci, Then Recombination of these to make a functional gene.
        - o Note: this is the  $\alpha$ -Chain in TCRs.
      - (Note: Important Enzymes Involved in both B/T-Cell Receptor Gene Rearrangement)
        - o RAG-1 Recombinase
        - o RAG-2 Recombinase
        - o Ligases

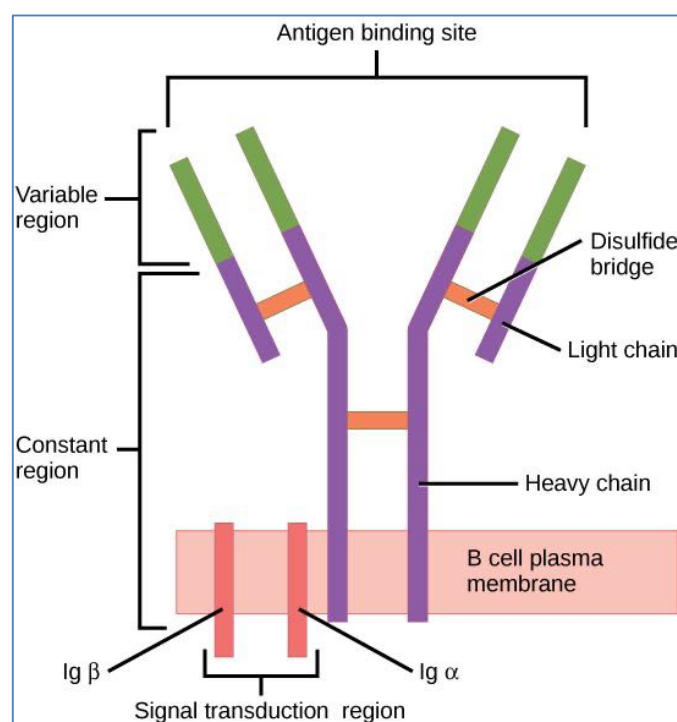


Source: Unattributable

- **In B-Cells ONLY (In Periphery - Following B-Cell Activation):**
  - (I.e: T-Cells don't change after Ag-Binding, but B-Cells do)
  - In addition to Ag-Receptor Gene Rearrangement, B-Cells also undergo the following:
    - **Somatic Hypermutation (AKA: Affinity Maturation):**
      - – Single Amino-Acid Mutations are introduced into  $V_{(Variable)}$ -Region-Genes.
      - Result = Activated B-Cells with  $\uparrow$  &  $\downarrow$  Ag-Affinity.
      - **New Ag-Receptors (BCRs) are tested for Increased Affinity:**
        - Cells with Receptor Mutations that  $\downarrow$  Ag-Affinity  $\rightarrow$  Die:
        - Cells with Receptor Mutations that  $\uparrow$  Ag-Affinity  $\rightarrow$  Survive.
      - $\rightarrow \rightarrow$  Proliferation of *High-Affinity* B-Cells.
    - **Ig-Class Switching:**
      - –  $F_C$  Region-Genes of IgM are Replaced with  $F_C$  Region-Genes for IgG/IgA/IgE.
      - **Requires  $T_{H1/2}$ -Cell Help:**
        - **Note:** Cytokines from CD4- $T_H$ -Cells determine which Ab-Class is made.
        - **Note:** It is triggered at the time of B-Cell Activation & hence also Requires  $CD40_{(B-Cell)}:CD40L_{(T-Cell)}$  Interaction. (Note:CD128=CD40L)
      - $\rightarrow \rightarrow$  This change in Ab Constant-Regions  $\rightarrow$  Change in Ab Effector Function.
      - **Note:** This doesn't affect Ab-Affinity.
      - See '*Isotype Switching*' in the Antibody section For Details.



- **BCRs (B-Cell Receptors):**
  - **Morphology:**
    - **BCRs are Surface-Bound Antibodies** (Either IgM<sub>(Monomeric)</sub> or IgG):
      - **Immunoglobulin-Like-Structure:**
        - Have a Pair of **Heavy Chains** & a Pair of **Light Chains**
        - Each chain has a **Variable** and **Constant** region.
      - **BCR Isotypes:**
        - Naive B-Cells express IgM & IgD –Type BCRs.
  - **Functional Regions:**
    - **Variable Region (F<sub>ab</sub>):**
      - BCRs (like Antibodies) Bind **Whole Antigen Directly**. (As opposed to TCRs which only recognise processed peptide presented on MHCs).
    - **Constant Region (F<sub>c</sub>):**
      - Signal Transduction once bound to Ag.
      - Internalisation of Ag for Processing & Presentation on MHC-II.
  - **Antigen Binding Sites** (Same for Abs):
    - = the Variable Regions of partnered Heavy & Light Chains (V<sub>H</sub> & V<sub>L</sub>).
    - Within these Variable Regions are Ag-Specific **Complementarity-Determining Regions (CDRs)**.
      - These CDRs allow **binding of Intact Antigen** by adhering to epitopes on the outside of folded antigenic proteins. (See diagram)
    - **Note: Typically, Ag's bind to Ab's via Non-Covalent Forces**, rather than chemically binding:
      - Ie: Electrostatic Forces,
      - Hydrogen Bonding,
      - Van-der-Waal's Forces,
      - Hydrophobic Forces.
  - **Generation of Ag-Receptor Diversity:**
    - **(In 1<sup>o</sup>-Lymphoid Organ - Bone Marrow)**
      - Antigen-Receptor Gene Rearrangement
    - **(In 2<sup>o</sup>-Lymphoid Organs – Lymph Nodes/Spleen)**
      - Somatic Hypermutation
      - Ig-Isotype Switching



- **TCRs (T-Cell Receptors):**

○ **Morphology:**

- Are Membrane-Bound **Heterodimer** Receptors that **Resemble Antigen Binding Sites on Abs:**
- **Heterodimer** = Has a Pair of Chains (**Either  $\alpha$ - $\beta$  or  $\gamma$ - $\delta$** ) depending on T-Cell Lineage.
  - \*  **$\alpha$  $\beta$  T-Cells Predominate** → CD4 (helper & regulatory) or CD8 T-Cells.
  - **$\gamma$  $\delta$  T-Cells = Minority** → Mimic cells of the Innate Immune System → Reside in Lymphoid & Epithelial Tissues (Eg: Skin/Repro-Tract/GIT), & Recognise Whole Antigen (as opposed to  $\alpha$  $\beta$  T-Cells; - Recognise only Peptide:MHC complexes).
  - Each chain has a **Variable (V)** and **Constant (C)** region
    - V & C Regions are Coded for by Separate Genes.

○ **Functional Regions:**

▪ **Variable Region ( $F_{ab}$ ):**

- **TCRs ONLY RECOGNISE Processed Peptide Complexed to MHC**
  - (on APCs, Semi-Activated Macrophages & Semi-Activated B-Cells).
- Resembles Ag-Binding Site of Antibodies.

▪ **Constant Region ( $F_c$ ):**

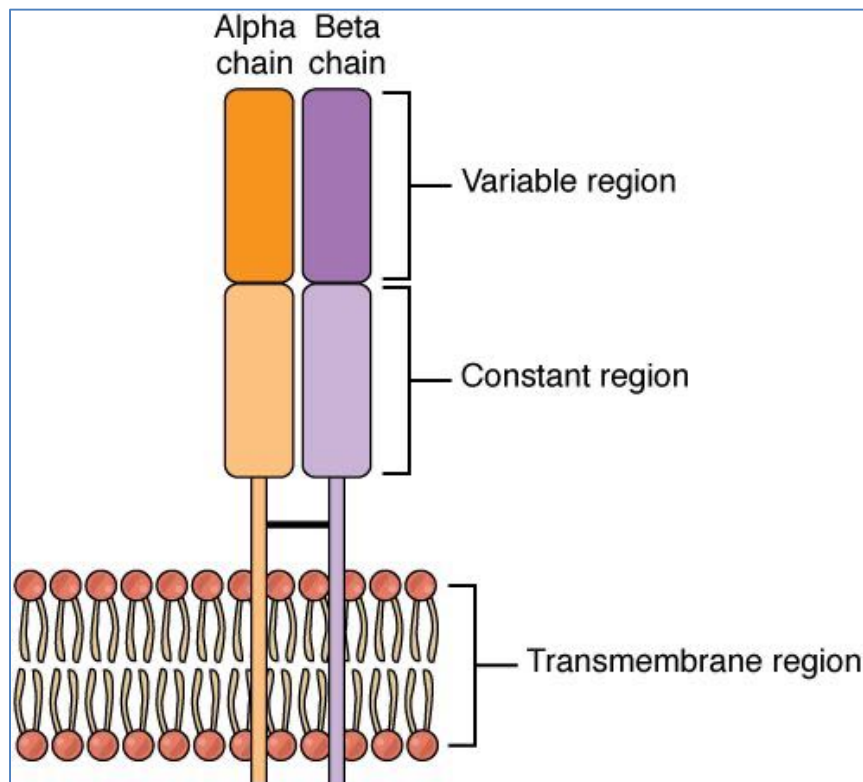
- Signal Transduction once bound to Ag.

○ **Antigen Binding Sites (Same for Abs):**

- = the Variable Regions of partnered  $\alpha$  $\beta$ - or  $\gamma$  $\delta$ -Chains
  - **$\alpha$  $\beta$ -Chains → Recognise Processed Peptide on MHC-I/II.**
  - **$\gamma$  $\delta$ -Chains → Recognise Whole Antigen** (Similar to cells of Innate Immune System)

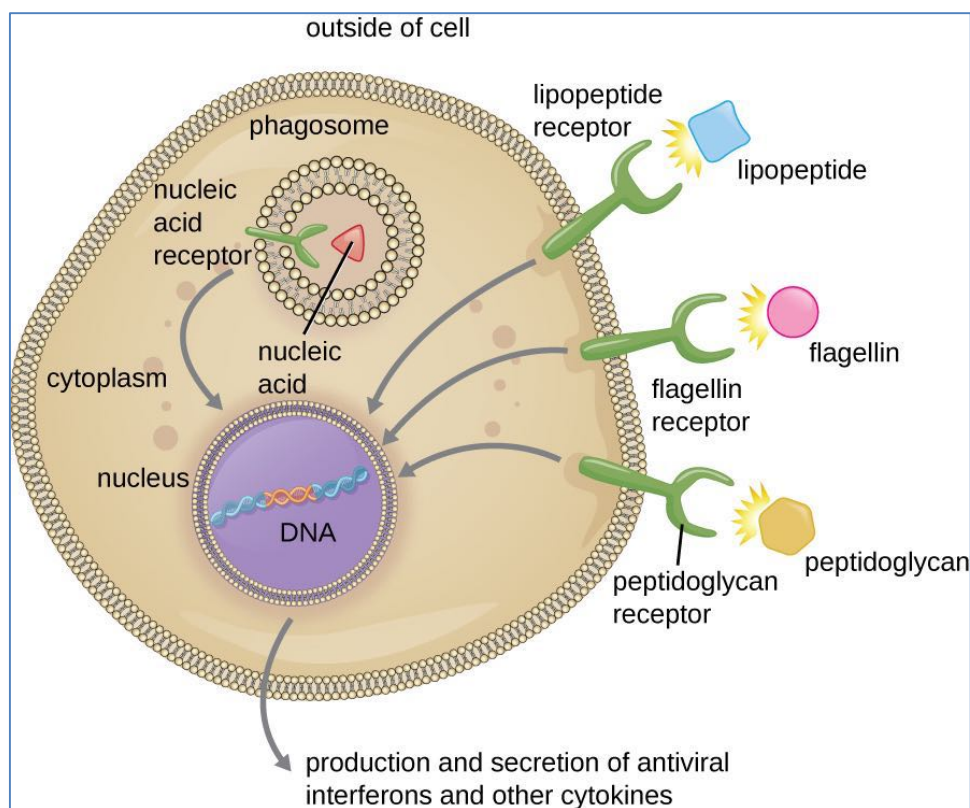
○ **Generation of Ag-Receptor Diversity:**

- **(In 1<sup>o</sup>-Lymphoid Organ - Thymus)**
  - Antigen-Receptor Gene Rearrangement
- (NO Ig-Isotype Switching.)



### **PAMPs – Pathogen Associated Molecular Patterns:**

- **Molecules Regularly expressed on the surface of Pathogens, but NOT on the Body's own Cells.**
- They allow Rapid Recognition of Invaders by the Innate Immune System → Rapid Immune Response.
  - o (Recognition of PAMPs is via Toll-Like Receptors (TLR's) & Pathogen-Recognition Receptors (PRRs))
- Hence, they provide a mechanism for Non-Specific immunity, until a More Specific Defence can be mounted by the Adaptive Immune System.
- **PAMPs are typically critical to the pathogen's function & cannot be eliminated through evolution. Such conserved features in pathogens include:**
  - o **Bacterial PAMPs:**
    - **Lipopolysaccharides (LPS) – Found on Gram-Negative Bacteria. Recognised by TLR-4.**
    - Flagellin (from Bacterial Flagella) – Found on Gram-Positive Bacteria. Recognised by TLR-5-
    - Lipoteichoic Acid – Found on Gram-Positive Bacteria. Recognised by TLR-2.
    - Lipoarabinomannan (LAM) – Associated with Tuberculosis Bacteria (Gram Positive). Recognised by TLR-2.
  - o **Viral PAMPs:**
    - Double-Stranded RNA (dsRNA) – Recognised by TLR-3.
    - Viral DNA

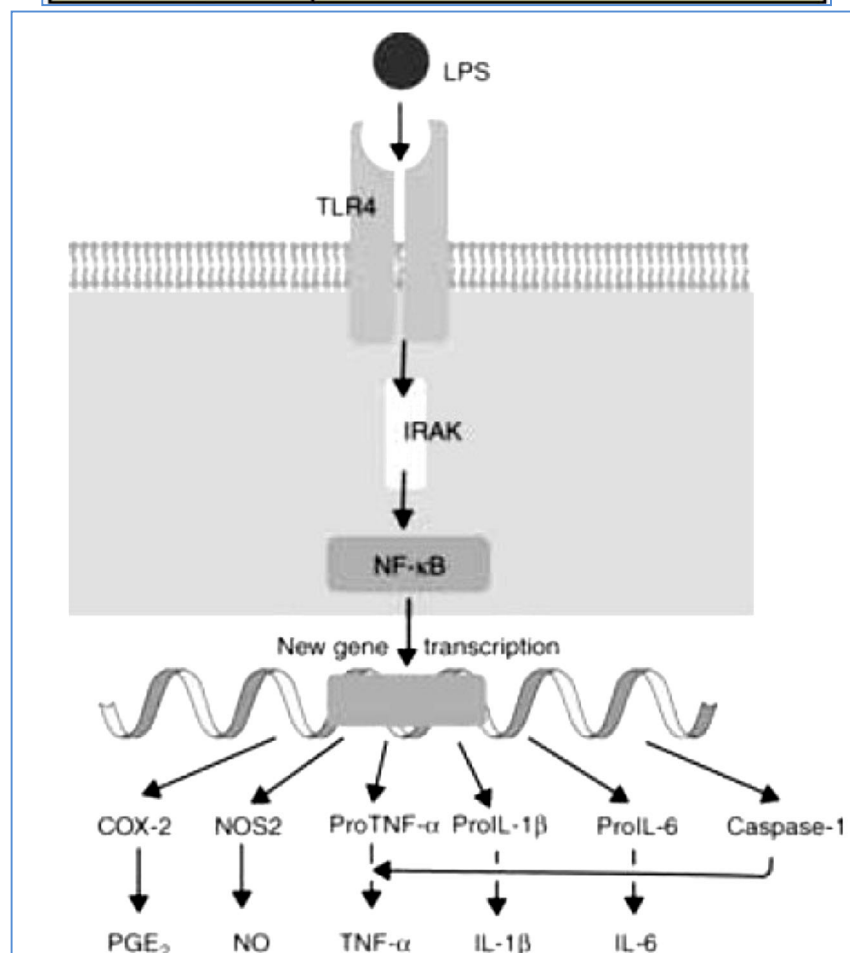


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### **TLR's – Toll-Like Receptors:**

- **A Class of *Pattern-Recognition Receptors* that play a key role in the *Innate Immune System* by recognising **PAMPs on Microbes.****
- There are ~15 different TLRs Primarily **Expressed on Antigen-Presenting Cells** (Dendritic Cells, Macrophages, & B-Lymphocytes).
- **Different TLRs can recognise multiple different PAMPs** on different microbes. (Ie: Have *Low Ag-Specificity*)
- **Major TLRs & Their Ligands:**
  - o **\*TLR-4: Recognises LPS (Lipopolysaccharide) – found on Gram-Negative Bacteria.**
  - o **TLR-5: Recognises Flagellin on Gram-Positive Bacteria.**
  - o **TLR-2: Recognises Lipoteichoic Acid (Gram-Positive) & Lipoarabinomannan (LAM) on TB.**
  - o **TLR-3: Recognises Double-Stranded RNA (dsRNA) on Viruses.**
- **Activated TLR's → Activate Transcription Factors → Causing the Production & Release of Cytokines (Including Chemokines) → Alert & Attract the Immune System to the Microbe.**
  - o Note: Cytokines produced depend on specific TLR stimulated.

Innate immune recognition by Toll-like receptors	
Toll-like receptor	Ligand
TLR-1:TLR-2 heterodimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI ( <i>T. cruzi</i> ) Zymosan (yeast)
TLR-2:TLR-6 heterodimer	
TLR-3	dsRNA
TLR-4 dimer (plus MD-2 and CD14)	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)
TLR-5	Flagellin
TLR-7	ssRNA
TLR-8	G-rich oligonucleotides
TLR-9	Unmethylated CpG DNA



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