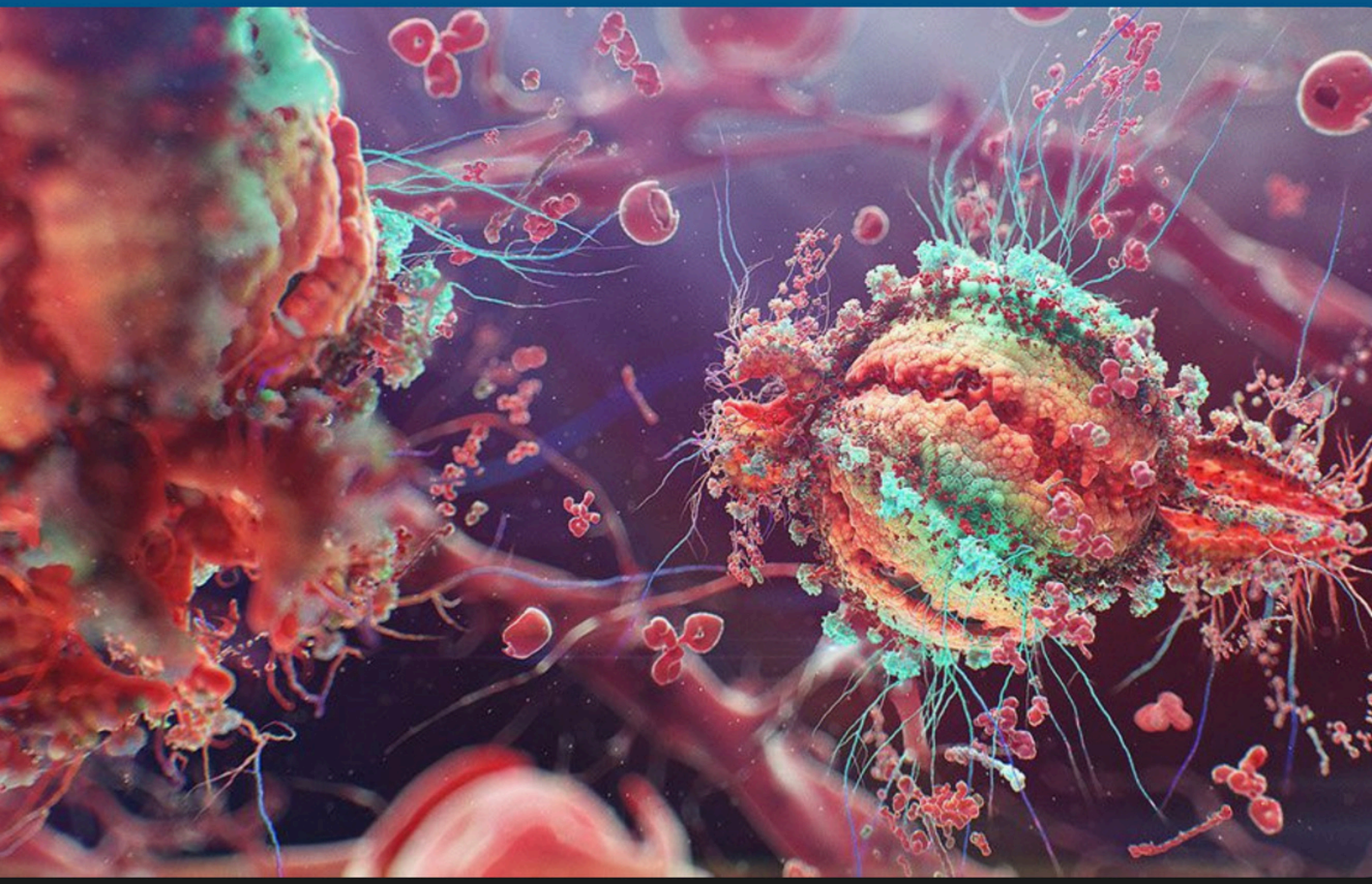
IMMUNOLOGY & RHEUMATOLOGY

TAILORED FOR MEDICAL STUDENTS, USMLE, PLAB, PA & NURSING



4th EDITION

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PDF

147 PAGES

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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

OVERVIEW OF THE IMMUNE SYSTEM

The Immune System:

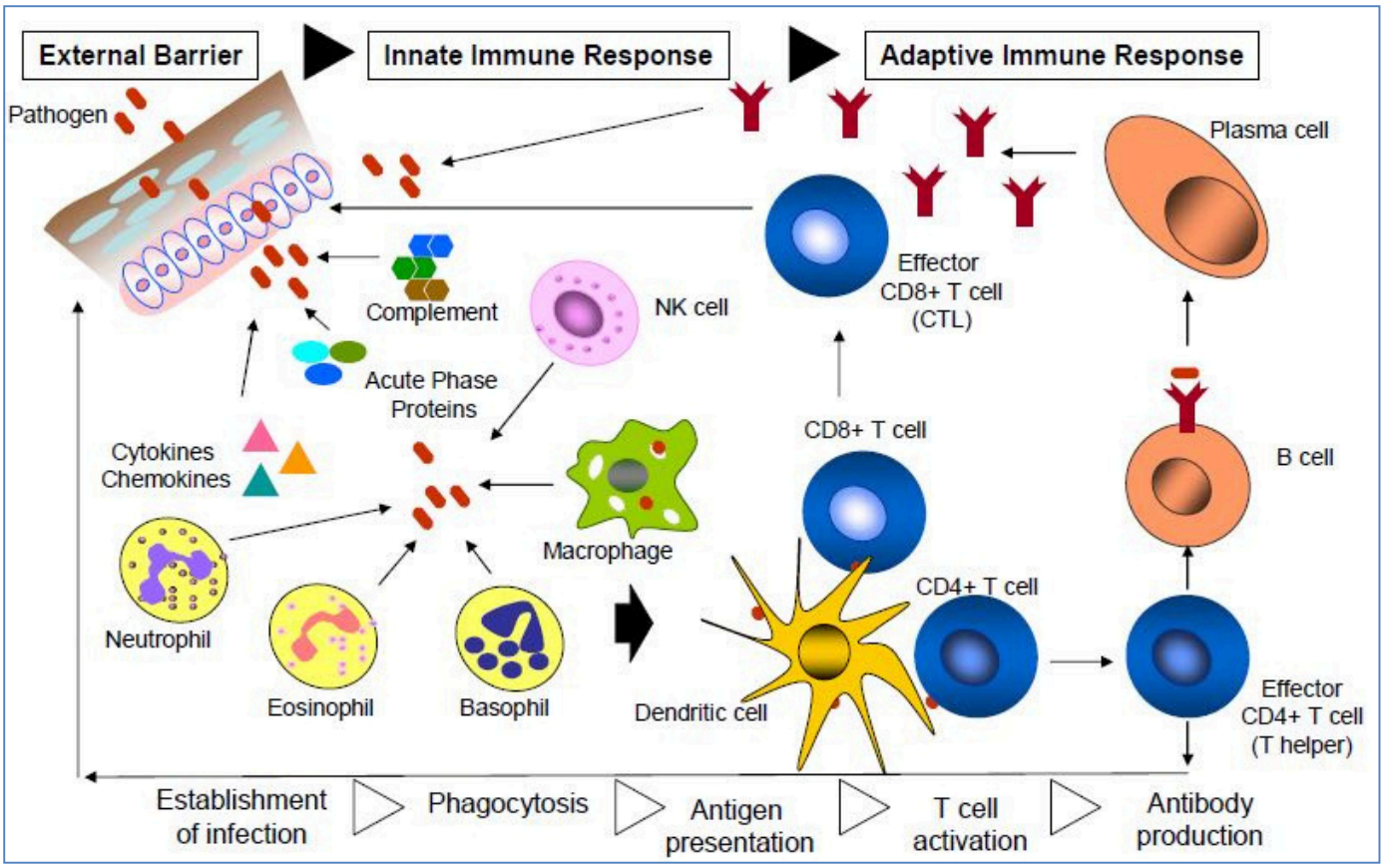
- The immune system is more a ***functional*** **system rather than an** ***anatomical*** **or** ***organ-based*** system.
- **Consists of:**
  - a diverse array of molecules
  - -and trillions of immune cells (especially lymphocytes).
  - These molecules & immune cells inhabit lymphoid tissues & circulate in body fluids.
- **Functions to protect the body from:**
  - Most infectious microorganisms
  - Cancer cells
  - Transplanted organs
  - Grafts
  - 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.
  - 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

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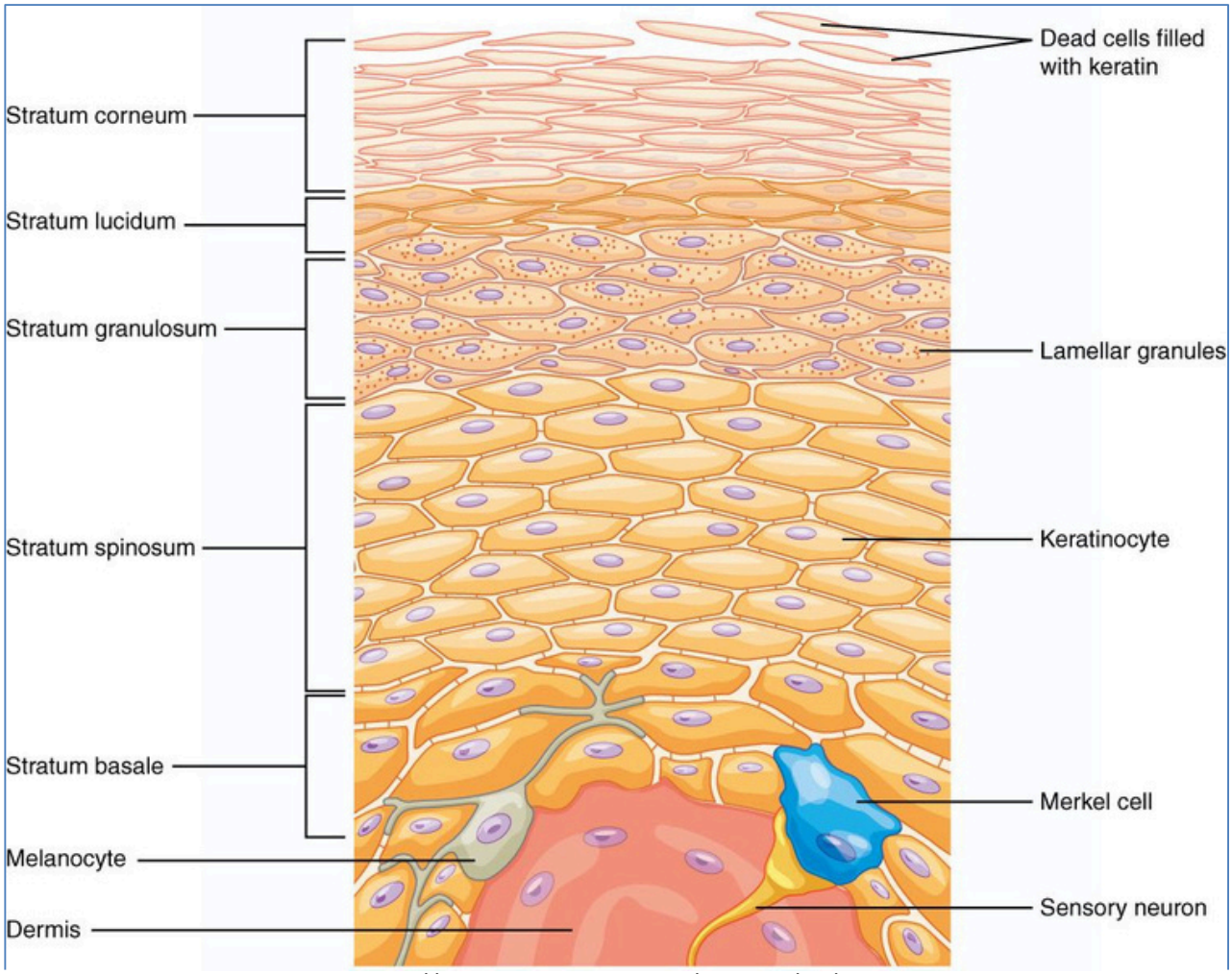
	Protective Elements			Characteristics		
	Barriers	**Proteins**	**Cells**	**Specificity**	**Memory**	**Tolerance**
Innate	Skin Epithelia Chemicals	Complement system Inflammation (Acute Phase Proteins)	Phagocytes and NK cells	PAMPs	No	Yes
Adaptive	Epithelial-Lymphocytes	Antibodies	Lymphocytes (T and B)	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**.
- **1st Line of Defence: Surface Barriers:**
  - **Role: Prevents Entry of Pathogen**
    - **Skin**
      - Stratified
      - Heavily keratinised



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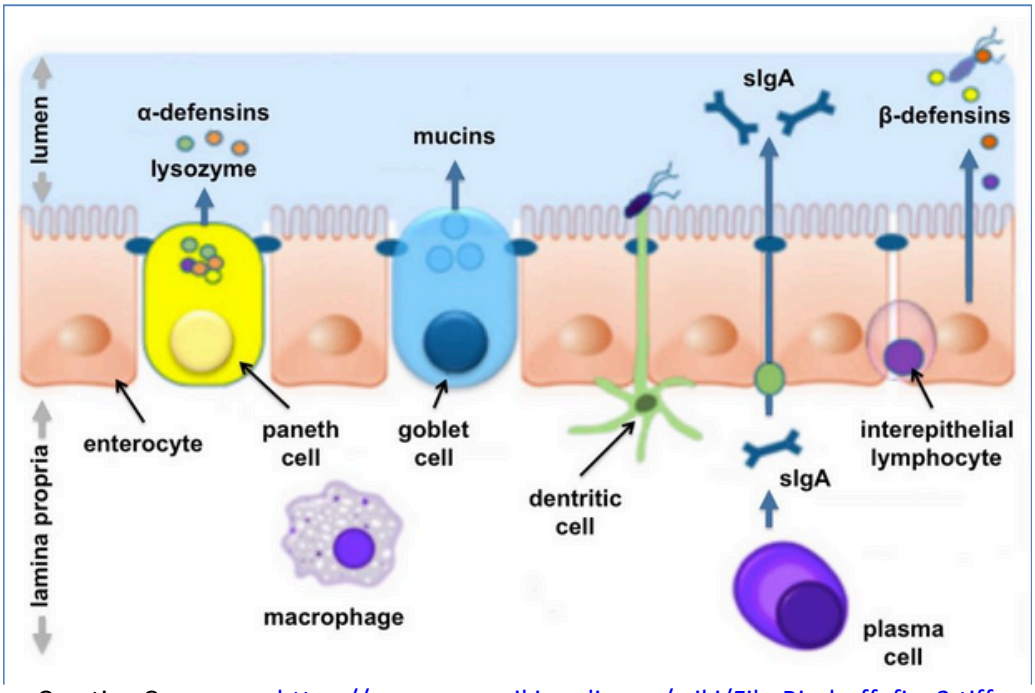
§ **Mucous membranes**

- 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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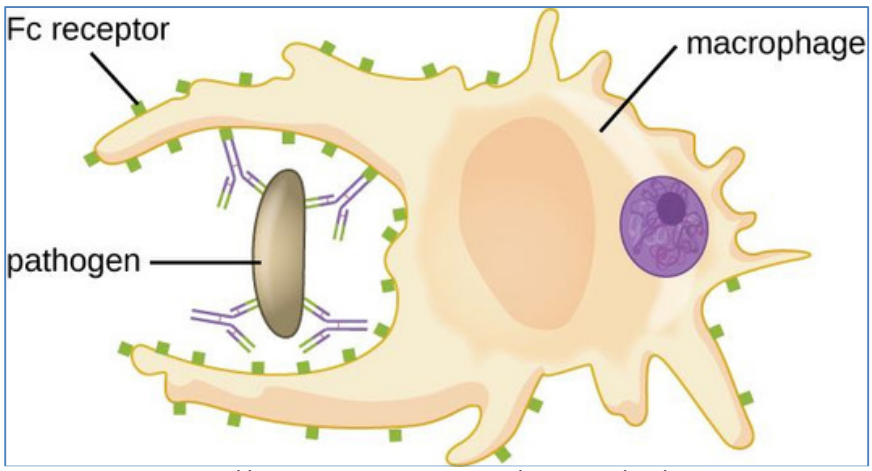
- **2nd Line of Defence: Internal Defences:**
  - **Role: Prevents Spread of Pathogen If Surface Barriers are Breached**
    - § **Macrophages** – Large phagocytic cells derived from bone-marrow precursors & found in Tissues throughout the body. They are involved in all phases of the immune system;
      - Engulf and Kill invading Microorganisms – Innately
      - Engulf and Kill Microbes 'marked' by an Adaptive Immune Response.
      - o 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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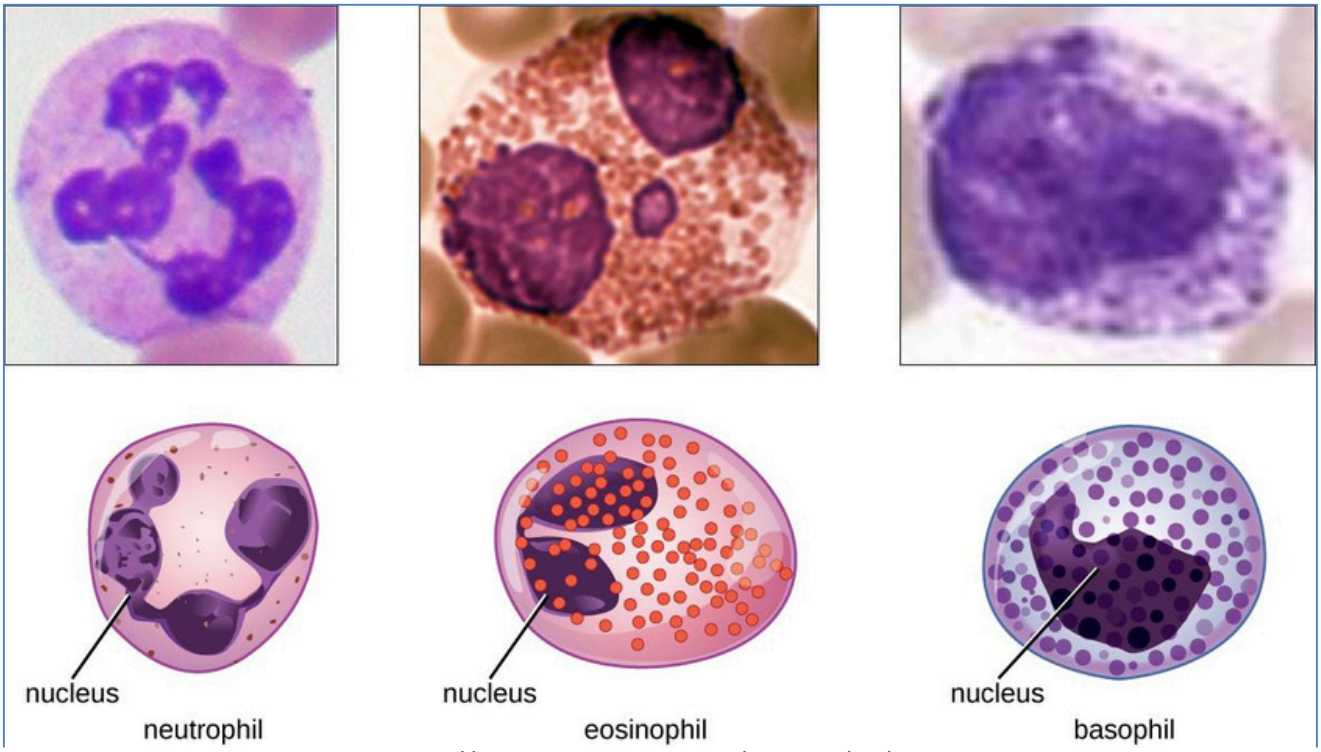
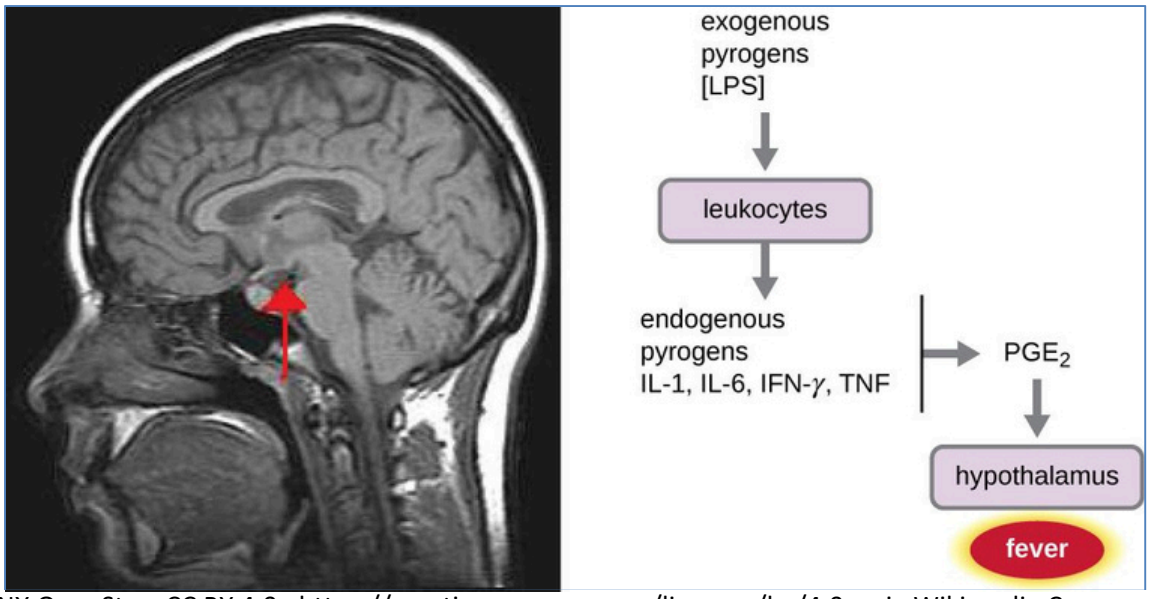
§ **Granulocytes –** possess cytoplasmic granules. named according to the stainability of the cytoplasmic granules. They are 'Polymorphonuclear' – (Multi-shaped lobed nucleus)

- **Neutrophils** –they release toxic chemicals into the extracellular fluid, killing both the target and themselves. (kamikaze)
  - o Most Numerous in blood samples 40-75%.
  - o Most Important Granulocyte.
  - o Phagocytic – Engulf invaders coated with Antibodies & Complement, damaged cells & debris.
  - o 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.
  - o Weakly Phagocytic
  - o Life-Span = 12 Days in Tissues - OR - 30min in Blood
  - o Kills extracellular organisms (Eg: Parasites) by excreting toxic chemicals onto their prey.
  - o Involved in Antigen Presentation & Destroy Tumour Cells.
- **Basophils** – Granules stain with **Basic** Dyes → Hypersensitivity & Allergic Reactions.
  - o Least Numerous
  - o Non-Phagocytic
  - o Granules contain Histamine, Serotonin & Prostaglandins → ↑Inflammation, ↑ Perm eability of Capillaries → ↑ Phagocyte m igration to site of infection.



§ **Fever**
- When exposed to foreigners, leukocytes & macrophages secrete pyrogens → increases the body's thermostat.
- Increases m etabolic rate, kills m icrobes, speeds up repair.



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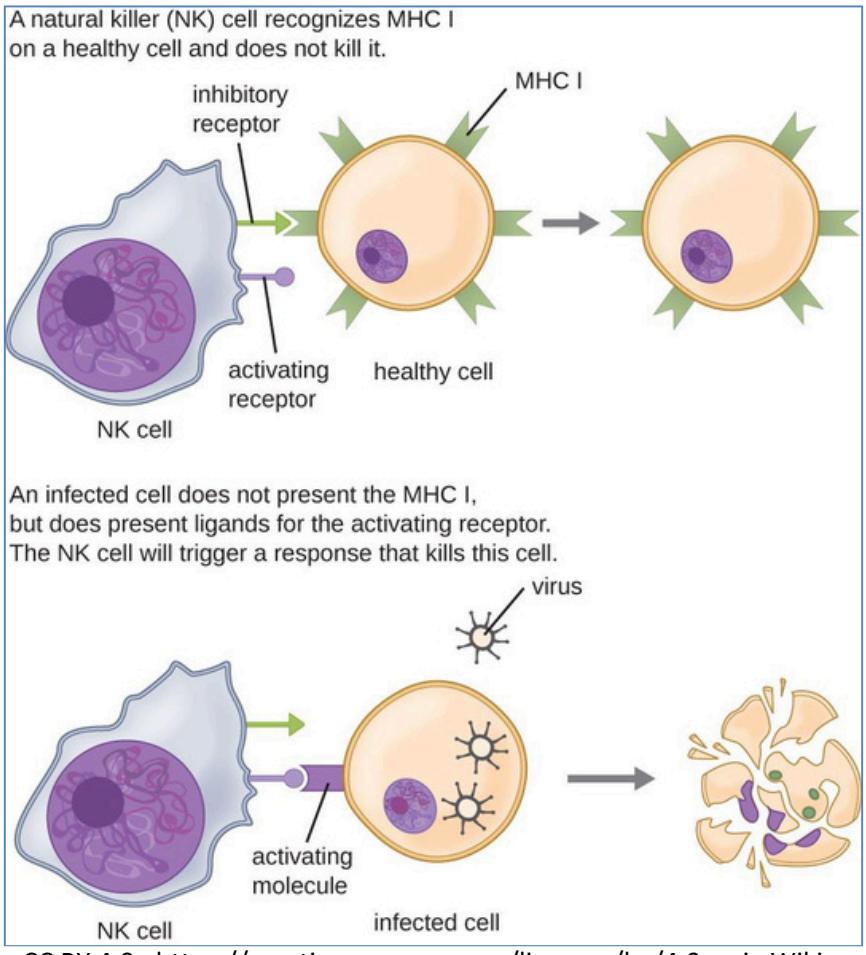
§ **Natural Killer cells** - Large, Granular, **Lymphoid-Derived** cells, which kill malignant cells, and cells infected by Intracellular pathogens (viruses/bacteria).
- Police the body in blood & lymph
- Can lyse & kill cancer cells & virus-infected cells
- Target all cells that lack 'self' surface receptors (non-specific)
- Kill by latching onto invaders and inducing apoptosis.
- Also secrete potent chemicals that promote inflammation



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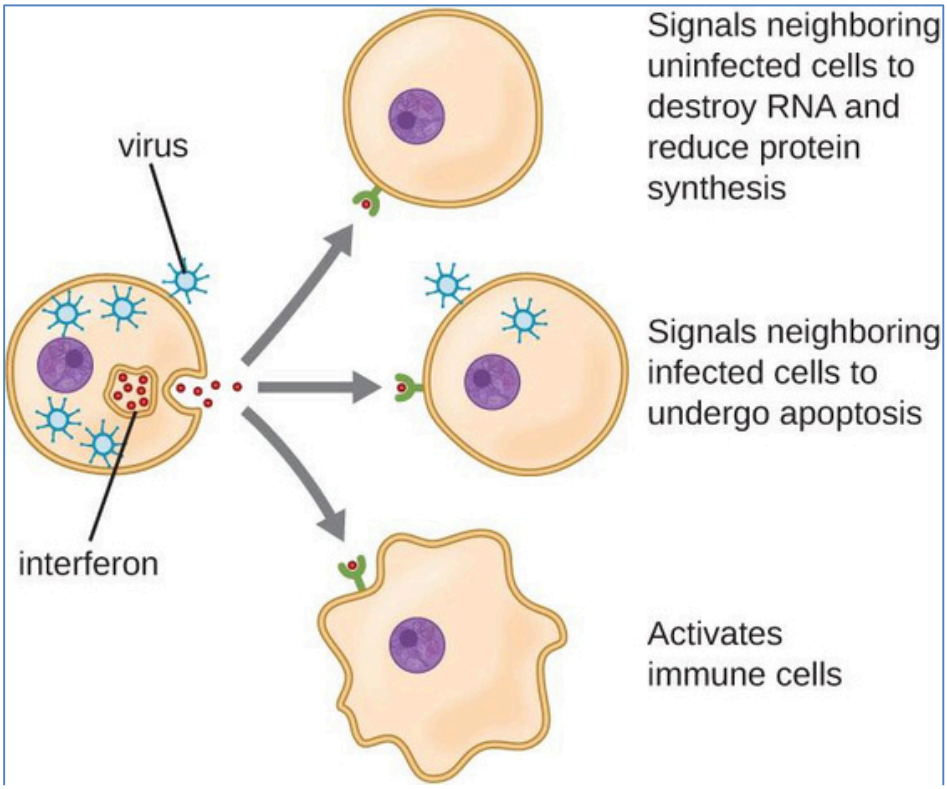
§ **Antimicrobial proteins (Eg: Interferon & Complement):**

- 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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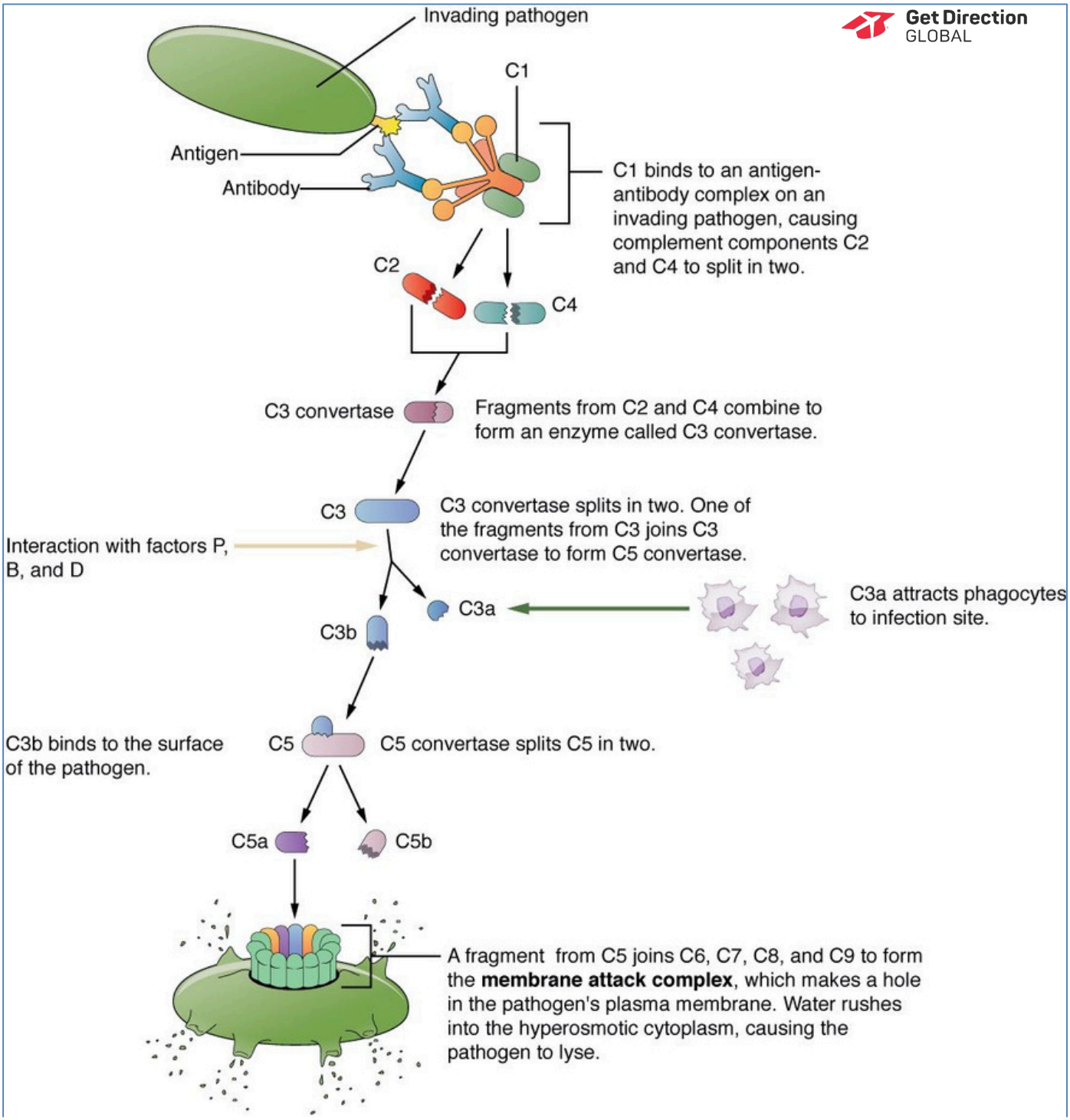
- **Complement Proteins –** A group of over 30 small Pro-Enzymes (Zymogens) produced by the liver, which are widely distributed through blood & tissues. When stimulated via one of 3 pathways (Classical, Alternative & MB-Lectin), self-amplifying proteolytic cascades are initiated leading to:
  - o **1- Opsonisation of pathogens by C3b** → Targets foreign particles for Phagocytosis.
  - o **2- Lysis of antibody-coated cells by the Membrane Attack Complex** → Creates a pore in the PM of bacteria.
  - o **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 im portant role in activating the Adaptive Im m une 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)



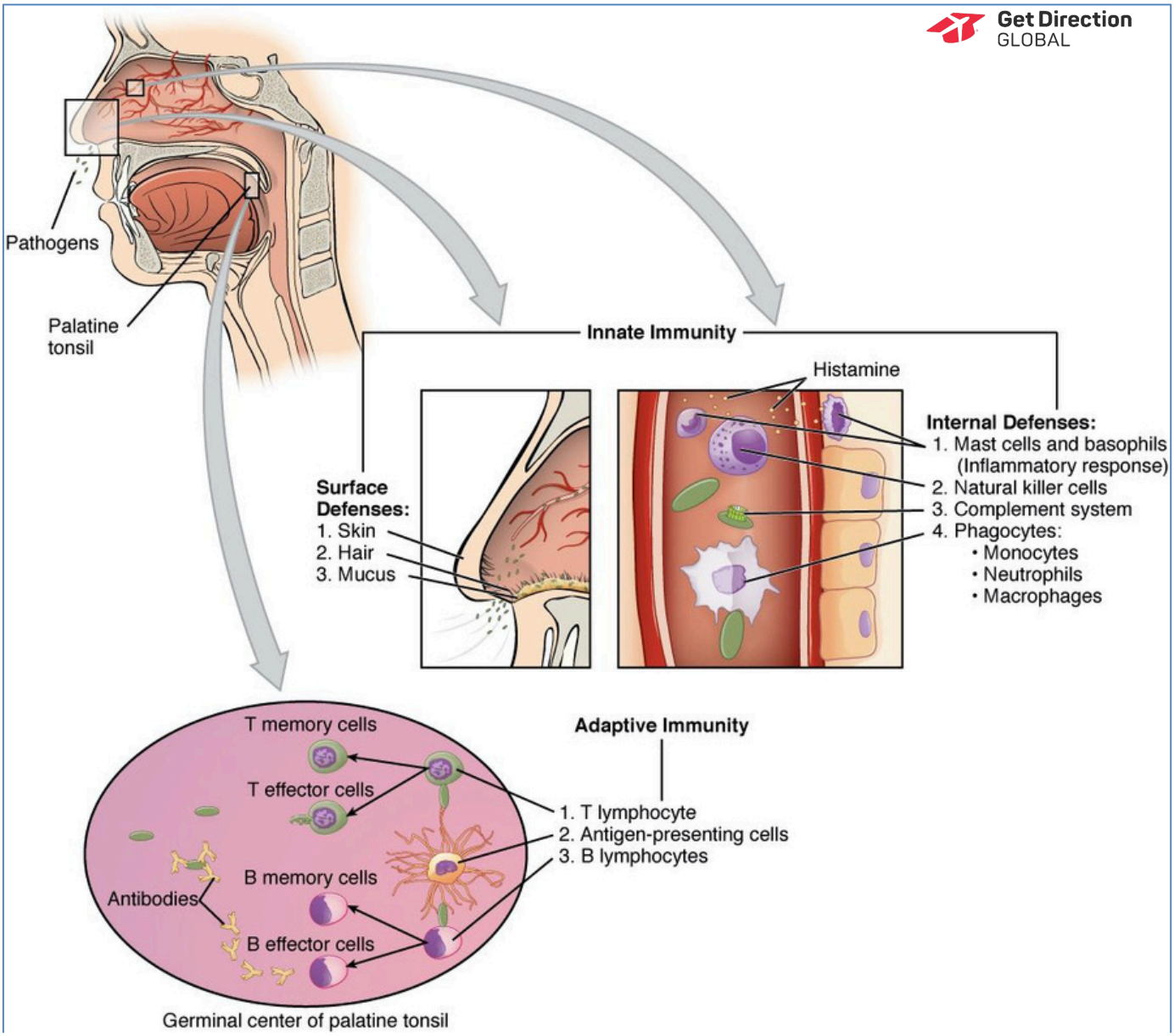
Complement Cascade and Function The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

§ **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 Im portant M ediators:**
- o **IL-6:**
  - § Pyrogenic action on Hypothalamus → Fever
  - § Stimulates the Acute Phase Response (in liver).
  - § Activates Lymphocytes during Antigen-Presentation.
- o **TNF-α:**
  - § 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.
- o **Note: Septic Shock –** Systemic Release of pro-inflammatory cytokines (**TNF, IL-1, IL-6**, IL-8, IFN) from Neutrophils/M acrophages/Endothelial cells, plus pro-inflam m atory 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** & TNFa). **Relevant Examples include:**
- **CRP – (C-Reactive Protein)** →
  - o An Opsonising Agent for microbes → Phagocytosis (Similar action to Antibodies – except have broad specificity for PAMPs)
  - o Also Activates the ***Classical Pathway of the Complement Cascade***.
- **MBL – (Mannose-binding Lectin)** →
  - o Also an Opsonising Agent for microbes → Phagocytosis.
  - o Also Activates the ***Lectin Pathway in the Complement Cascade***.
- **SP-A & SP-D:**
  - o Found in Alveolar Fluid & Also have Opsonizing Properties.

Note: Measurement of acute-phase proteins, especially CRP, is a useful marker of Inflammation.

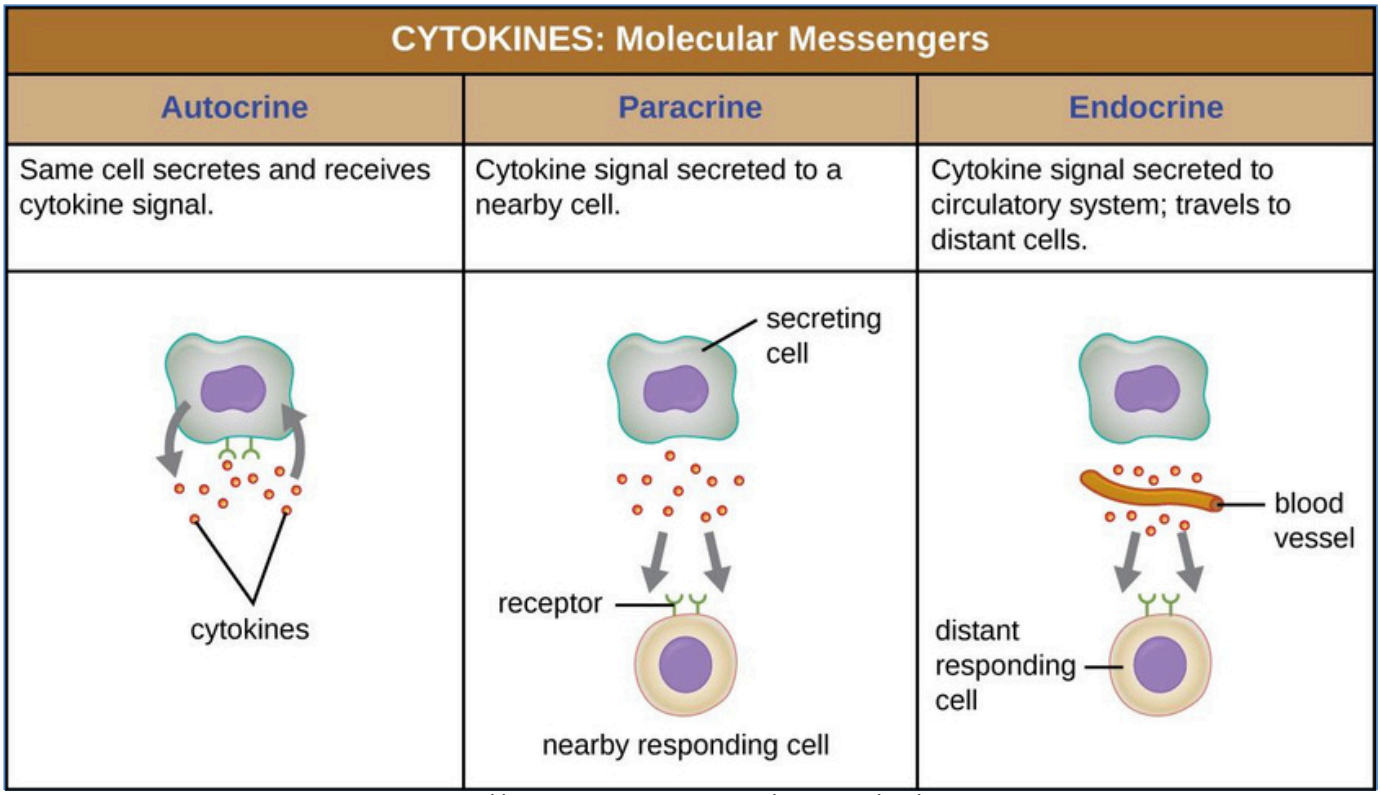


Cytokines:

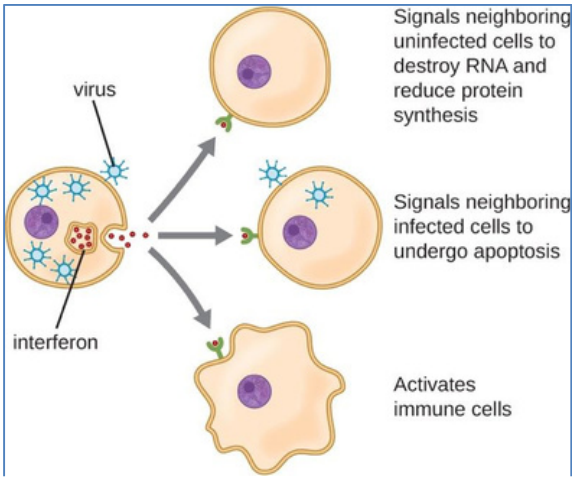
Literally: proteins made by cells that affect the behaviour of other cells. They act via specific cytokine receptors on the cells that they affect.

- **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 **Chemo**tactic Cyto**kines**. 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.



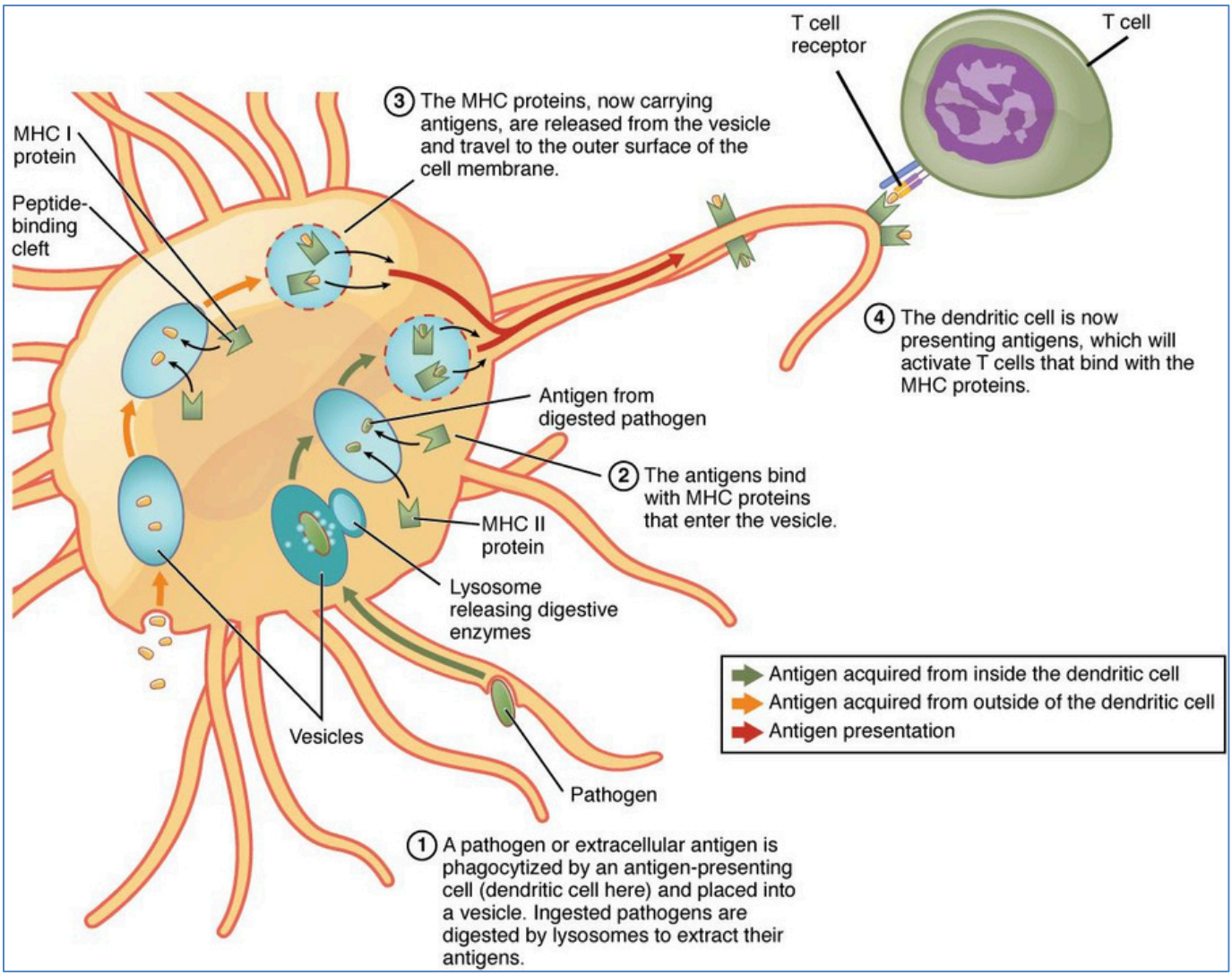
- **Im portant Cytokines:**
  - **IL-1, IL-6 & TNFa** –
    - Critical to the ***Acute Phase Response*** (or Synthesis of Acute Phase Proteins) Some **Acute Phase Proteins** mimic the action of Antibodies, but have broad specificity for PAMPs and depend only on the Cytokines for their production.
    - 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
  - **IFNy (Interferon-Gamma)** – the major cytokine-activator of Macrophages. (Produced by T-Helper cells, T-Cytotoxic Cells & NK-Cells).



Cytokine	Cell source	Target	Actions
Proinflammatory Cytokines			
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
Anti-inflammatory Cytokines			
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
Cytokines Involved in the Acquired Immune Response			
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.



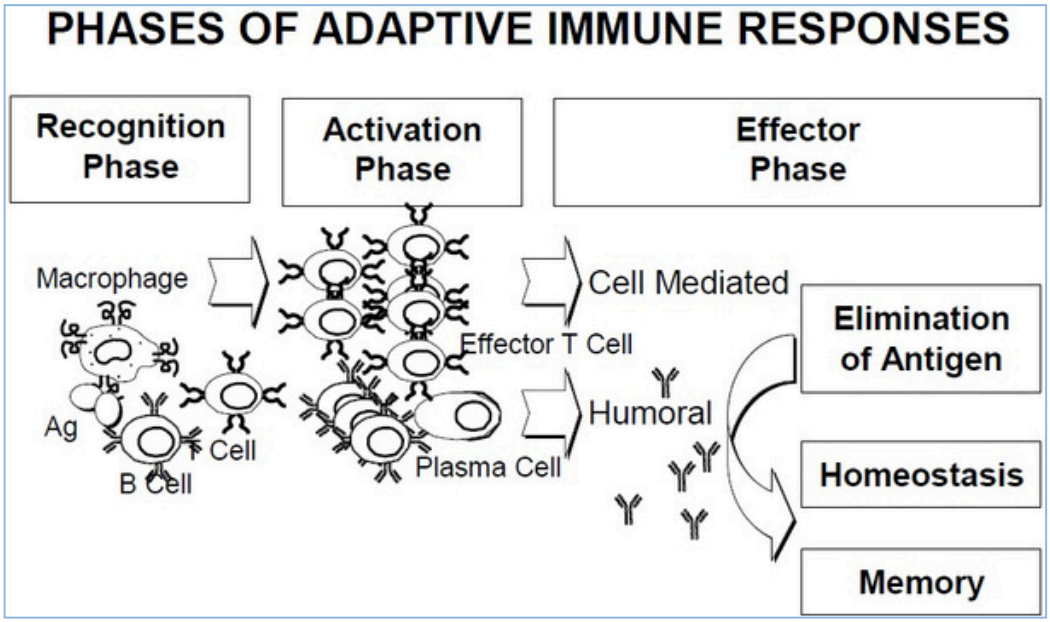
ADAPTIVE (SPECIFIC)IMMUNE SYSTEM:

- *Think of the Adaptive Immune System as "The body's elite special forces" – with high-tech weapons.*
- **5 Characteristics:**
  - o **>It is Specific:** recognises *particular* pathogens/antigens
  - o **>It is Systemic:** immunity isn't restricted to initial infection site
  - o **>It has Memory:** mounts stronger attacks on previously encountered pathogens.
  - o **>Self-Limitation:** Immune response wanes off following elimination of antigens.
  - o **>Self-Tolerance:** Immune system non-reactive to self-antigens.
- **Roles:**
  - o Tremendously amplifies the inflammatory response.
  - o Attack specific foreign substances – Incl: Antigens and abnormal body cells
  - o mounts stronger attacks on previously encountered pathogens.

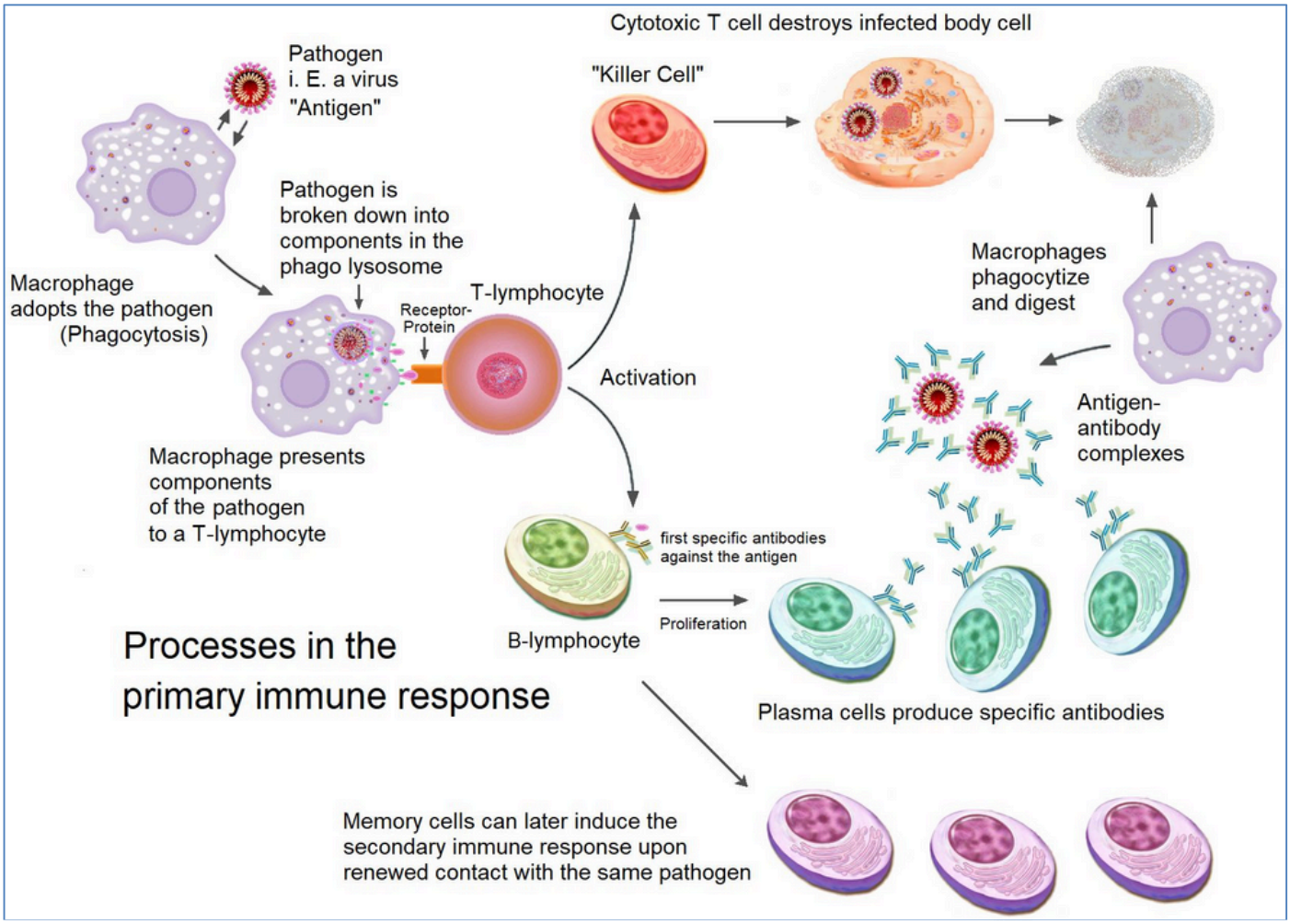
May be either Humoral OR Cell-Mediated depending on the Microbe.

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:**
  - o **Recognition Phase: TLRs** & **PRRs** on **Macrophages & Dendritic Cells** recognise **PAMPs** on the A**ntigens**, & 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.
  - o **Activation Phase:** Activated Dendritic Cells migrate to Lymph Nodes, where they activate Naive T-Cells, → W hich activate Naive B-Cells → secrete Antibodies.
  - o **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.



- **The body's 3rd line of defence (Humoral & Cellular Immunity):**
  - o **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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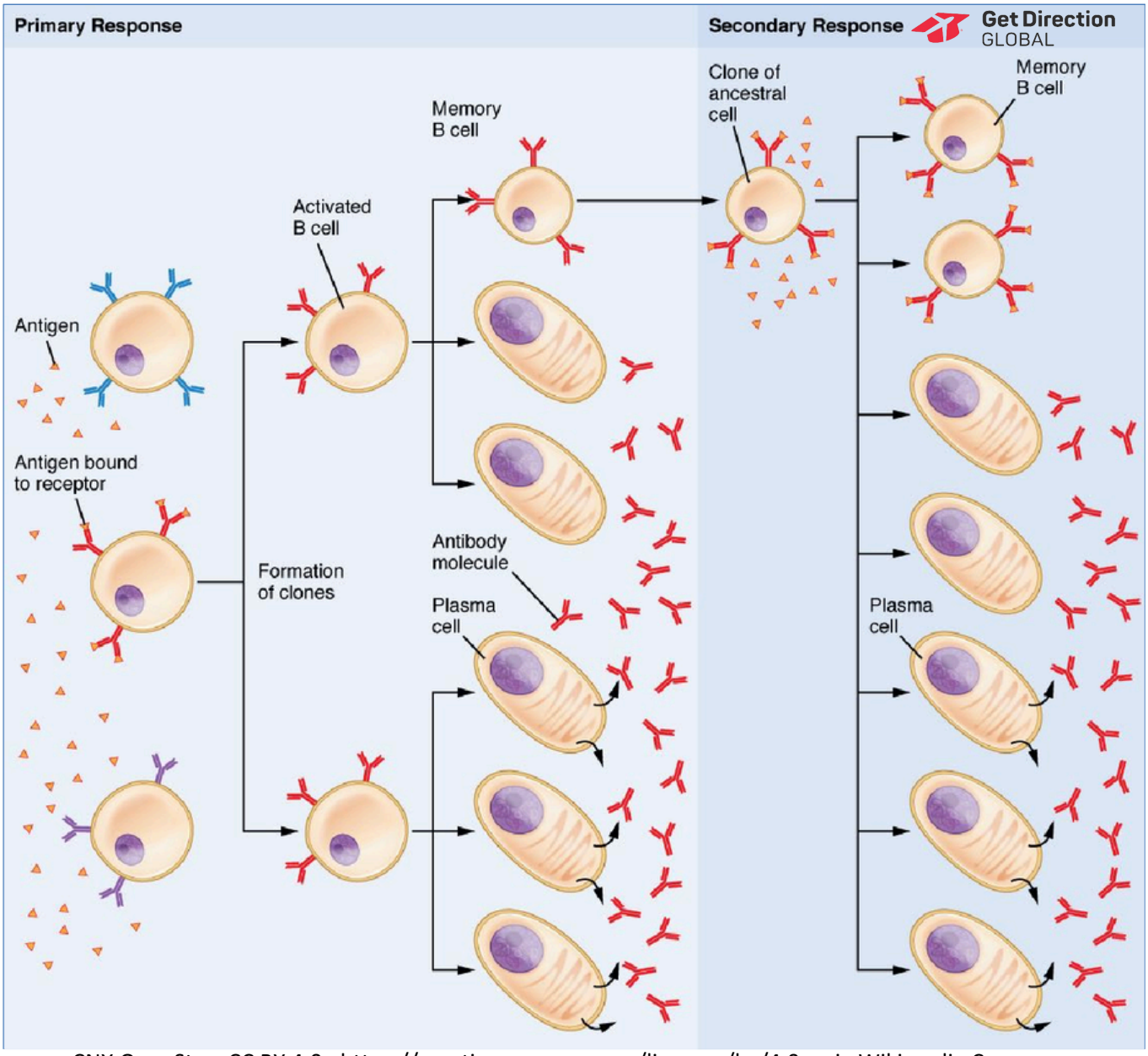
- o **b) HUMORAL IMMUNITY** (aka. Antibody-mediated immunity) -Immunity can be **transferred** from person-person **via serum**
  - § **B Cells (B-Lymphocytes**)
  - § **Make antibodies** against soluble antigens.
    Antibodies (Immunoglobulins):
    - Circulate freely in blood & lymph
    - **Neutralises** bacteria/toxins/& viruses →marks for destruction by phagocytes or compliment.



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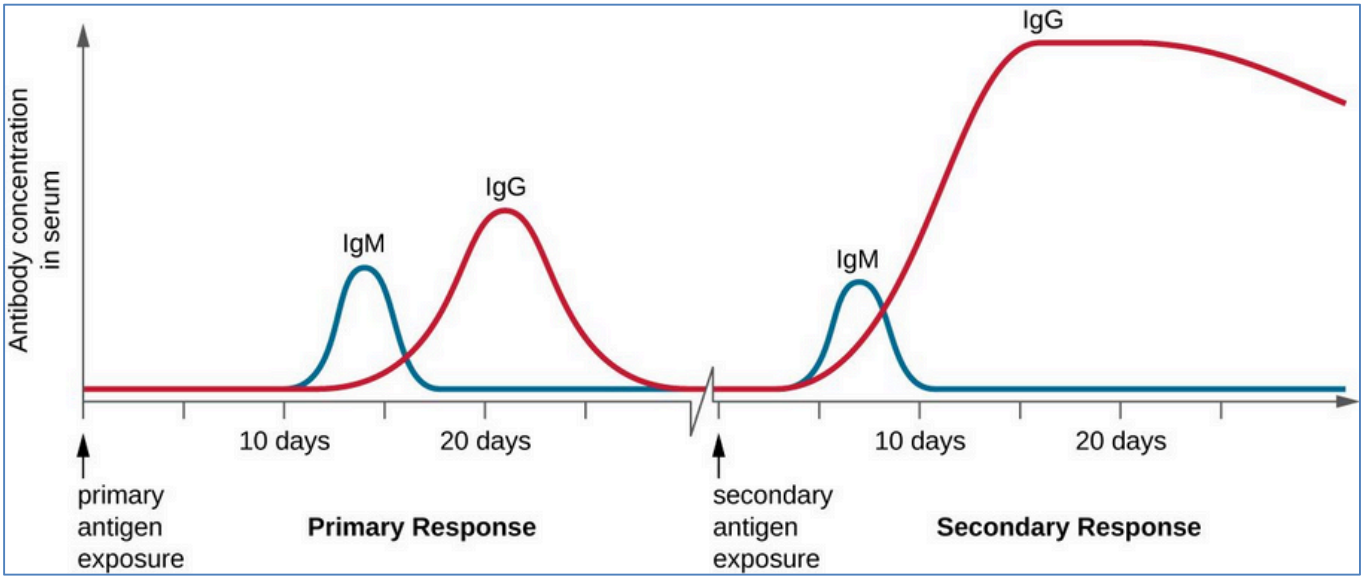

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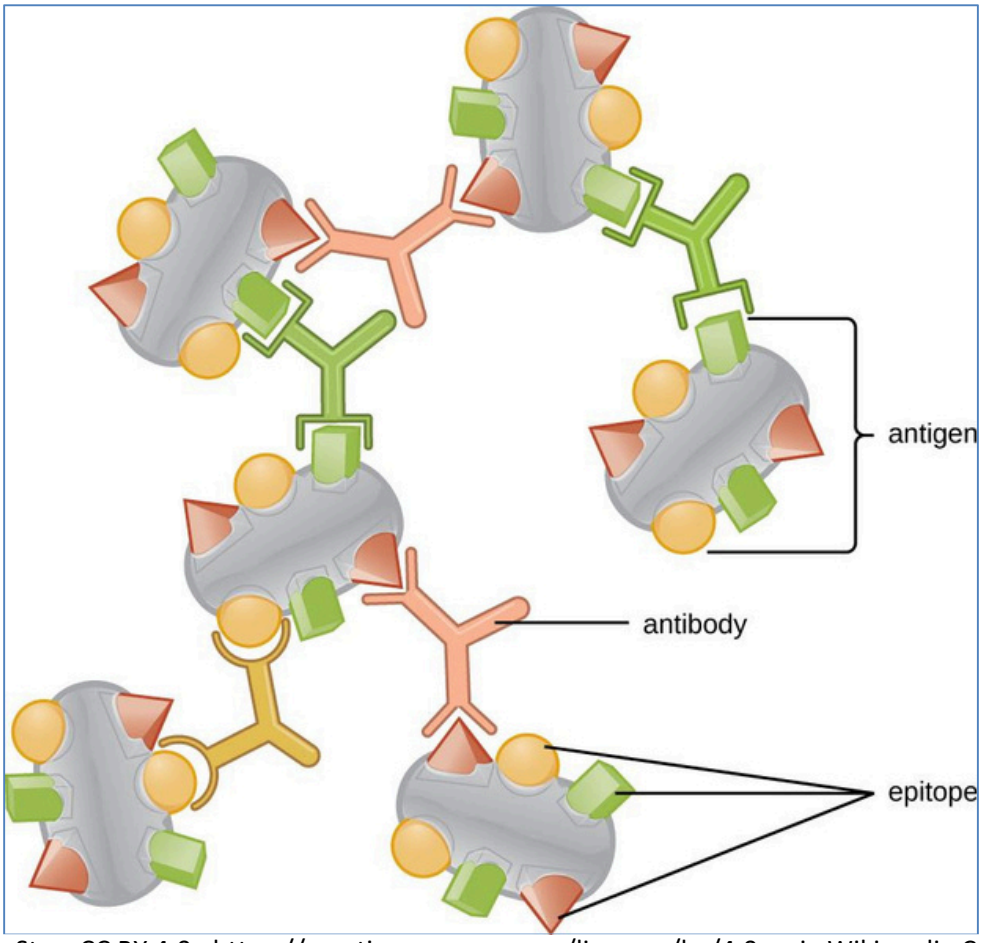
(Note: Once the body has Memory B-Cells from the first immune response, the immune reaction to the second exposure is m uch quicker and has a higher antibody yield. Is the prim ary m echanism behind vaccines)

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 **Anti**body-**Gen**erating ability.
    - o However some antigens don't cause antibody production; Ie: 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 2o Lymphoid Organs)
        - § ↑Ag. Dose
- **"Epitopes":** A single Antigen can have multiple *Sites* (or Epitopes) which are Immunogenic.



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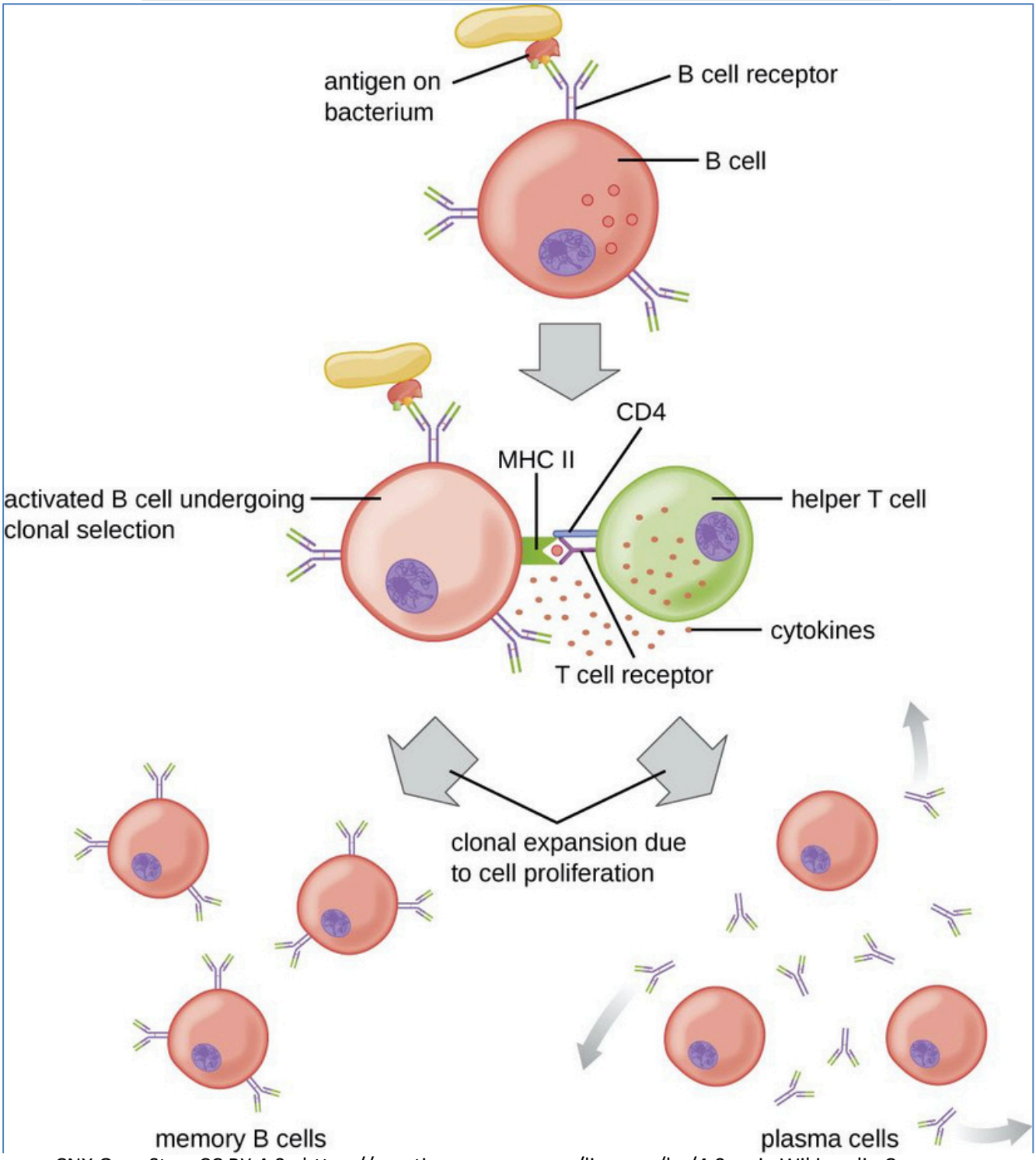
- ***"Thymus-Dependent Antigens"*:**
  - Antigens recognised by **B-Cells** which require Ag-Specific CD4-Helper-T-Cell help in order to Activate the B-Cell → Plasma Cell → Secrete Antibodies.

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.



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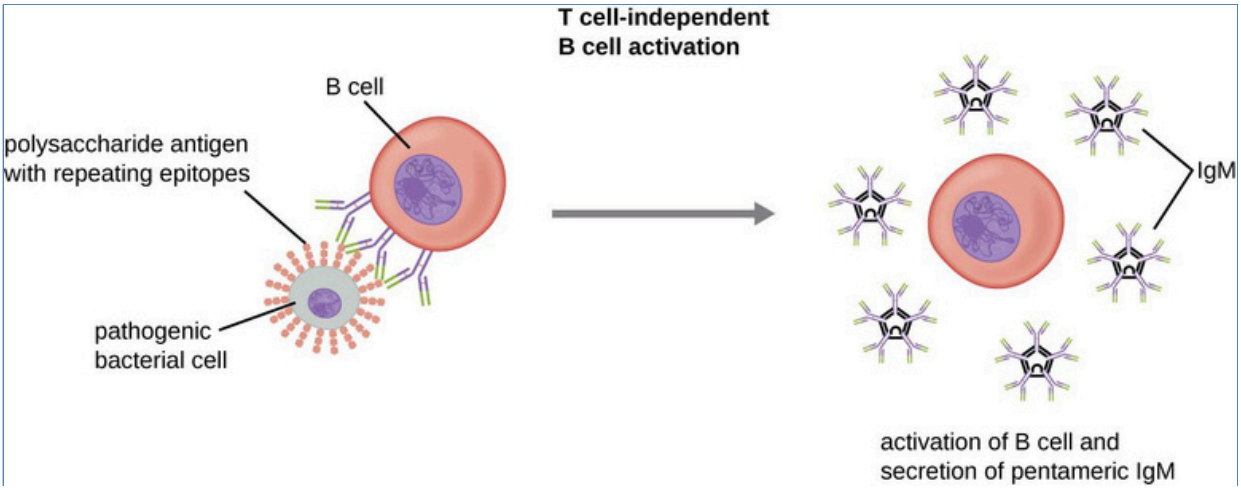
- ***"Thymus-Independent Antigens"*:**
  - o Antigens recognised by **B-Cells** which, *by themselves*, are enough to cause B-Cell Activation (& subsequent Ab-secretion) *Without CD4-Helper-T-Cell* Assistance.



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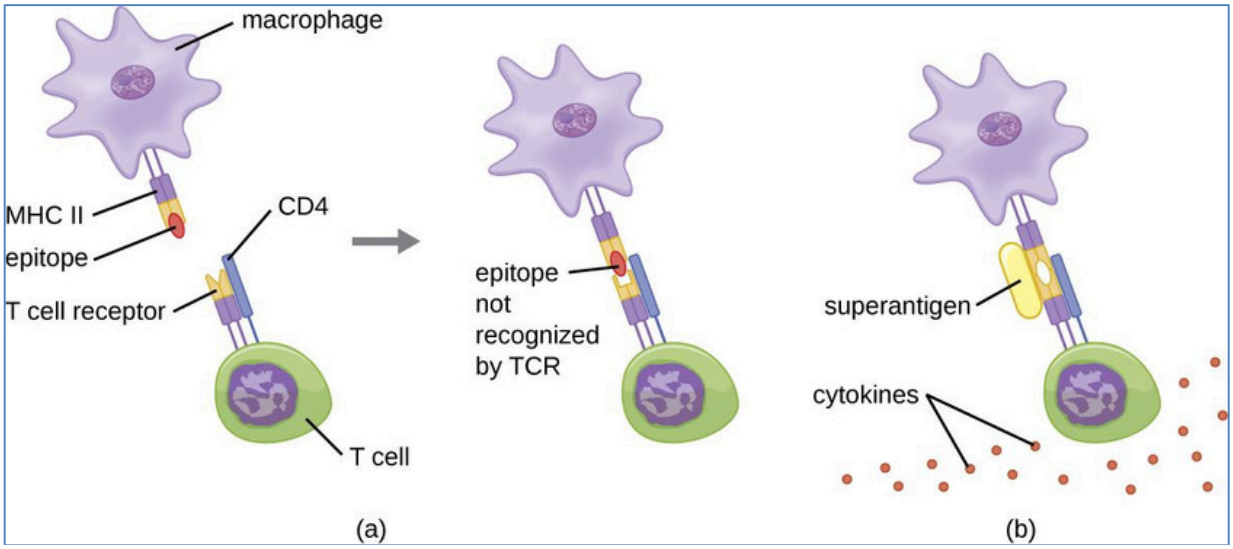
- ***"Superantigens"*:**
  - o Bacterial or Viral Antigens that *Non-Specifically* activate T-Cells *Without being Processed by APCs*.
  - o T-Cell responses are therefore *also Non-Specific* & hence are *Maladaptive* for host & helpful to pathogen. (See section on MHC for details)



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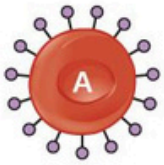
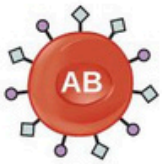
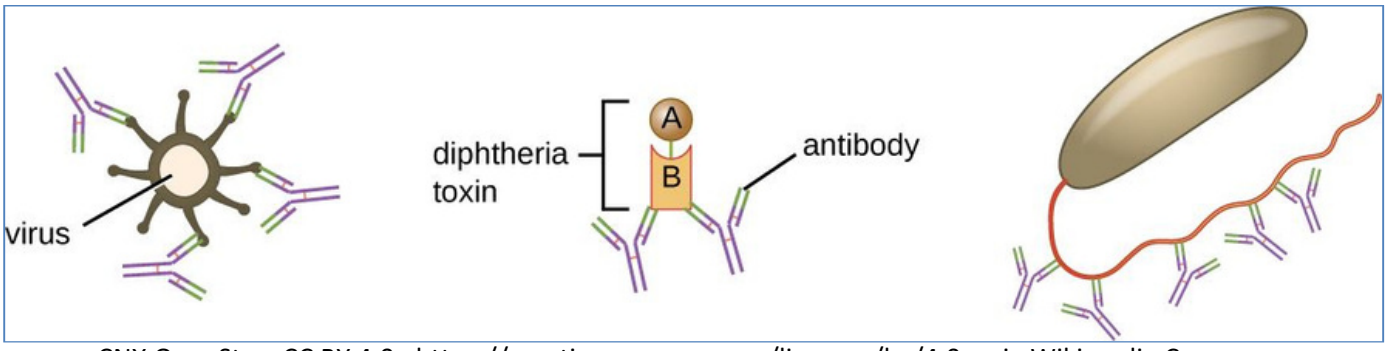
- **Common Antigens:**
  - o **Bacterial Antigens:**
    - § (See Pathogen-Associated Molecular Patterns - PAMPs)
    - § Flagellin
    - § Capsule
    - § Cell Wall
    - § Bacterial Toxins (Endotoxins & Exotoxins)
  - o **Viral Antigens:**
    - § (See Pathogen-Associated Molecular Patterns - PAMPs)
    - § Capsid Proteins
    - § Nucleoproteins
    - § Envelope Glycoproteins
  - o **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				
Isohemag-glutinins	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens on red blood cell	 A antigen	 B antigen	 A and B antigens	None

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:
    - o **1- Neutralisation** of Pathogens/Toxins → Phagocytosed.



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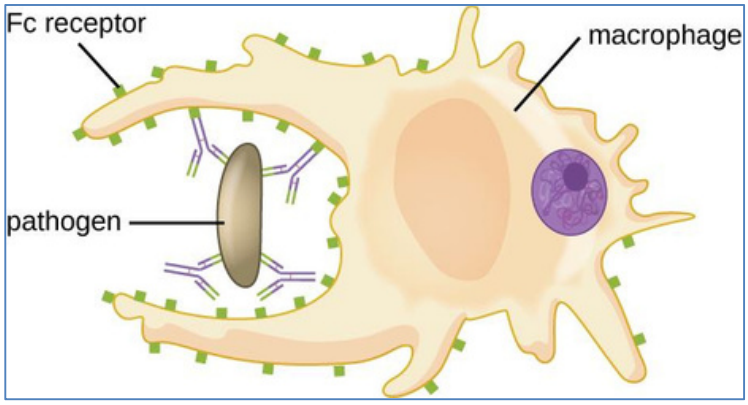
- o **2- Opsonisation** of Pathogen → Marks them for destruction by Phagocytes.



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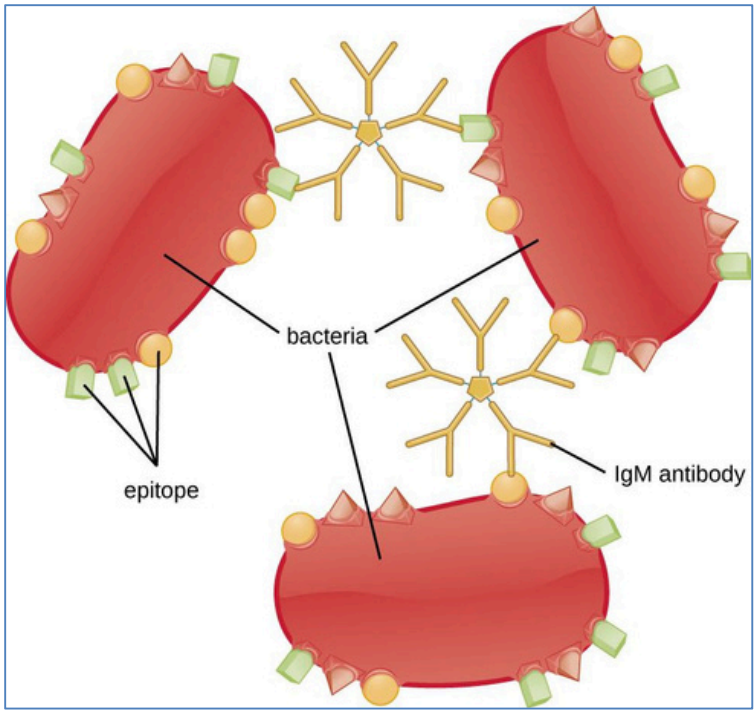
- o **3- Activation of Complement** → Lysis of Extracellular Bacteria → Phagocytosed.
- o **4- Agglutination** by binding to epitopes of two or more bacteria simultaneously → Forms aggregates of inactivated crosslinked bacteria.



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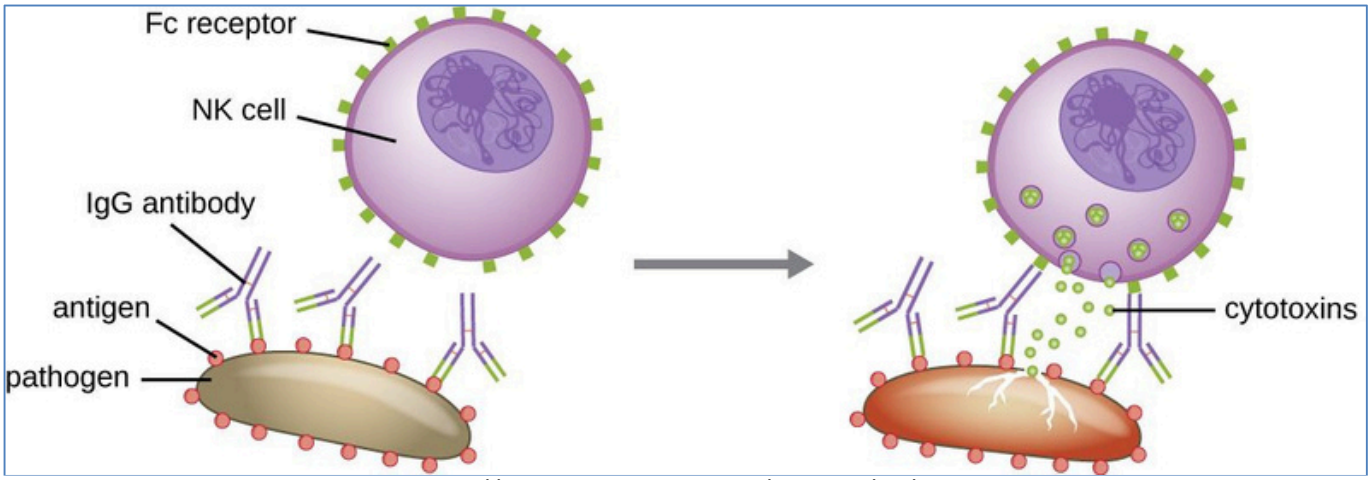
- **5- Ab-Dependent Cellular Cytotoxicity (ADCC)** → Lysis of a Target Cell that has been bound by Specific Antibodies:
  - **Eg: NK-Cells** → Lysis of a Pathogen-Infected Cell.
  - **Eg: Eosinophils (Via IgE)**→ Kills Parasites that are too big for phagocytosis.

Antibody-dependent cell-mediated cytotoxicity (ADCC)



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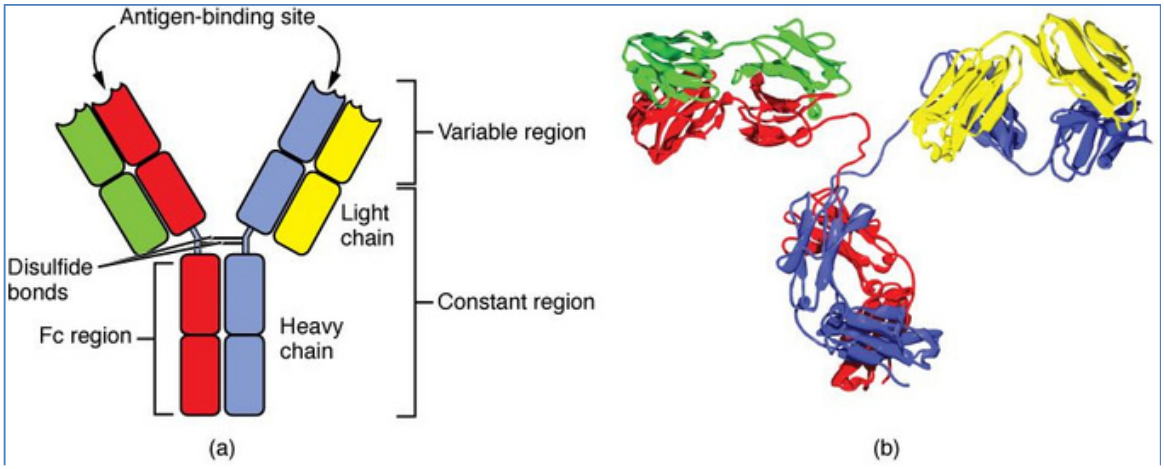
- **W here Are They Found?**
  - On their own (in plasma)
  - As Antigen-Receptors on B-Cells (BCRs).
- **Structure:**
  - **Y-Shaped molecule:**
    - Arms = Antigen Binding Sites
    - Tail = Constant Region
  - **2x Heavy (Long) Chains & 2x Light (Short) Chains:**
    - Each chain has a ***Constant 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 (VH & VL).
    - 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:**
    - **Fab = Antigen Binding Site**
    - **FC = Constant Region**
    - **VH = Variable Region of a Heavy Chain**
    - **VL = Variable Region of a Light Chain**
    - **CH = Constant Region of a Heavy Chain**
    - **CL = 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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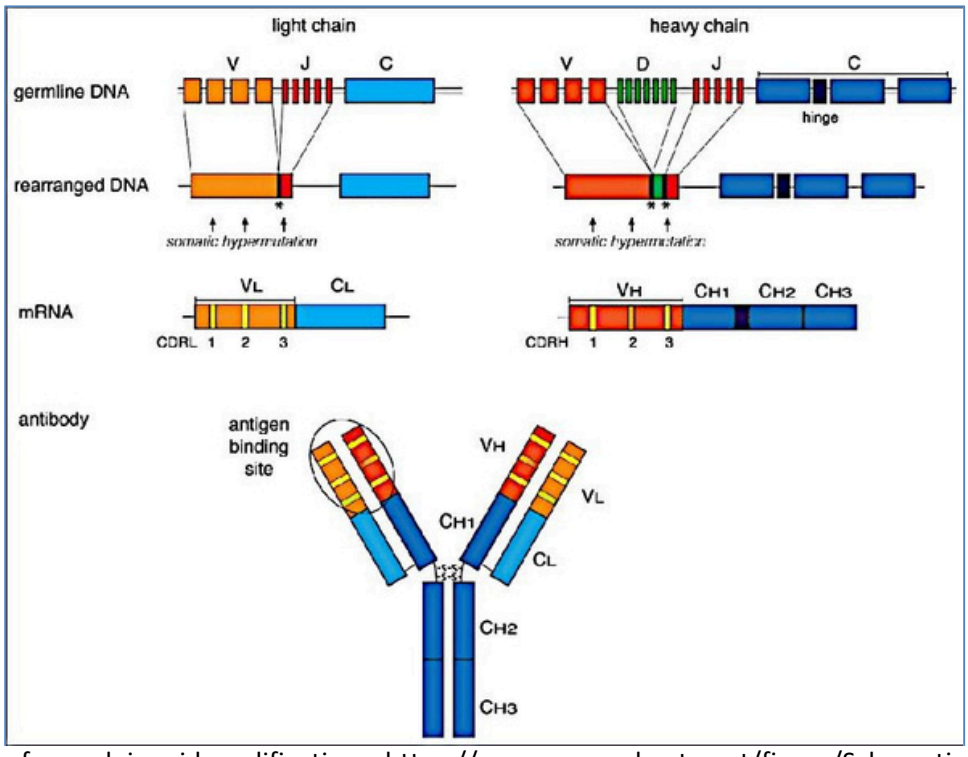
- **Generating Diversity of Antibody-Repertoire:**
  - **Why is it important?**
    - Since Antibodies & Ab-based receptors (in this case BCRs & also the Fab on TCRs) are the only *Activators & Effectors* of the Adaptive Immune System, they have to be able to *Evolve* to keep up with *Evolving Pathogens*.
  - **How does it happen?**
    - **Primary Diversification Mechanisms (During B/T-Cell Maturation In 1o 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).

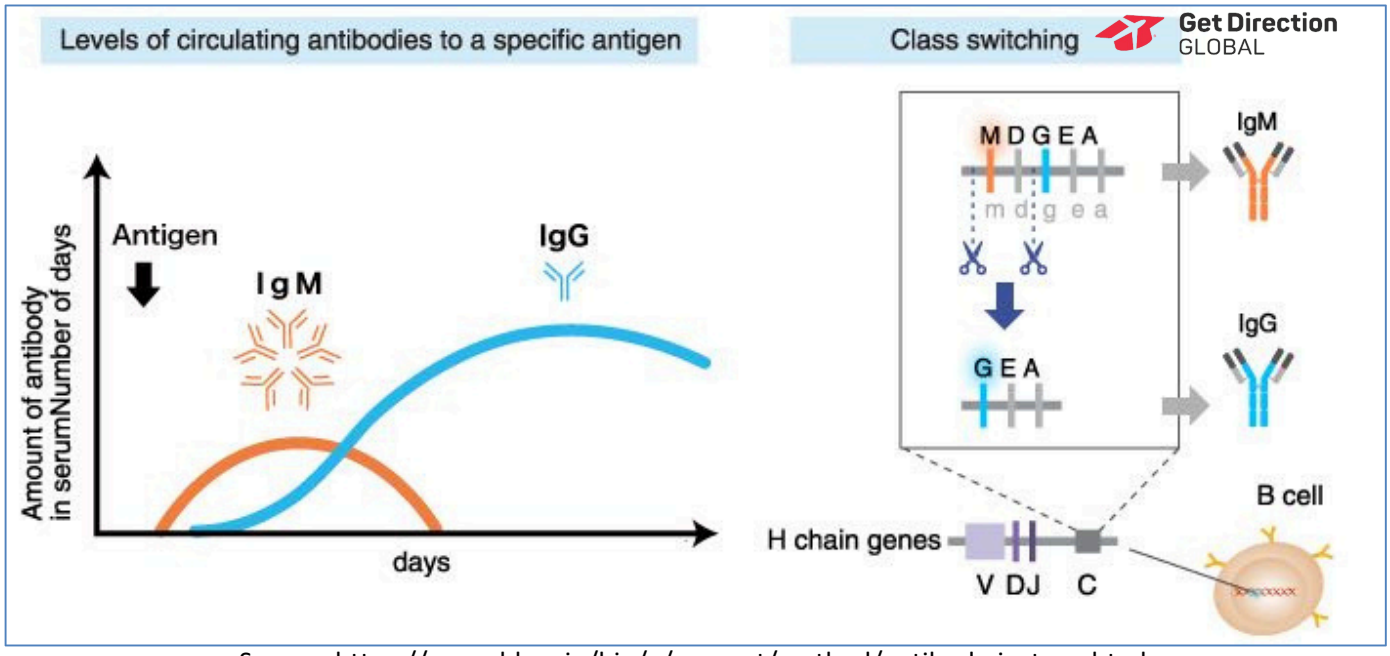


Antibodies specific for nucleic acid modifications: https://www.researchgate.net/figure/Schematic-overview-of-the-organization-and-expression-of-immunoglobulin-Ig-genes_fig1_315756763

§ **Secondary Diversification Mechanisms [B-Cells Only] (In 2o Lymphoid Organs):**

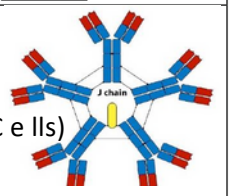
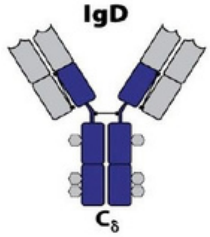
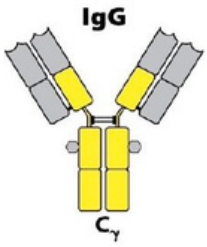
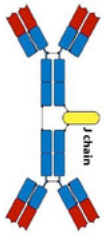
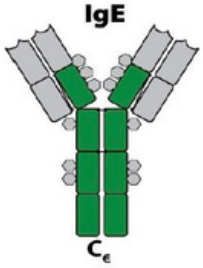
- **Somatic Hypermutation:**
  - o Occurs in Activated B-Cells in Germinal Centres.
  - o – Single Amino-Acid Mutations are introduced into Variable-Region-Genes.
  - o Result = Activated B-Cells with Increased *AND* Decreased Ag-Affinity.
  - o **New Ag-Receptors (BCRs) are tested for Increased Affinity:**
    - § Cells with Receptor Mutations that Decrease Ag-Affinity → Die:
    - § Cells with Receptor Mutations that Increase Ag-Affinity → Survive.
  - o **→→Proliferation of High-Affinity B-Cells**.
  - o **→→↑Ab Affinity**
- **Isotype Switching:**
  - o Occurs in Activated B-Cells in Germinal Centres.
  - o – FC Region-Genes of IgM are Replaced with FC Region-Genes for IgG/IgA/IgE.
  - o **Requires TH1/2-Cell Help:**
    - § **Note:** Cytokines from CD4-TH-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
  - o This change in Ab Constant-Regions → Change in Ab Effector Function.
  - o See Below For Details:

- **'Isotype Switching':**
  - o **IgM & IgD are the *Default* Abs** Expressed on Naive B-Cells (as BCRs)
  - o **IgM** is the 1st Ab-Isotype to be secreted by B-Cells (Plasma Cells)
  - o However, IgM has limited versatility & therefore the body requires different Isotypes of that same Antibody for different effector functions.
  - o ***Activated B-Cells* (Plasma Cells) Undergo *Class-Switching* → Secrete:**
    - § ***IgG1/2/3/4***
    - § ***IgA***
    - § ***IgE***
  - o **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:**TH-Cell Binding Requires CD40(B-Cell):CD40L(T-Cell) Interaction
      - **If the Ag was a *Thymus Dependent Antigen* →**
        - o Th-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* →**
        - o 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-TH-Cells determine which Ab-Class is made.
    - § **Note:Ab Specificity doesn't change**.
  - o **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.

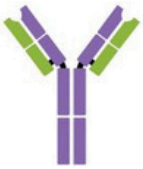
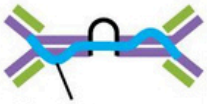
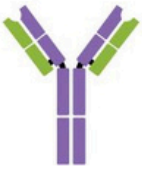


Source: https://ruo.mbl.co.jp/bio/e/support/method/antibody-isotype.html

- **The 5 Isotypes:**

Isotype	Functional Specialisation	Morphology	Picture
IgM	**- 1st Ab Produced in a Primary Humoral Response.** - **Neutralisation** - **Opsonisation of Bacteria** - **Activates Complement Cascade** **- Act as B-Cell Ag-Receptors (BCRs).** - (Serum T1/2 = 10 Days)	- Pentamer (5 Monomers) (M assive M olecule → Relatively Cumbersome) - (N o te : M o n o m e ric o n B -C e lls)	
IgD	**- Act as B-Cell Ag-Receptors (BCRs).** - (Serum T1/2 = 3 Days)	- Monomer	
IgG	**- The Major Serum Ab-Isotype.** **- The 2nd Ab produced in Humoral Response.** **- Responsible for most Ab Reactions.** - **Neutralisation** - **#1 - Opsonisation of Bacteria** - **Activates Complement Cascade** **- The ONLY Isotype in PLACENTAL TRANSFER.** **- Also DIFFUSES into EXTRAVASCULAR SITES.** - 4 Sub-Classes (IgG1, IgG2, IgG3, IgG4) - (Serum T1/2 = 7-21 Days; depending on Sub-Classes)	- Monomer	
IgA	**- The Major Ab in Mucosal Immunity (Secretions)** - Saliva - Tears - GIT - Bile - Colostrum/Breast Milk - Respiratory Tract - Urinary Tract **Functions:** - **Neutralisation** - **Opsonisation of Bacteria** **- Transported Across Epithelium** **- Also DIFFUSES into EXTRAVASCULAR SITES.** - Very Little Found in Plasma. - (T1/2 = 6 Days)	- Dimer (In Secretions) - Monomer OR Dimer (In Serum)	
IgE	**- Major Ab in Allergic Reactions & Inflammation.** **- M ajor Ab in Parasitic Infection.** - Very Little Found in Plasma. - F C-R e g io n b in d s to M a st C e lls → A lle rg y : - Histamine Release - Serotonin Release - Other Vasoactive Amines - (Serum T1/2 = 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			 Secretory component		
Heavy chains	γ	μ	α	δ	ε
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.

Antigen Receptors (on B & T-Lymphocytes):

- Lymphocytes become *Immunocompetent* BEFORE meeting their antigens. (Ie: 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.

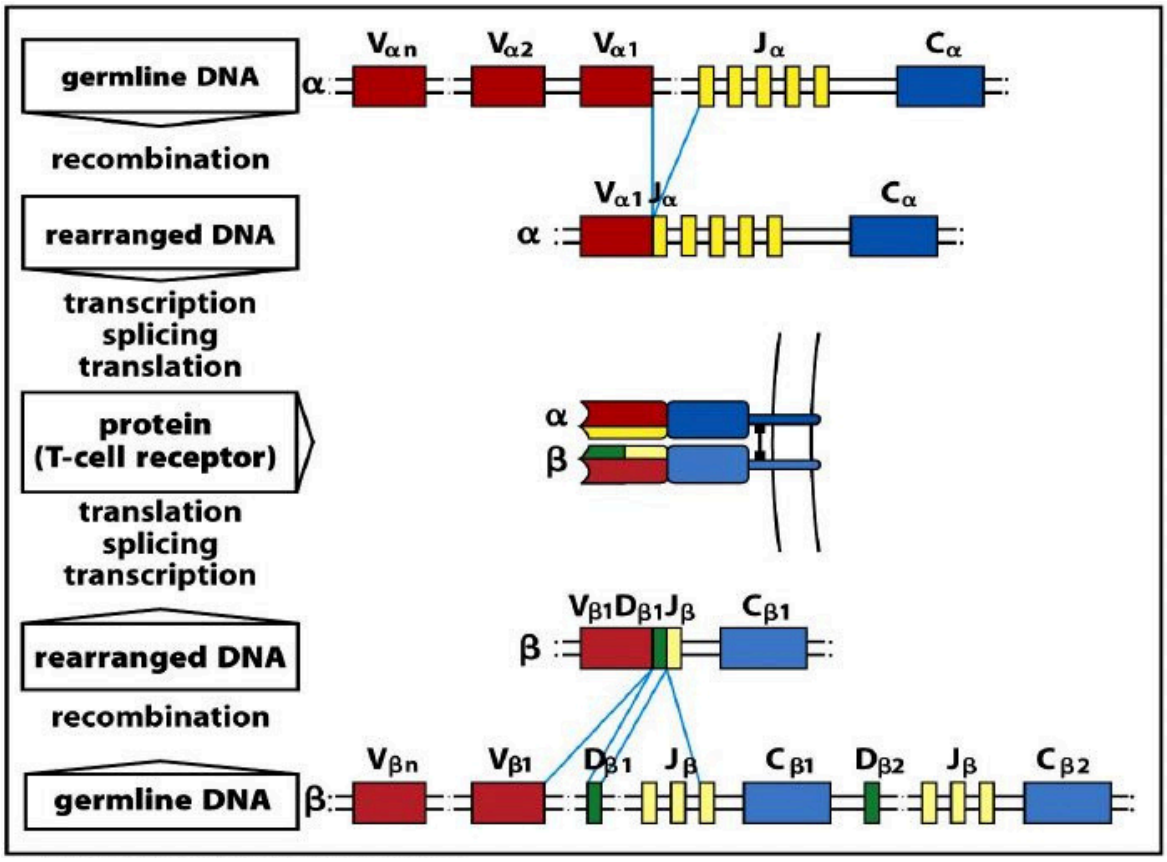
(Note:TCRs = T-CellAntigen Receptors; BCRs = B-CellAntigen Receptors)

- **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 1oLymphoid Organs – BM & Thymus):**
    - § **Ag-Receptor Gene Rearrangement (Ig-Gene (B-Cells); TCR-Gene (T-Cells)):**
      - **1st: 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 β-Chain in TCRs.
      - **2nd: 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 α-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):**
  - (Ie: 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 ↑&↓ Ag-Affinity.
    - **New Ag-Receptors (BCRs) are tested for Increased Affinity:**
      - Cells with Receptor Mutations that ↓Ag-Affinity → Die:
      - Cells with Receptor Mutations that ↑Ag-Affinity → Survive.
    - **→→Proliferation of *High-Affinity* B-Cells**.
  - **Ig-Class Switching:**
    - – FC Region-Genes of IgM are Replaced with FC Region-Genes for IgG/IgA/IgE.
    - **Requires TH1/2-Cell Help:**

Note: Cytokines from CD4-TH-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)

- **→→This change in Ab Constant-Regions → Change in Ab Effector Function**.
- **Note:** This doesn't affect Ab-Affinity.
- See *'Isotype Switching'* in the Antibody section For Details.

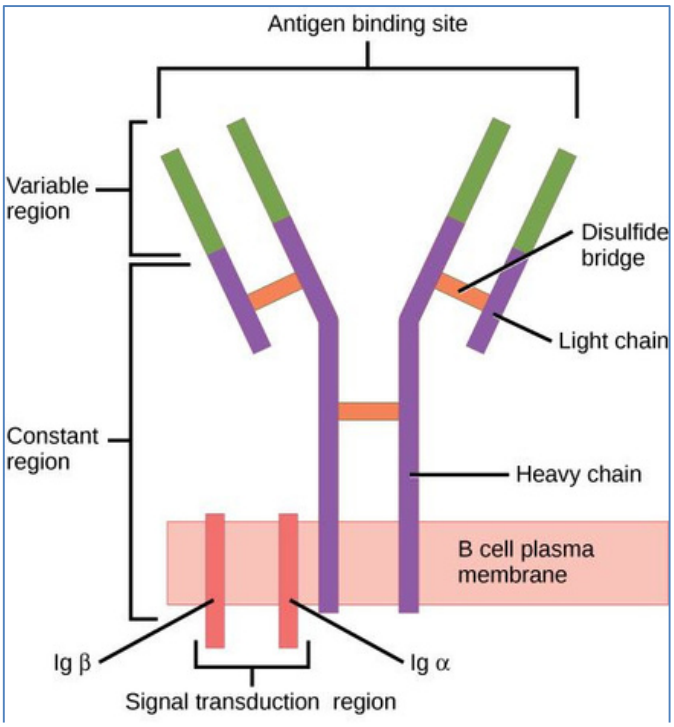
- **BCRs (B-Cell Receptors):**
  - o **Morphology:**
    - § **BCRs are Surface-Bound Antibodies** (Either IgM(Monomeric) or IgG)**:**
      - **Immunoglobulin-Like-Structure:**
        - o Have a Pair of **Heavy Chains** & a Pair of **Light Chains**
        - o Each chain has a **Variable** and **Constant** region.
      - **BCR Isotypes:**
        - o Naive B-Cells express IgM & IgD –Type BCRs.

  - o **Functional Regions:**
    - § **Variable Region (Fab):**
      - BCRs (like Antibodies) Bind Whole Antigen Directly. (As opposed to TCRs which only recognise processed peptide presented on MHCs).
    - § **Constant Region (FC):**
      - Signal Transduction once bound to Ag.
      - Internalisation of Ag for Processing & Presentation on MHC-II.

  - o **Antigen Binding Sites** (Same for Abs)**:**
    - § = the Variable Regions of partnered Heavy & Light Chains (VH & VL).
    - § Within these Variable Regions are Ag-Specific ***Complemtarity-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.

  - o **Generation of Ag-Receptor Diversity:**
    - § **(In 1o-Lymphoid Organ - Bone Marrow)**
    - §
      - Antigen-Receptor Gene Rearrangement

      (In 2o-Lymphoid Organs – Lymph Nodes/Spleen)
      - Somatic Hypermutation
      - Ig-Isotype Switching



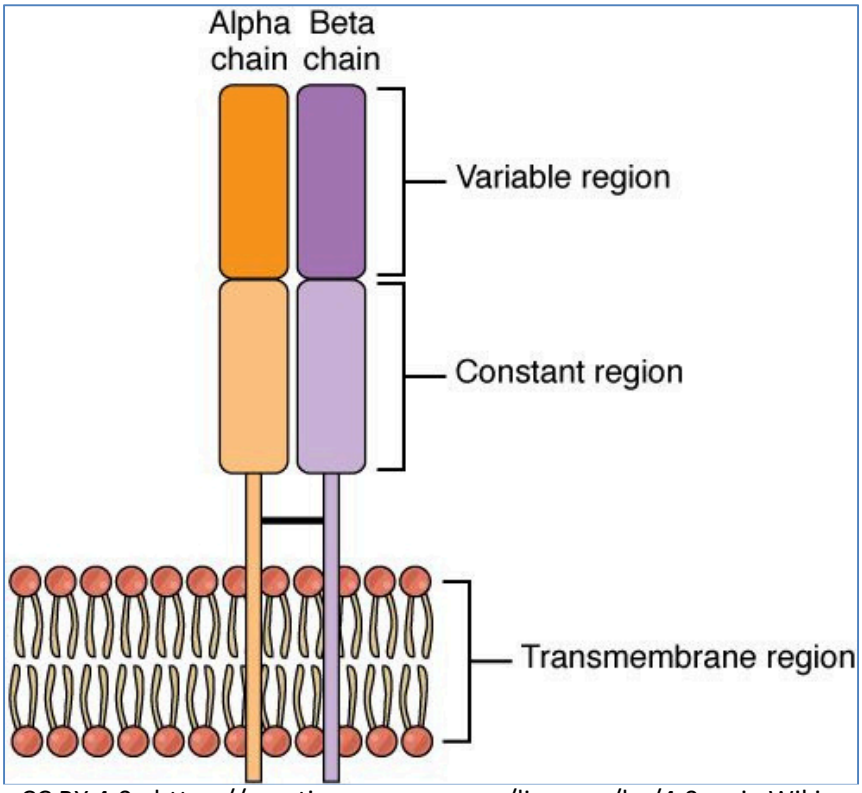
- **TCRs (T-Cell Receptors):**
  - **Morphology:**
    - Are Membrane-Bound ***Heterodimer*** Receptors that **Resemble Antigen Binding Sites on Abs:**
    - ***Heterodimer* =** Has a Pair of Chains (**Either α-β or γ-δ**) depending on T-Cell Lineage.
      - *** αβ T-Cells Predominate** → CD4 (helper & regulatory) or CD8 T-Cells.
      - **γδ 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 αβ 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 (Fab):**
      - **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 (FC):**
      - Signal Transduction once bound to Ag.

  - **Antigen Binding Sites** (Same for Abs)**:**
    - = the Variable Regions of partnered αβ- or γδ-Chains
      - **αβ-Chains → Recognise Processed Peptide on MHC-I/II**.
      - **γδ-Chains → Recognise Whole Antigen** (Similar to cells of Innate Immune System)

  - **Generation of Ag-Receptor Diversity:**
    - **(In 1o-Lymphoid Organ - Thymus)**
      - Antigen-Receptor Gene Rearrangement

    (NO Ig-Isotype Switching.)



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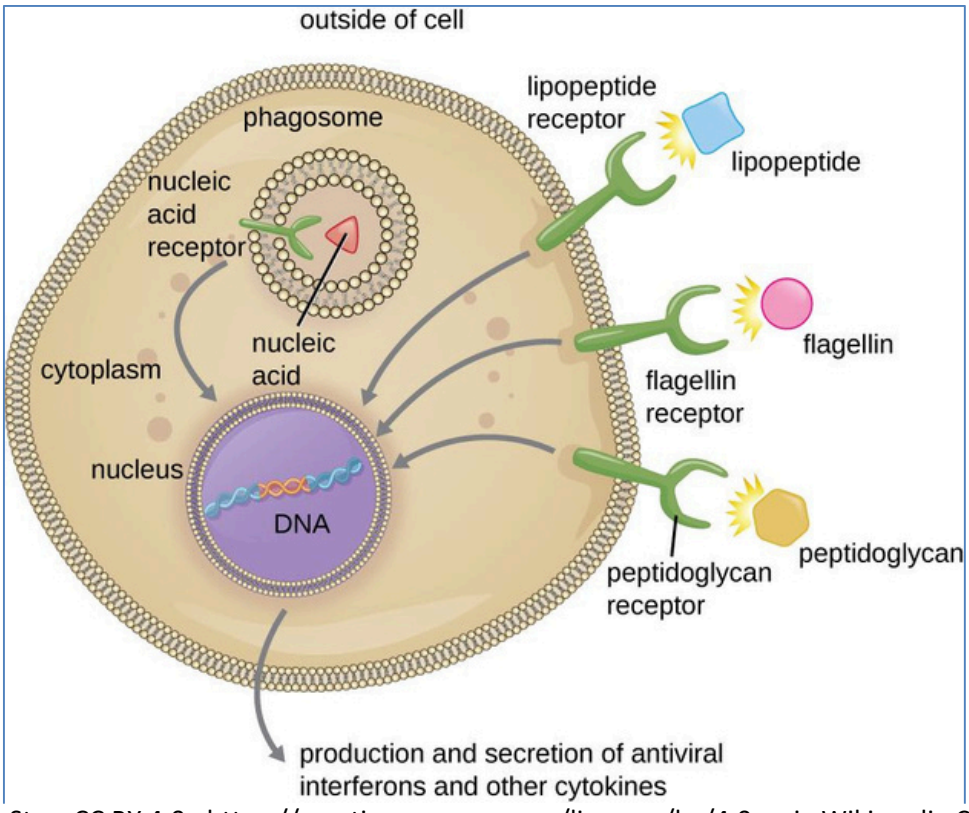
PAM Ps – Pathogen Associated M olecular Patterns:

- **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:

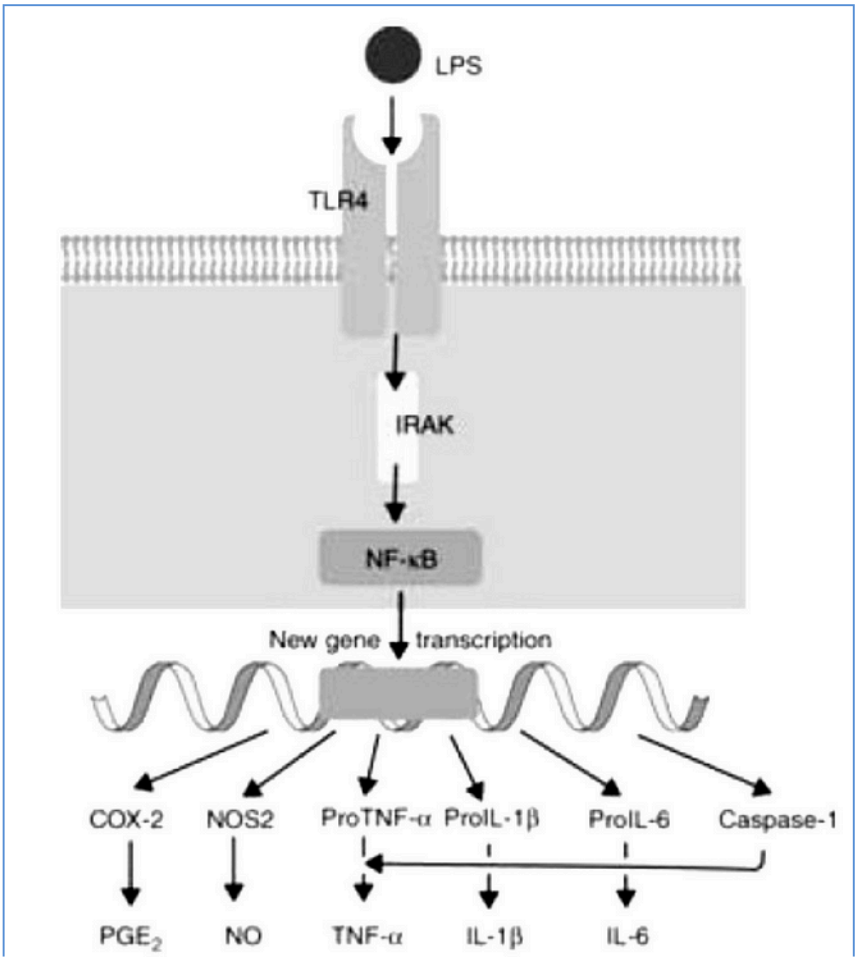
- **A Class of *Pattern-Recognition Receptors* that play a key role in the *Innate Immune System* by recognising PAM Ps on M icrobes.**
- There are ~15 different TLRs Primarily **Expressed on Antigen-Presenting Cells** (Dendritic Cells, Macrophages, & B-Lymphocytes).
- **Different TLRs can recognise 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 (*T. cruzi*) 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

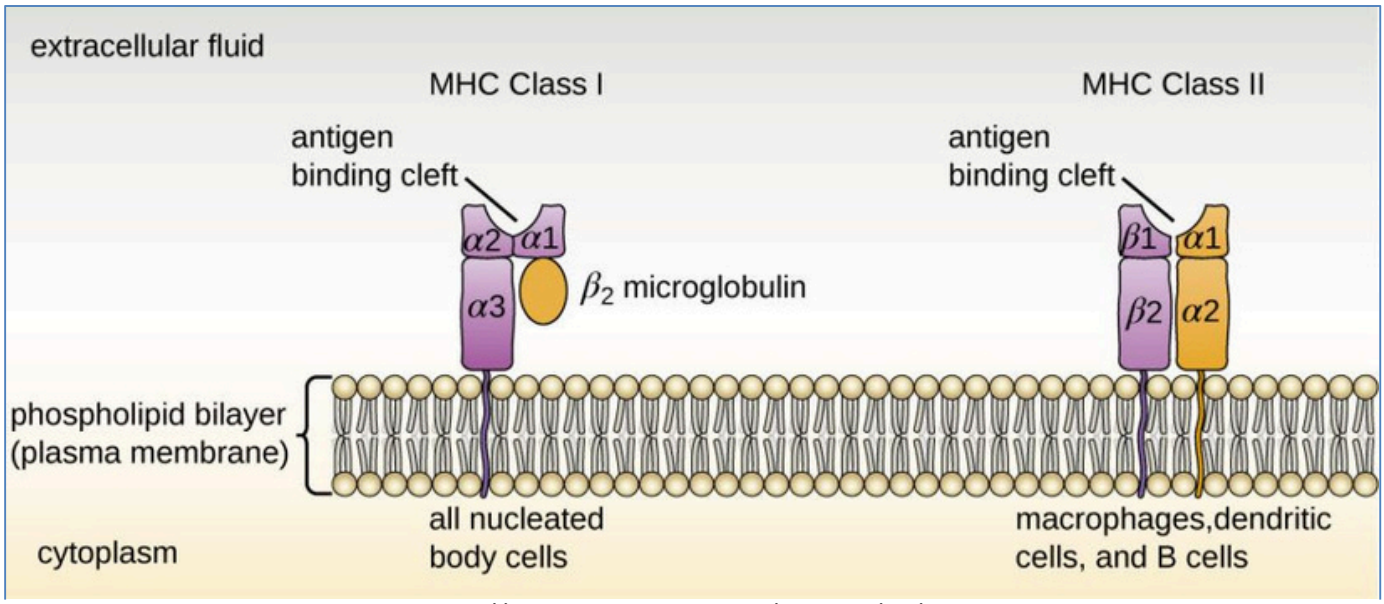


MAJOR HISTOCOMPATABILITY COMPLEXES

MHCs (Self-Antigens)

- **Note: T-Cells can only recognise Ag when it is bound to Compatible MHC Molecules. (Not free Ag).**
  - **Therefore, MHC's Main Function = To *Enable T-Cells* to recognise Antigen.**

- **What is MHC?**
  - **MHC is also known as HLA ("Human Leucocyte Antigens")**
  - **Both MHC Classes are encoded by MHC Genes Located on the Short Arm of Chromosome 6.**
  - **Are Cell Surface GlycoProteins – Ie: "Self Antigens":**
    - High diversity of MHC throughout the population
      - (Ie: Different people have different 'Self-Antigens')
      - – The Basis of Transplant Rejection.
    - Note: Identical twins have the same MHC's.
  - **Molecular Structure:**
    - **Structure of MHC-I:**
      - 2 Polypeptide chains
      - Note: One of the chains contains a **β2 Microglobulin** which *Isn't* coded by MHC genes.
      - Only has 1x Intracellular Domain
    - **Structure of MHC-II:**
      - 2 Polypeptide Chains
      - Both domains of MHC-II are encoded by MHC Genes.
      - Has 2x Intracellular Domains



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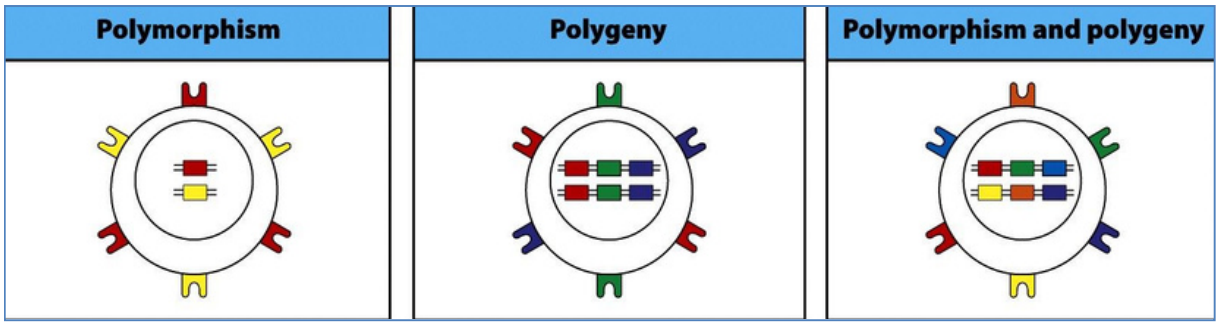
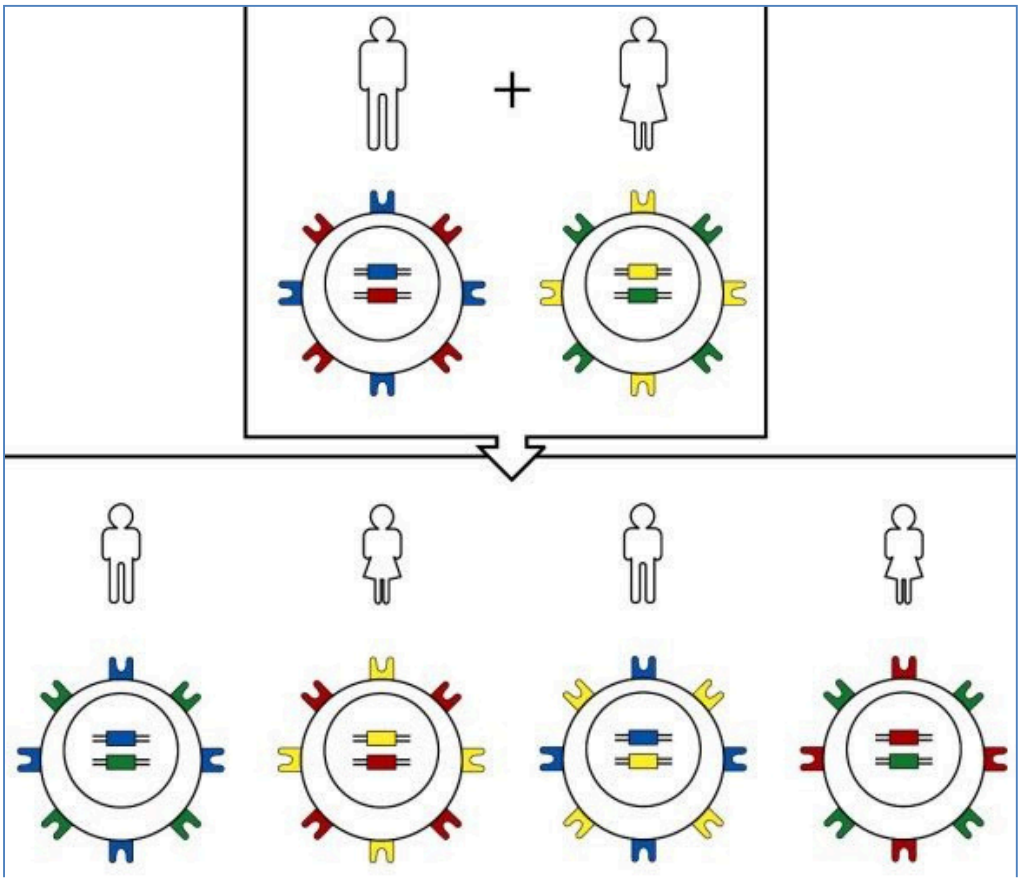
- **MHC Diversity – Due to *Polygeny & Polymorphism*:**
  - **Polygeny:**
    - **There are Several Different Class I & II Genes throughout the population that seem to have the sam e functions**.
      - **Note:** Each of the genes have different locations on Chromosome 6.
    - **There are 3x Class-I Genes:**
      - **HLA-A**
      - **HLA-B**
      - **HLA-C**
    - **There are 3x Class-II Genes:**
      - **HLA-DR**
      - **HLA-DP**
      - **HLA-DQ**
  - **Polymorphism:**
    - There are hundreds of Alleles of the above genes dispersed throughout the population.
    - Note: Expression of MHC Genes is ***Codominant*** (Ie: People are usually Heterozygous for different MHC alleles – and Express BOTH)



Source: Unattributable

- **M HCs Are Rem arkably Sim ilar Am ongst 1st-D egree Relatives**. **W hy?**
  - **MHC Haplotypes – Linked sets of MHC Genes**, which are located at *Multiple Loci* on a single Chromosome, but are *close enough together* that they are *Inherited Together* as a Package.
  - Ie: Haplotypes are too close together to be subject to Meiotic 'Cross-Over' (or *'Synapsis'*).



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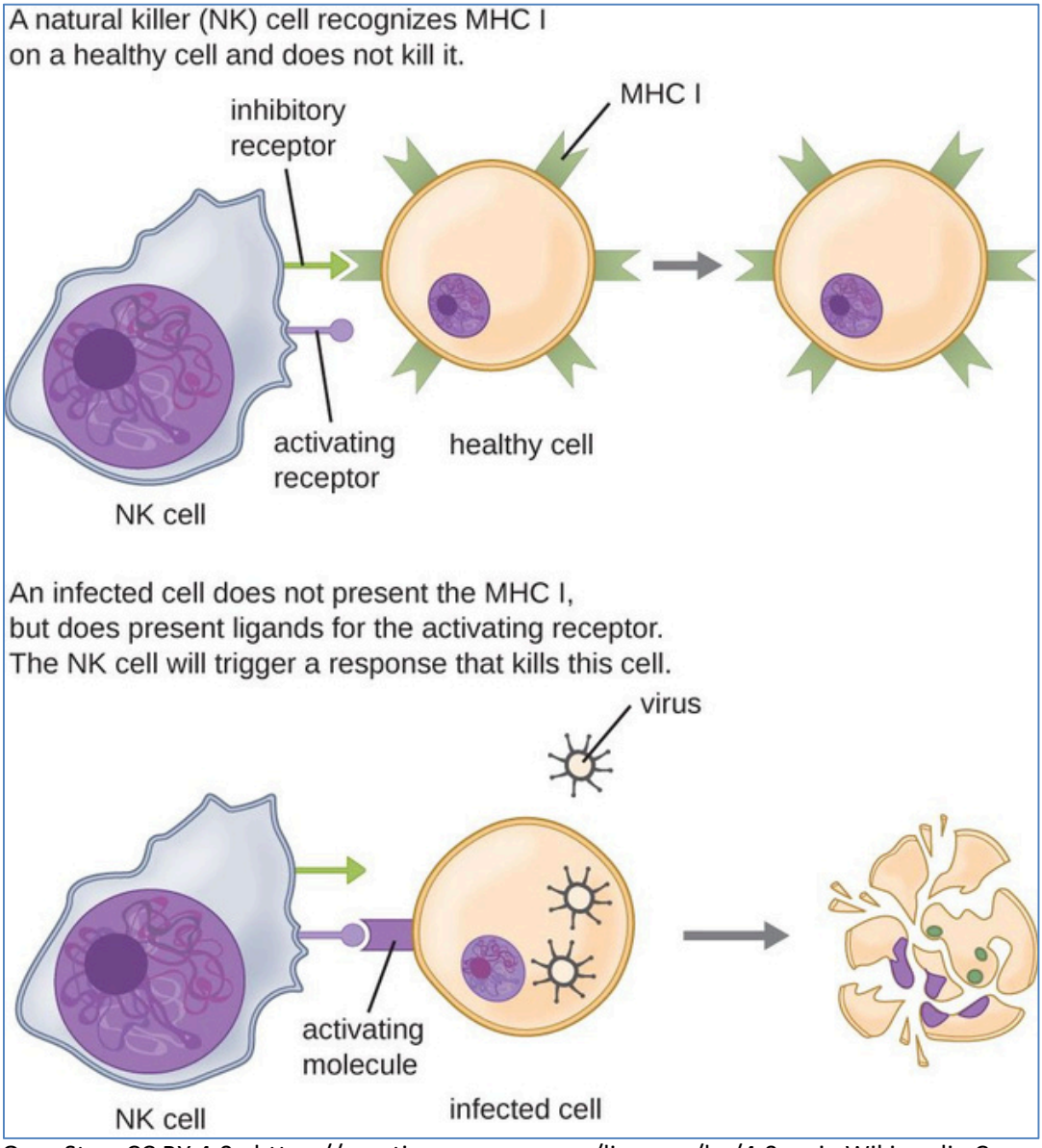
- **Important Classes of MHCs & Their Specific Functions:**
  - o ***Class-I-MHCs:**
    - § **Found on ALL Nucleated Cells & APCs. (These are the 'Self-Antigens')**
    - § • Note: Not Expressed on Red Blood Cells
    - § **- allow Positive & Negative Selection of CD8-T-Cells [in the Thymus].**
    - § **- allow APCs to Present Viral/Cancer Peptides to Cytotoxic T-Cells.**

      - allow Virally-Infected/Cancerous cells to be *Targeted & Killed* by Cytotoxic T-Cells



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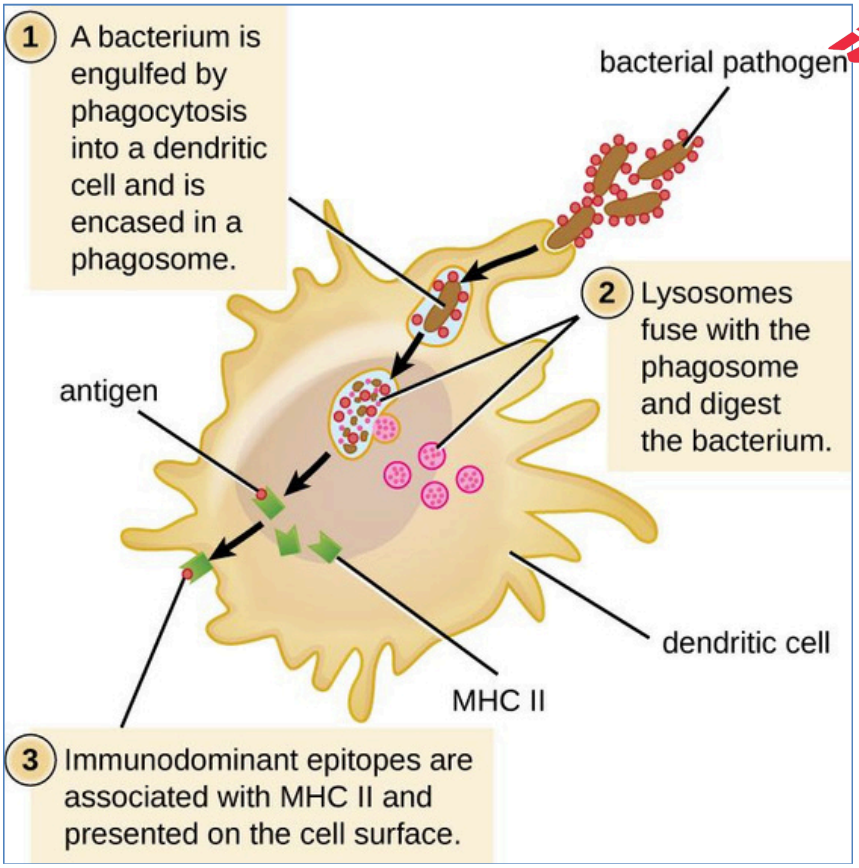
  - o ***Class-II-MHCs:**
    - § **Found ONLY on APCs & Semi-Active Macrophages & Semi-Active B-Cells.**
    - § • Note: Not Expressed on Red Blood Cells
    - § **- allow Positive & Negative Selection of CD4-T-Cells [in the Thymus].**
    - § **- allow APCs to Present Antigen to Naive TH-Cells → Activates TH-Cells to → Effector Cells.**
    - § **- allow Partially-Activated Macrophages to *Request TH-Cell Help* → More Phagocytic.**

      - allow Partially-Activated B-Cells to *Request TH-Cell Help* → Fully Active B-Cells → Ab's.



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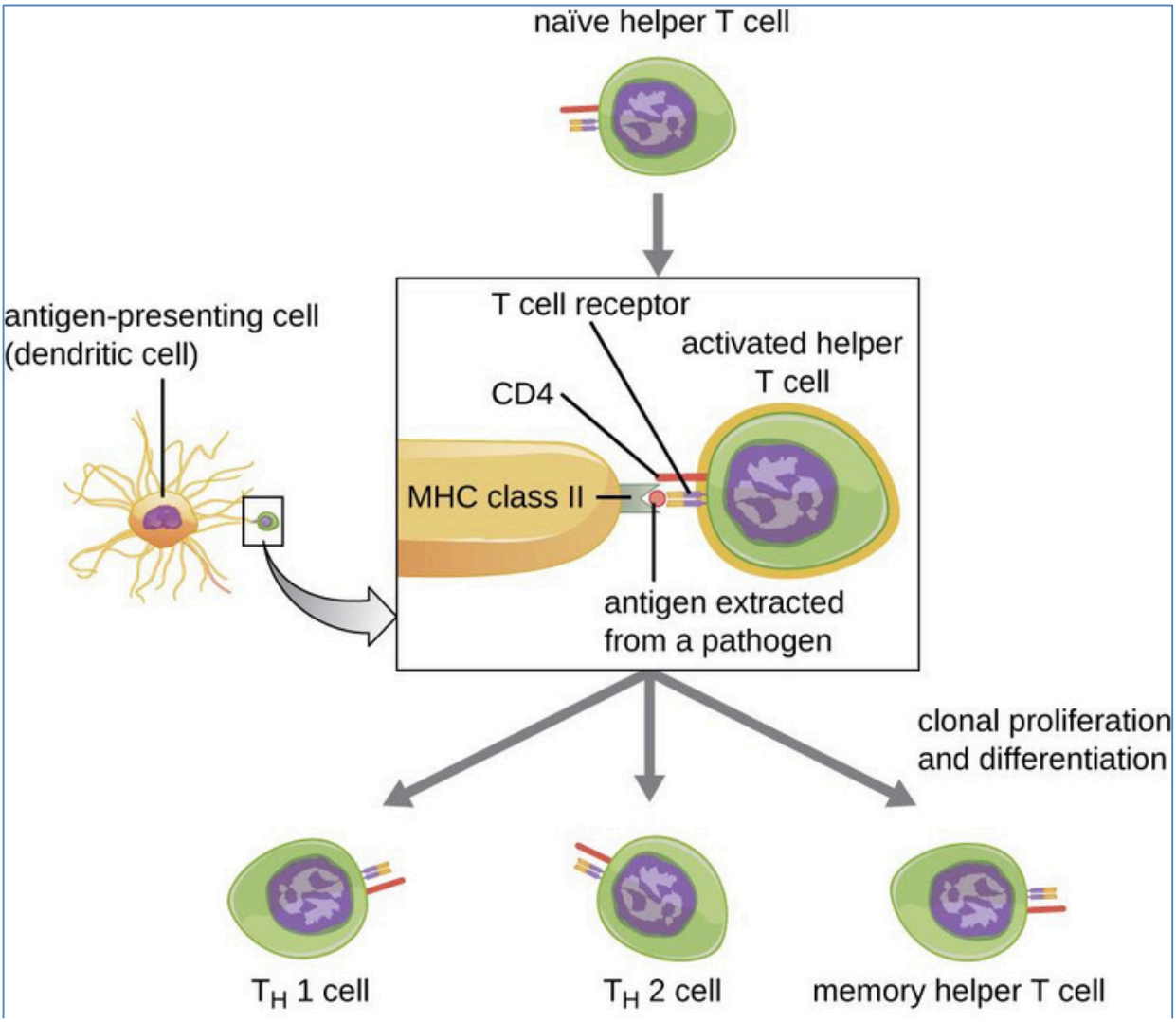

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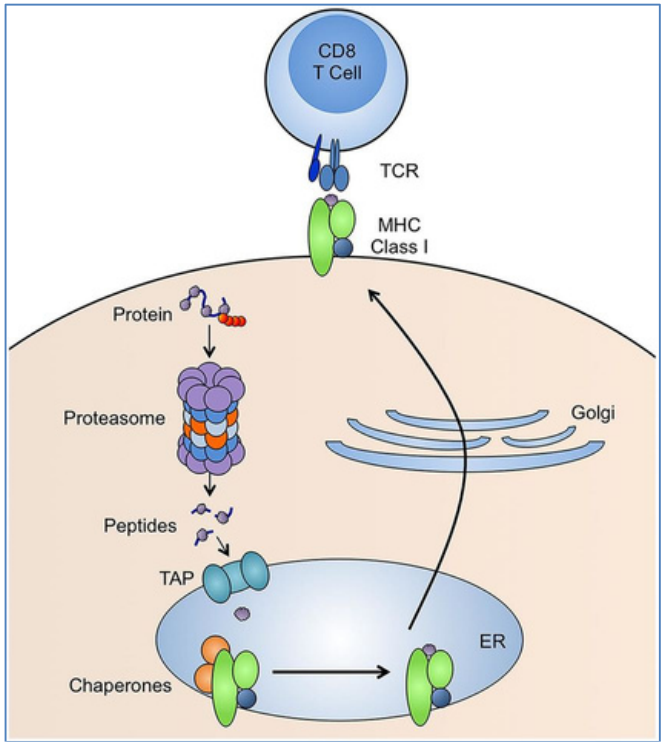
- **Summary of MHC Functions:**
  - **Facilitate Antigen Presentation by APCs to T-Cells. (CD4 & CD8 – Depending on MHC Class):**
    - **[In the Thymus] APCs → Facilitate Positive & Negative Selection of CD4 & CD8 T-Cells.**
    - **[Outside Thymus]APCs→Alert Corresponding CD4 & CD8 T-Cells to the Presence of Antigen**
    - **Remember:** T-Cell Specificity is *Genetically Determined* & therefore, Presentation of Ag to T-Cells only really *Alerts* the Relevant T-Cells to the *Presence* of Ag, and stimulates them to becom e Effector T-Cells. (Ie: APCs don't *"Sensitise*" T-Cells to Antigen, they just *Alert* them)
  - **Allow Partially-Activated Macrophages to *Request TH-Cell Help*:**
    - TH-Cells help Macrophages to Become Fully Active → More Phagocytic.
  - **Allow Partially-Activated B-Cells to *Request TH-Cell Help*:**
    - TH-Cells help B-Cells → B-Cells Become Fully Activated → Secrete Antibodies.
  - **Allow Virally-Infected/Cancerous somatic cells to be *Targeted & Killed* by TC-Cells:**
    - TC-Cells recognise pMHC-I presented on virally-infected/cancerous cells → Kill Cells.

- **The 2 Mechanisms of Attaching Peptide to MHC and Delivering it to the Surface:**
  - **Peptide Presentation by MHC-I:**
    - **Antigens presented on MHC-I are typically *Endogenous*** (Ie: Are synthesized within the cell), and are often the result of Viral-Infection/Genetic Mutation/Cancer.
      - - Allows TC-Cells to recognise "*Altered Cells*" and target them for destruction.
    - **Antigen Proteins Must First be Broken Down into Peptides:**
      - **How? – By *Proteasomes* = Proteolytic structures in the Cytosol which Degrade--:**
        - Defective Ribosomal Products (DRiPs)
        - Old Cytosolic Proteins
        - Viral Proteins
        - Cancer/Mutated Proteins.
    - **Peptide Fragments are Loaded onto MHC-I *Inside the Endoplasmic Reticulum*.**
      - Therefore, *Cytosolic* Peptide Fragments must be *Transported* into the ER.
      - **How? – By "*TAP*" Transporters in ER Membrane:**
        - TAP Transporters → Carry Peptides from the Cytosol to the ER.

      '*Chaperone Proteins*' are important in loading Peptide onto MHC-I:
        - Peptide Fragments freely bind to MHC-I in the ER.
    - **pMHC-I is then sent to the Surface where it will interact with CD8-TC-Cells.**
    - **Note: Viruses can block many of the above stages to prevent pMHC-I Presentation.**
    - **Note: Defects in TAP can also prevent pMHC-I Presentation.**

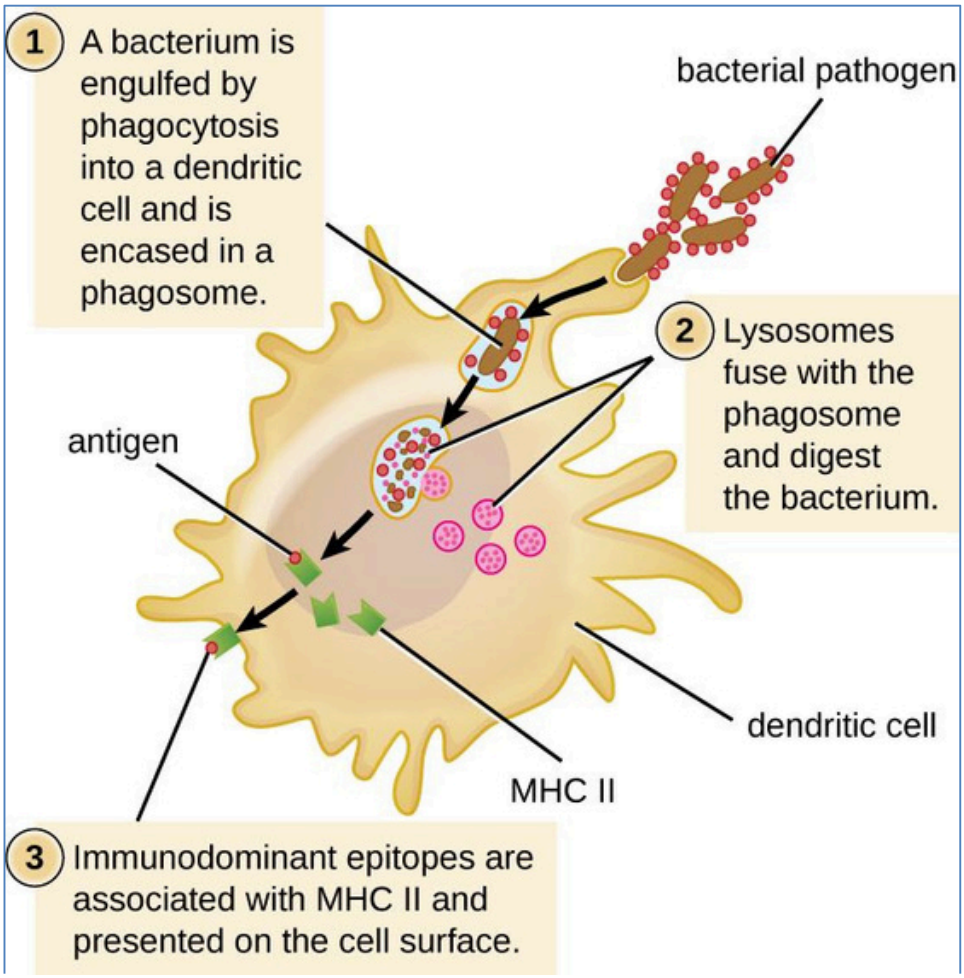


The Immunoproteasome and Viral Infection: https://www.researchgate.net/figure/MHC-class-I-antigen-presentation-pathway-Proteins-with-ubiquitin-tags-red-spheres-are_fig2_272512098

- **Peptide Presentation by MHC-II:**
  - **Antigens presented on MHC-II are typically *Exogenous*** (Ie: From extracellular pathogens), which have been phagocytosed and degraded into peptide fragments.
    - - Allows new/novel antigens to be presented to the immune system.
    - - However, it requires an Acidic Environment.
  - **Antigen Proteins Must First be Broken Down into Peptides:**
    - **How? – By Acid in Phagolysosomes:**
      - Any Extracellular Antigen is Phagocytosed into an Phagosome.
      - The Phagosome is then Fused with an Acid-Filled Lysosome.
      - Acid in the resultant Phagolysosome Denatures Protein and Activates Proteases.
      - Antigen is broken down into Peptide Fragments.
    - **Q: So How does MHC-II Protect Itself in a Low pH Environment?:**
      - **A: By associating with a "*Class-II-associated Invariant Chain Peptide*"(CLIP):**
        - **Note:** Really Crappy Acronym (*Invariant Chain = 'LI'*)

      Functions of the '*Invariant Chain*' (CLIP):
        - **1)** Blocks the Peptide-Binding-Groove on MHC while inside the ER & also during exogenous protein-degradation in Acidic Lysosomes.
        - **2)** Targets the Delivery of MHC to *Acidic Lysosomes* (Ie: Prevents MHC binding to peptide in non-phagocytic compartments)
  - **Peptide Fragments are Loaded onto MHC-I *Inside the Endocytic Vesicles*:**
    - **Note:** There will be Many Different Peptides of the same Antigen in a single
    - Lysosome.

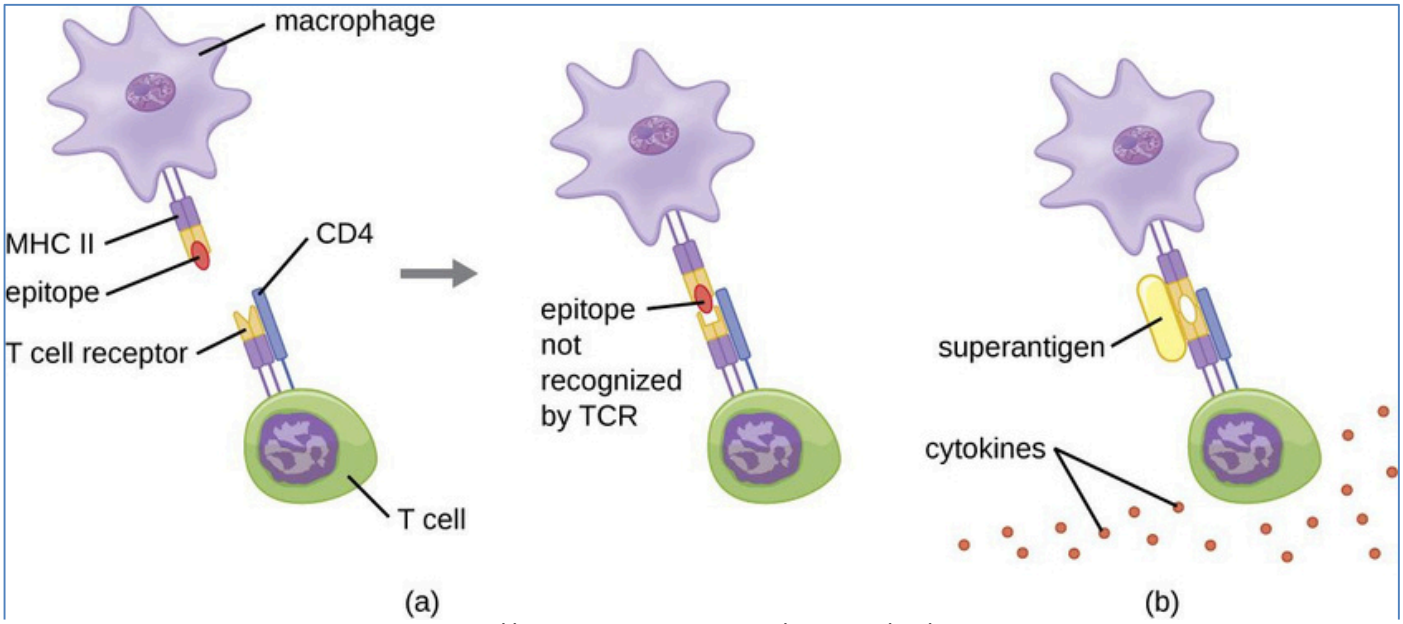
    HLA-DM Molecules (which are also present in lysosomes) are **activated by Low pH** → and **releases CLIP** from M H C-II → Allow s *Antigenic Peptides* to bind.
  - **pMHC-II is then Sent to the Surface where it will interact with CD4-TH-Cells**.



W hat is "M HC Restriction"?:

- o **T-Cell Antigen Recognition is "MHC-Restricted" Meaning:**
  - § A T-Cell Receptor (TCR) will only bind to a Peptide-MHC Complex on 2 Conditions:
    - **1)** The MHC Molecule is Compatible
    - **2)** The Peptide displayed is Specific to that TCR.
- o **Note: Some Pathogens Disable MHC Restriction by Production of *Superantigens***.
  - § Leads to→ Inappropriate activation of Non-Specific T-Cells→ Maladaptive Immune Response

- ***"Superantigens"*:**
  - o **Bacterial or Viral Antigens that *Non-Specifically* activate T-Cells *Without being Processed by APCs***.
    - § **Ie: They are able to facilitate TCR-MHC interaction without satisfying *either criteria* for C o m p a tib ility :**
      - **1)** The MHC Molecule doesn't need to be Compatible with the TCR.
      - **2)** The Peptide displayed on MHC doesn't need to be Specific to that TCR.
  - o **Note:** Bacterial Superantigens are free in plasma; Whereas Viral Superantigens are Membrane-Bound.
  - o **Resulting T-Cell responses are *Non-Specific* & are therefore *Maladaptive* for host but *Helpful* to the Pathogen**.
    - § **Since T-Cell activation is non-specific, it activates a *HUGE* number of T-Cells → Produce Cytokines**.
    - § **↑↑↑Excess Cytokines can lead to → Cytokine Toxicity. AKA: "*Cytokine Storm*", which can lead to → *"Toxic Shock Syndrome"*:**
      - ↓BP (& Postural Hypotension)
      - Tachycardia
      - Fever
      - Myalgia
      - Dizziness
      - Rash
    - § **Treatment of Toxic Shock Syndrome:**
      - Aggressive Symptomatic Treatment
      - Aggressive Antibiotics/Antivirals for the Pathogen.



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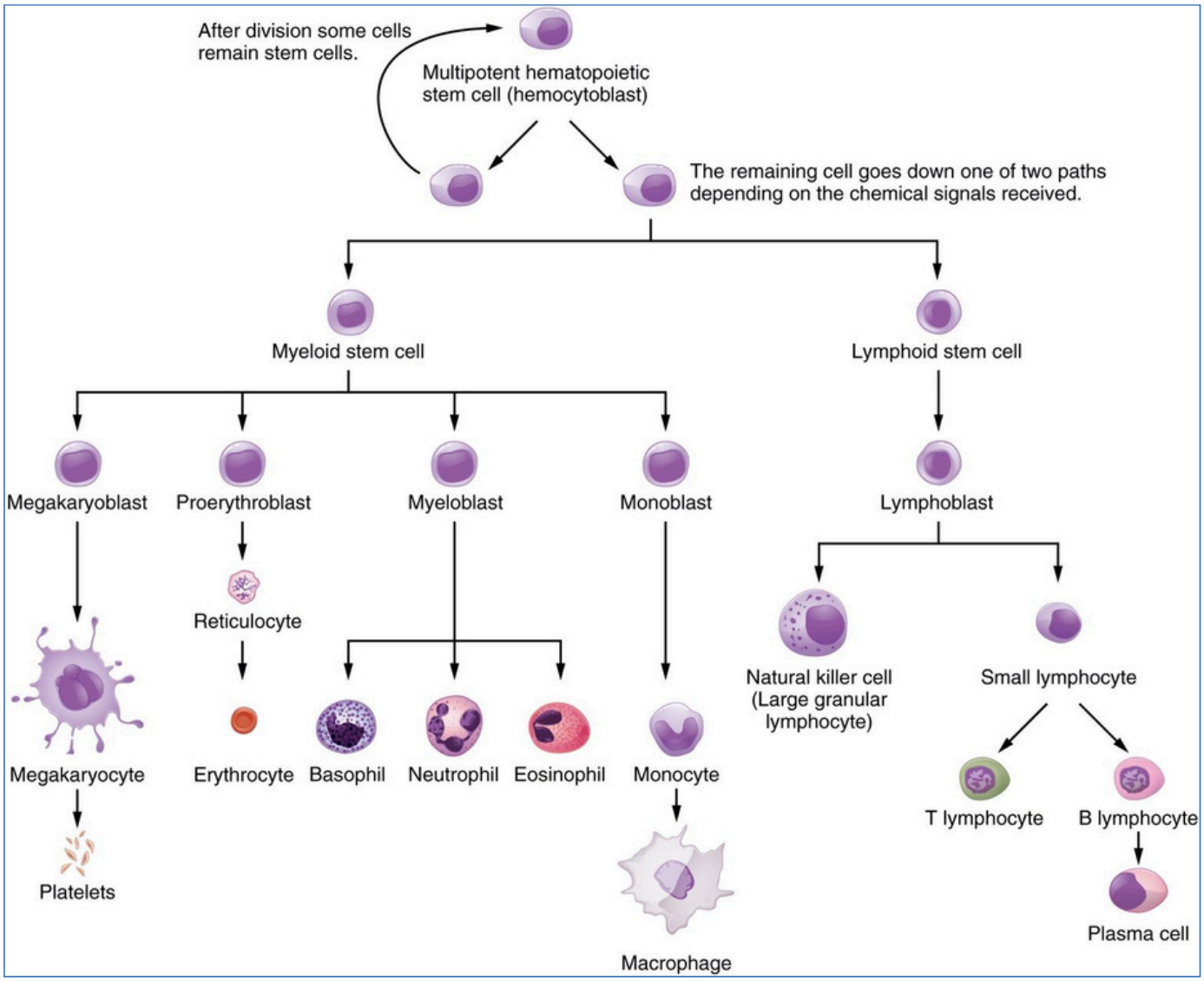
CELLS OF THE IMMUNE SYSTEM

The Cells of the Immune System Derive from Precursors in the Bone Marrow:



Blood Cell Counts:

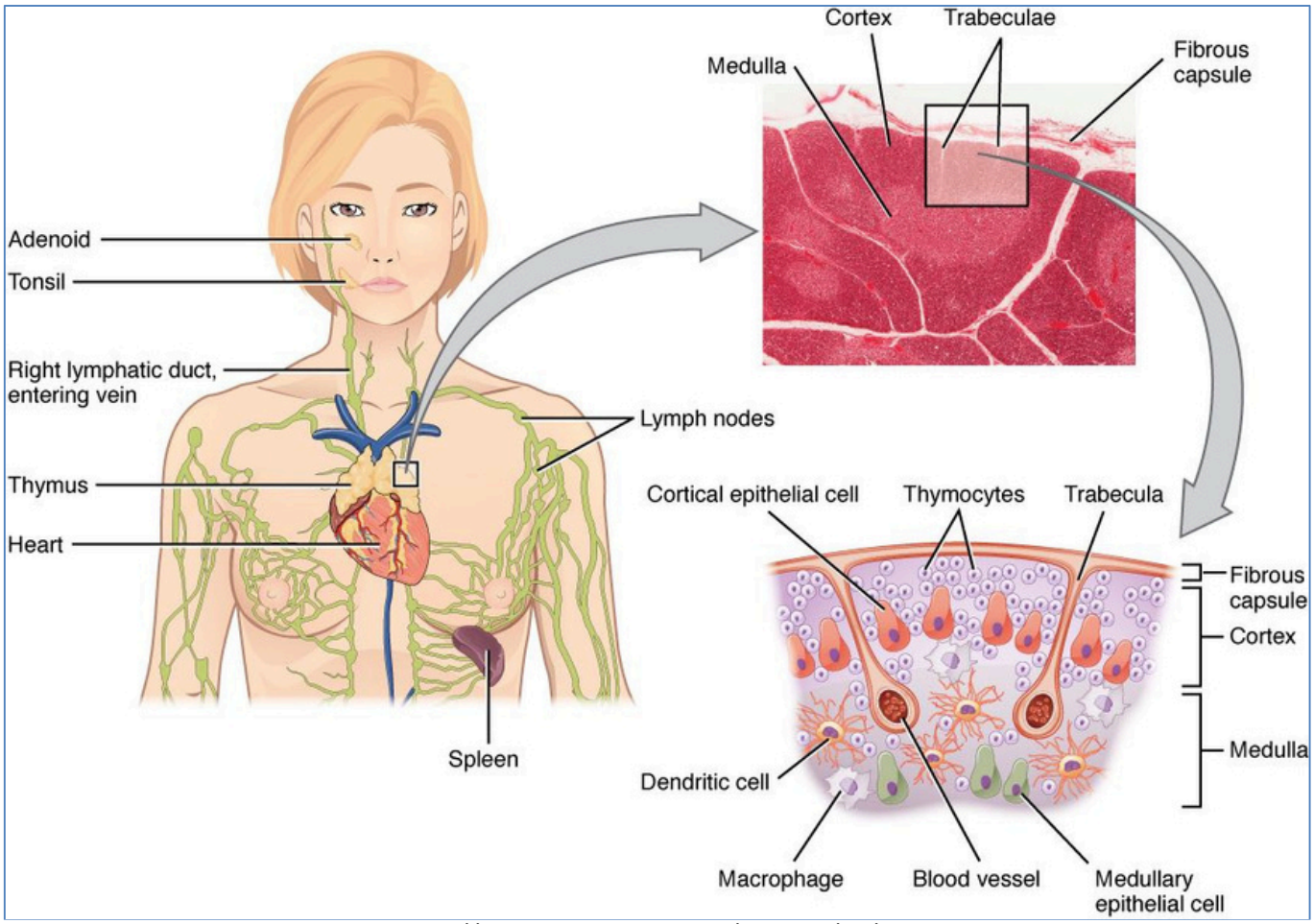
Cell type		Normal range / L	Percentage
Polymorphonuclear Leucocytes (Granulocytes)			
	Neutorphils	2.5 - 7.5 x 10^9/L	40 -75%
	Eosinophils	0.04 - 0.4 x 10^9/L	1 - 6%
	Basophils	0.01 - 0.1 x 10^9/L	0 -1%
Mononuclear Cells			
	Monocytes	0.2 - 0.8 x 10^9/L	2 -10%
	Lymphocytes	1.0 - 3.5 x 10^9/L	20 - 45%

In 2009 final year exam 30% of students given a blood report in cells/litre could not work out the concentration in cells/ml

Lymphoid Organs:

- **Lymphoid Tissue in General:** Composed of a type of loose Conn.Tissue called Reticular Connective Tissue. Macrophages live on the fibres of the Reticular Network, and huge numbers of Lymphocytes reside Temporarily in the spaces amongst the Reticular Network.
    - o **Note: Lymphocytes are constantly circulating between the Blood Vessels, the Lymphatic System & Lymphoid Tissues** to ensure that they are readily available to attend to infected/damaged sites quickly. For more on lymphocyte circulation, see **"Cell Adhesion Molecules"**.

- **1- Primary Lymphoid Organs:** Lymphoid organs where Lymphocytes (B&T) Develop & Mature (Ie: Become Immunocompetent). 'Immunocompetent' lymphocytes display specific Antigen Receptors on their surfaces, enabling them to recognise & bind to ONE specific antigen.
    - o **Sites of Lymphocyte Maturation:**
        - § **Red Bone Marrow:** ***Site of B-Cell Maturation***
        - § **Thymus:** ***Site of T-Cell Maturation***.
    - o **Basics of Immunocompetence (Maturation)** =
        - § **1-** T/B-Cell must be able to bind MHCs, since it is on these MHCs that Antigens are presented
        - § to it for recognition.
          & 2. The T/B-Cell must not react strongly to Self-Antigens normally found in the body. Developing T-Cells that don't fit these criteria are eliminated via Apoptosis.



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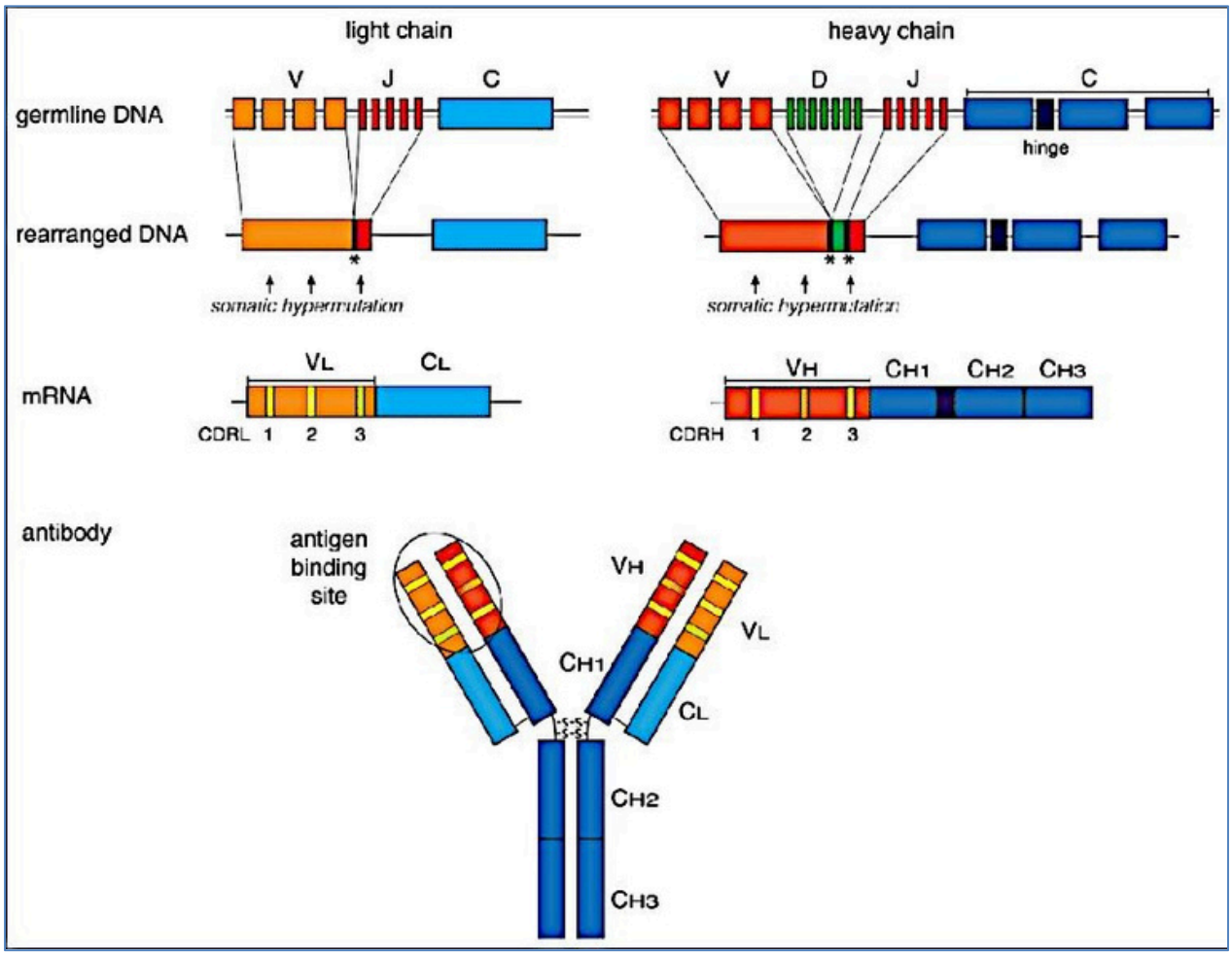
- **2- Secondary Lymphoid Organs:** (All other Lymphoid organs) - Those in which Naive Lymphocytes (mature, but virgin) encounter Antigens for the first time & are stimulated to become Effector & Memory Cells:
    - o **Lymph Nodes**
    - o **Spleen**
    - o **Mucosa-Associated Lymphoid Tissue (MALT)**
    - o **Tonsils**
    - o **Peyer's Patches (Liver)**
    - o **Adenoids**
    - o **Skin**

Lymphocyte Development & Activation:

- **Note: All Lymphoid Cells (B-Cells/T-Cells/NK-Cells) are derived from Lymphoid Progenitors in Bone Marrow**.
  - o **B-Cell Precursors -** *stay in Bone-Marrow*, where they become Mature, Naive B-Cells.
  - o **T-Cell Precursors -** *migrate to the Thymus*, where they become Mature, Naive T-Cells.
- **B-Cell Development:**
  - o **B-Cell Precursors in BM Receive Signals from BM-Stromal Cells → Triggers B-Cell Development:**
  - o **- In Bone Marrow:**
    - § **Step 1 – Ig(& BCR)-Gene Rearrangement:**
      - **1- 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.
      - **2- 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.
      - **Note: Important Enzymes Involved:**
        - o **RAG-1 Recombinase**
        - o **RAG-2 Recombinase**
        - o **Ligases**

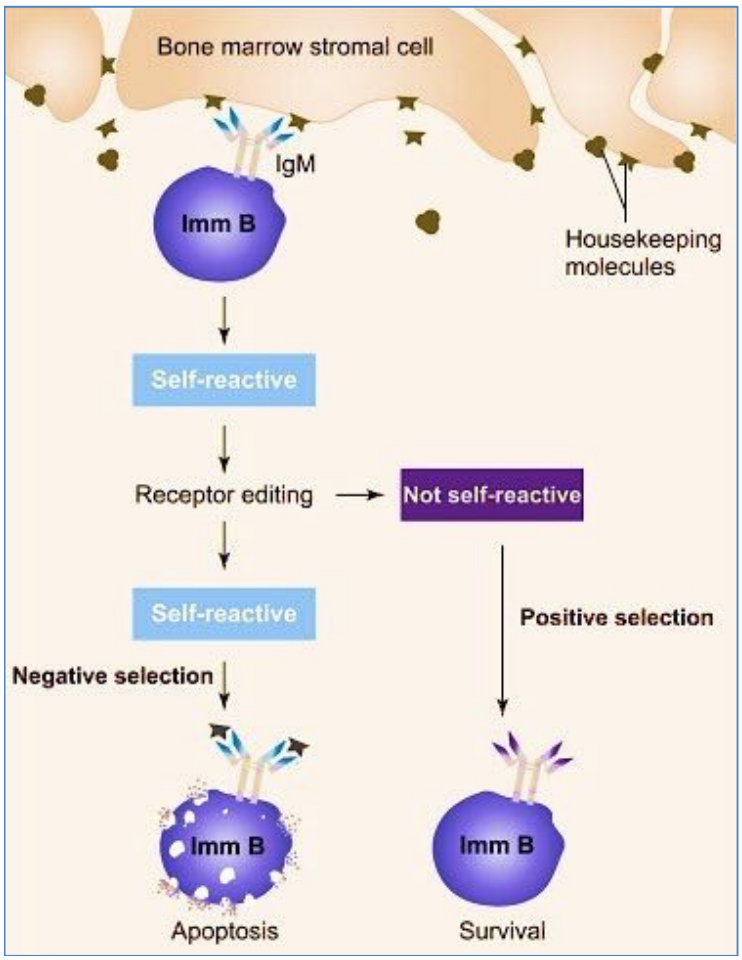


Antibodies specific for nucleic acid modifications - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Schematic-overview-of-the-organization-and-expression-of-immunoglobulin-Ig-genes_fig1_315756763

- § **Step 2 – IgM & IgD Expression:**
  - Following Ig-Gene Rearrangement, the first BCRs are Expressed on B-Cell Surface.
  - These initial BCRs are IgM and/or IgD.

§ **Step 3 – Negative Selection of Autoreactive B-Cells:**

- BCRs must be tested for Autoreactivity (Ie: Binding to Self-Antigen).
- B-Cells with Autoreactive BCRs are Negatively-Selected (Removed/Inactivated).



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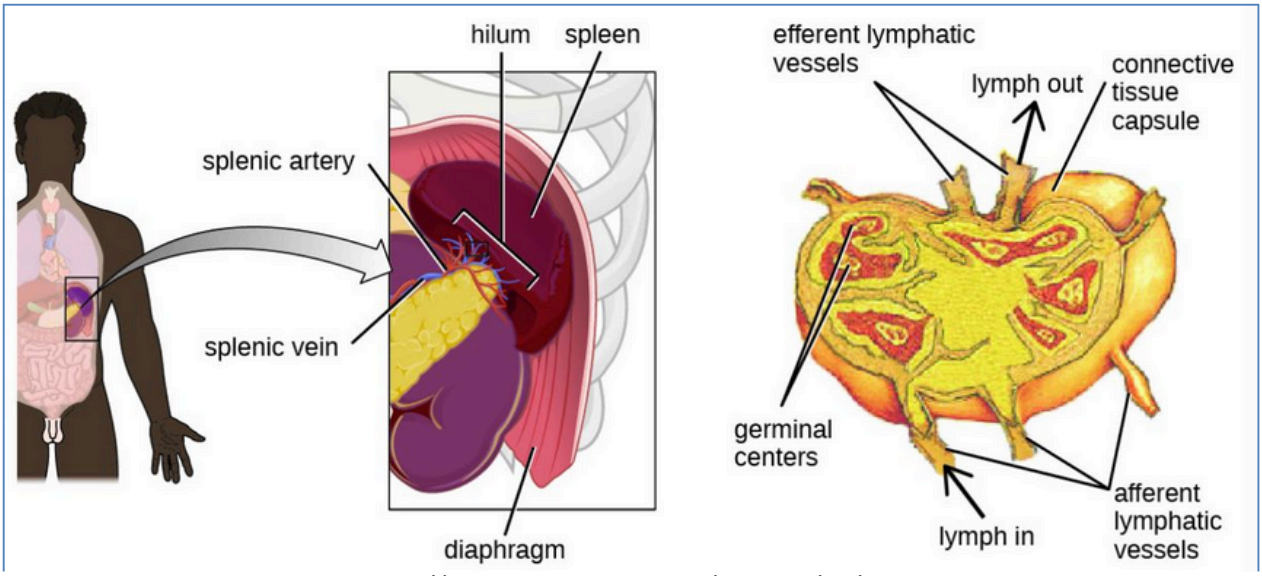
§ **Step 4 – Migration to Peripheral Lymphoid Organs:**

- Mature, Naive B-Cells leave Bone-Marrow → Migrate to 2o Lymphoid Organs.
- Homing of B-Cells to Follicles is Mediated by Chemokines.
- They Enter ***T-Cell Areas*** of ***2o Lymphoid Organs*** through ***High Endothelial Venules*** **(HEVs)** in a process called ***Diapedesis***.
- Note: See section on 'Cell-Adhesion Molecules' for details.
- Note: If B-Cells don't encounter their Specific Ag on their 1st pass, they recirculate.



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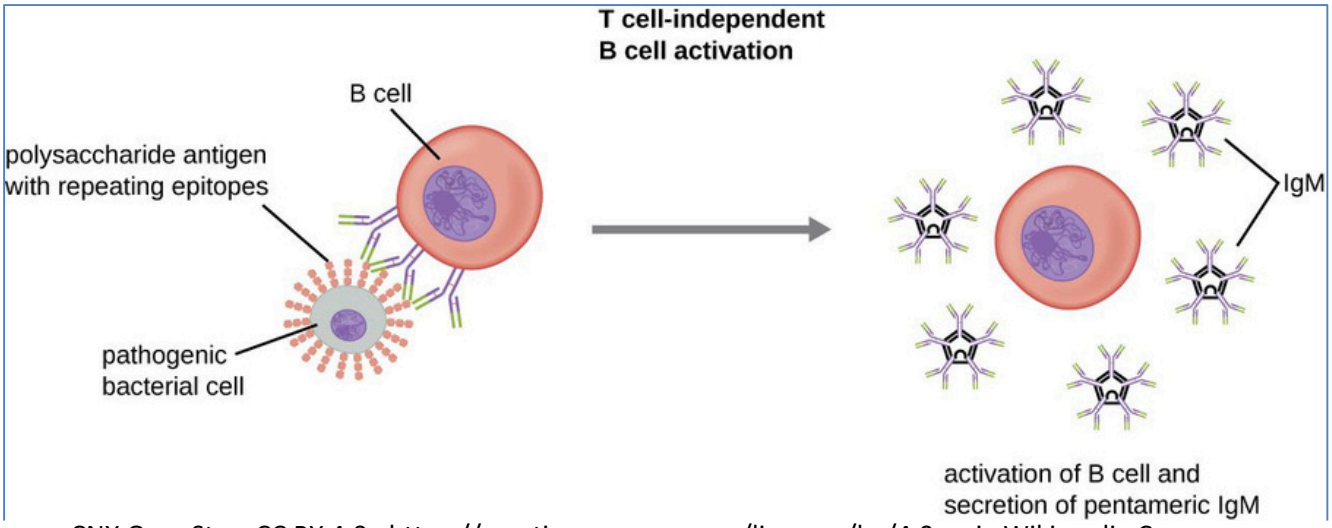
- **In 2o Lymphoid Organs (Ie: Lymph Nodes, Spleen, MALT):**
  - **Step 5 – B-Cell Activation (In T-Cell Areas):**
    - The Humoral Response is Initiated when Specific Antigen Cross-Links with BCRs.
    - **Ag. Is Internalised, Processed & Displayed as Peptides on Surface MHC-II**
    - **M olecules.**

Antigen-Mediated:

- ***Thymus Independent Antigens* →Activation Doesn't Require TH-Cell Help:**
  - B-Cell Activation *Without CD4-Helper-T-Cell* Assistance
- **→B-Cell ACTIVATION**...



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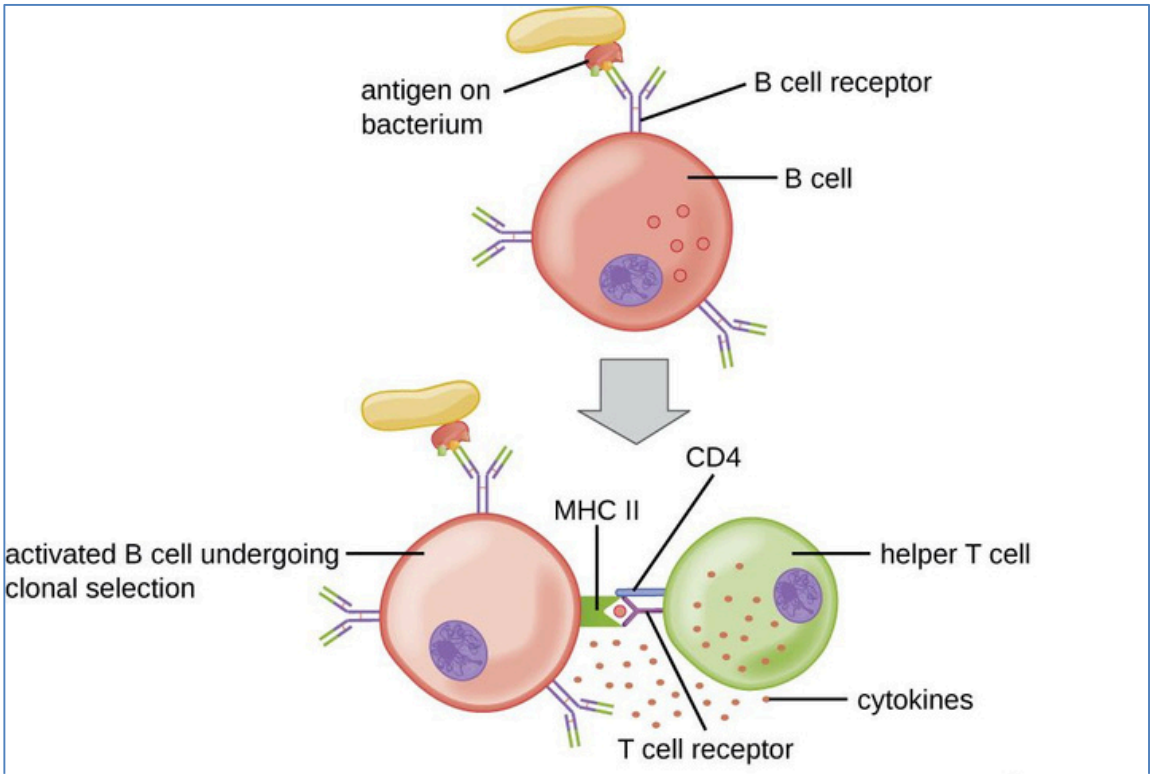
- **Th-Cell Mediated:**
  - ***Thymus Dependent Antigens* → Activation DOES Require TH-Cell Help:**
    - B-Cell Activation *Requires Th-Cell* Assistance
  - **B-Cell Encounters an Effector Th2-Cell that is Specific to that Ag.**
  - **B-Cell Activation Requires 3 Signals from Th-Cell:**
    - **1) pMHC-II:TCR Interaction**
    - **2) CD40(B-Cell):CD40L(T-Cell) Interaction**
    - **3) Paracrine Secretion of Cytokines onto B-Cells.**
  - **→B-Cell ACTIVATION**...



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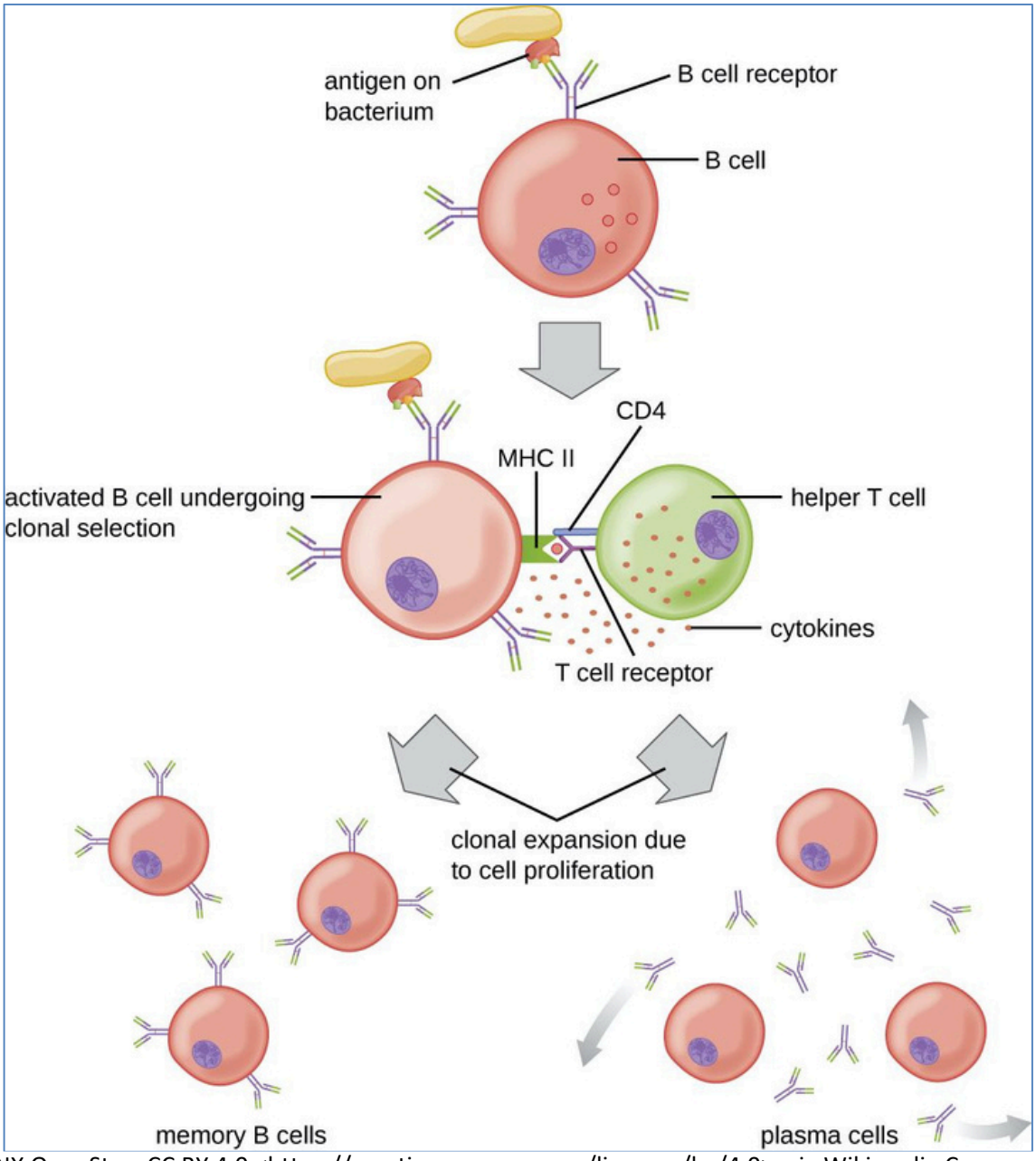
§ **Step 6 – Differentiation to Plasma Cells (In Germinal Centres):**

- Activated B-Cells Migrate from the T-Cell Areas to the Follicles (B-Cell Areas) & form
- ***Germinal Centres***.

  Germinal Centres = Sites of Rapid B-Cell Proliferation & Differentiation.
  - o B-Cells differentiate into Ab-Secreting Plasma-Cells (Or Memory B-Cells) in Germinal Centres.
  - o Plasma Cells migrate to Medulla, or back to Bone Marrow.
- **Note: During the Process of Differentiation, Secondary Ab-Diversification Mechanisms (Somatic Hypermutation & Isotype Switching)** take place.



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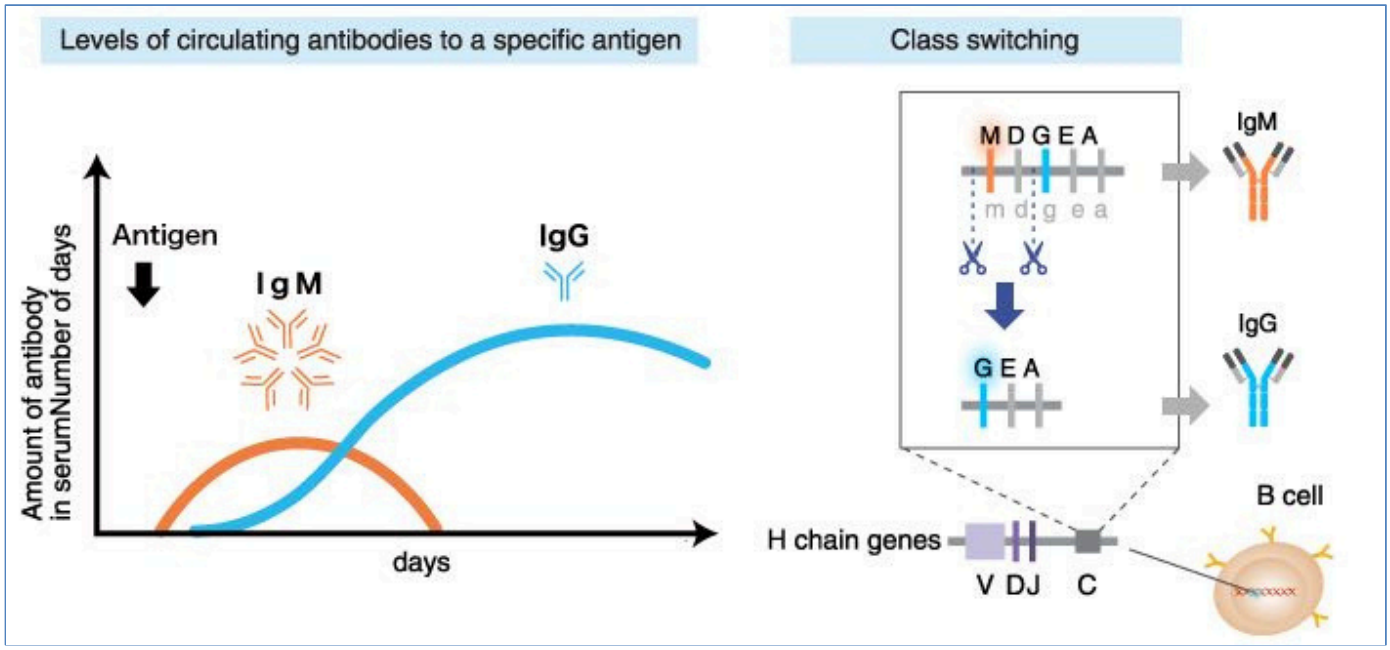
- **Somatic Hypermutation (AKA: Affinity Maturation):**
  - o – Single Amino-Acid Mutations are introduced into V(Variable)-Region-Genes.
  - o Result = Activated B-Cells with Increased *AND* Decreased Ag-Affinity.
  - o **New Ag-Receptors (BCRs) are tested for Increased Ag-Affinity:**
    - § Cells with Receptor Mutations that Increase Ag-Affinity → Survive.
    - § Cells with Receptor Mutations that Decrease Ag-Affinity → Die:
  - o **→→Proliferation of *High-Affinity* B-Cells**.

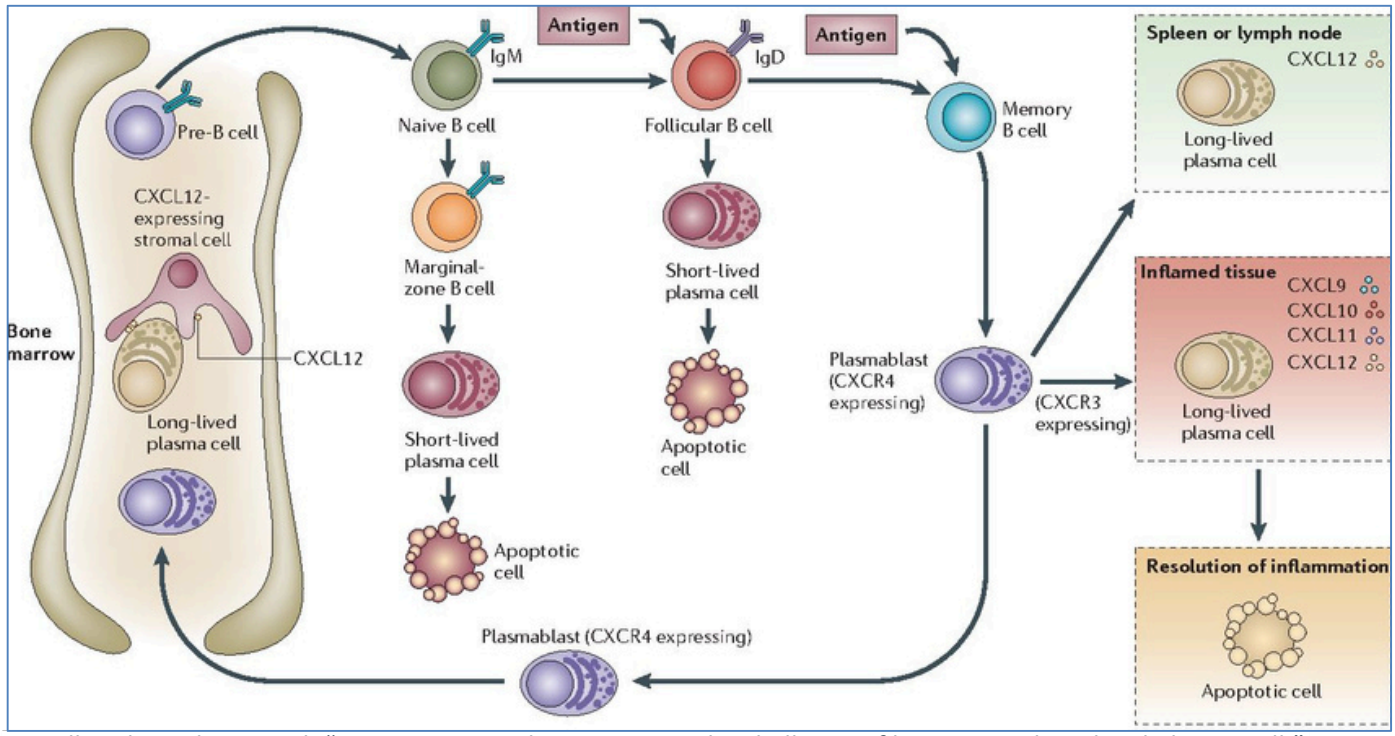
- **Isotype Switching:**
  - o – FC Region-Genes of IgM are Replaced with FC Region-Genes for IgG/IgA/IgE.
  - o **Requires TH1/2-Cell Help:**
    - § **Note:** Cytokines from CD4-TH-Cells determine which Ab-Class is made.
    - § **Note:** It is triggered at the time of B-Cell Activation & hence also Requires CD40(B-Cell):CD40L(T-Cell) Interaction
  - o **→→This change in Ab Constant-Regions → Change in Ab Effector Function**.
  - o **Note:** This doesn't affect Ab-Affinity.
  - o See *'Isotype Switching'* in the Antibody section For Details.



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

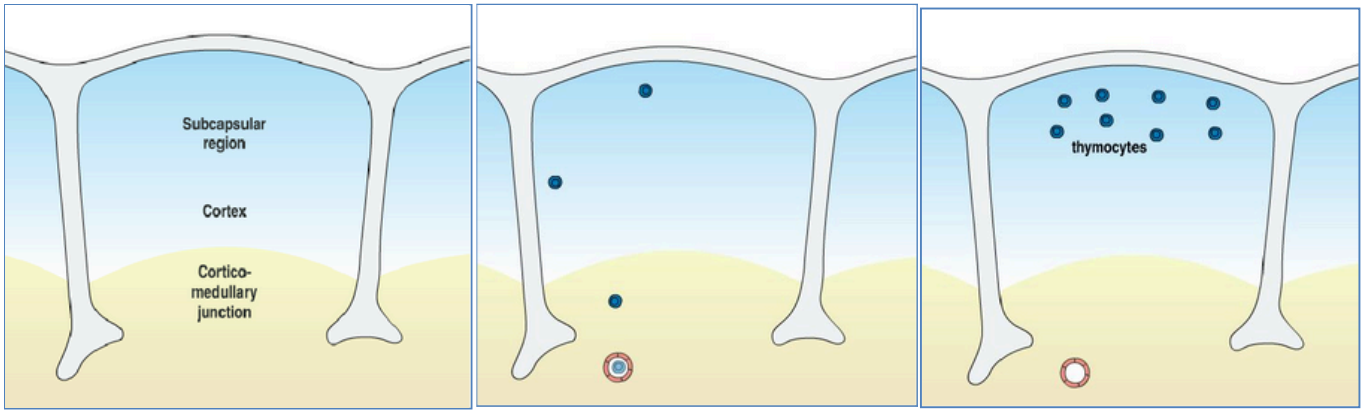
§ **Step 7 – Ab-Secretion:**

- Plasma Cells are activated, differentiated Long-Lived B-Cells that secrete Antibodies.



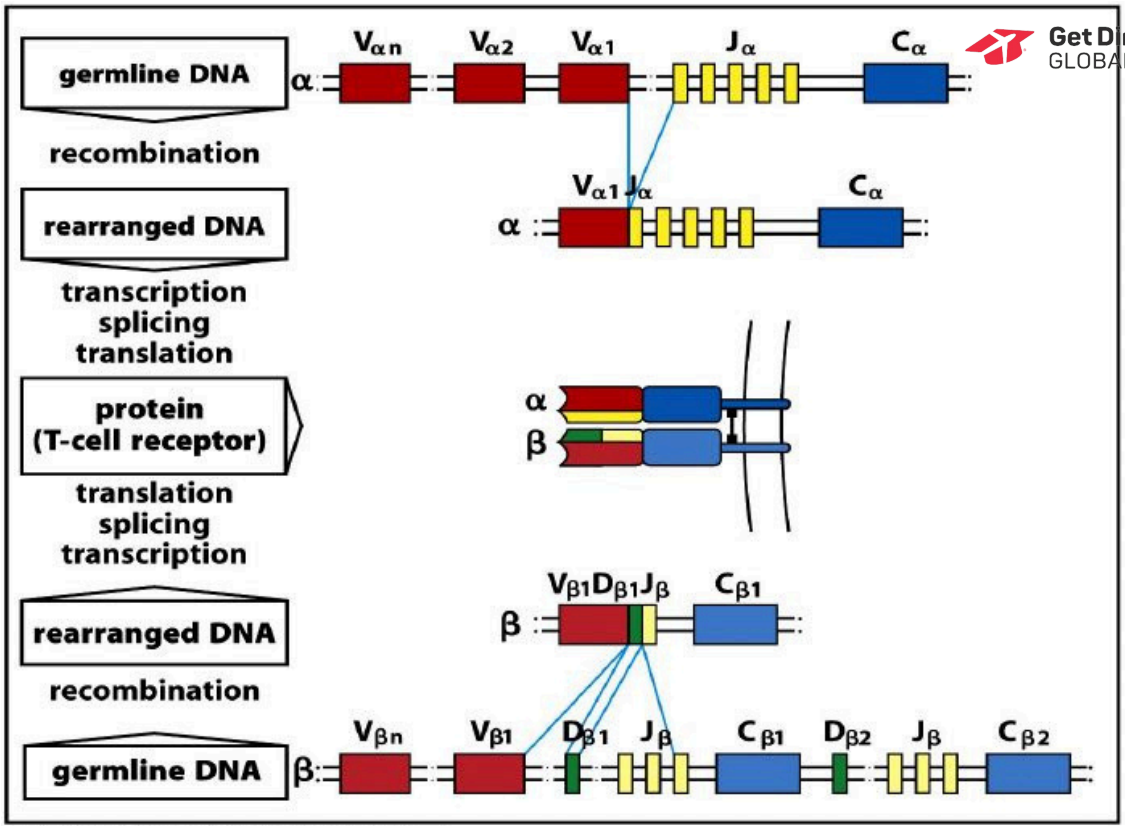
Radbruch, Andreas et al. "Competence and competition: the challenge of becoming a long-lived plasma cell." *Nature Reviews Immunology* 6 (2006): 741-750.

- **T-Cell Development:**
  - o - **In The Thymus:**
    - § **Step 1 – *Double Negative* Thymocytes Enter Thymus:**
      - During Embryogenesis, Immature, 'Double-Negative' (DN) Thymocytes Enter the Thymus via High Endothelial Venules in the *Cortico-Medullary Junction*.
        - o **Note:'Double-Negative'** = Expresses *Neither* CD4 *or* CD8
      - They then Migrate to the ***Sub-Capsular Region*** of the Thymus, where they begin TCR-Gene Rearrangement.



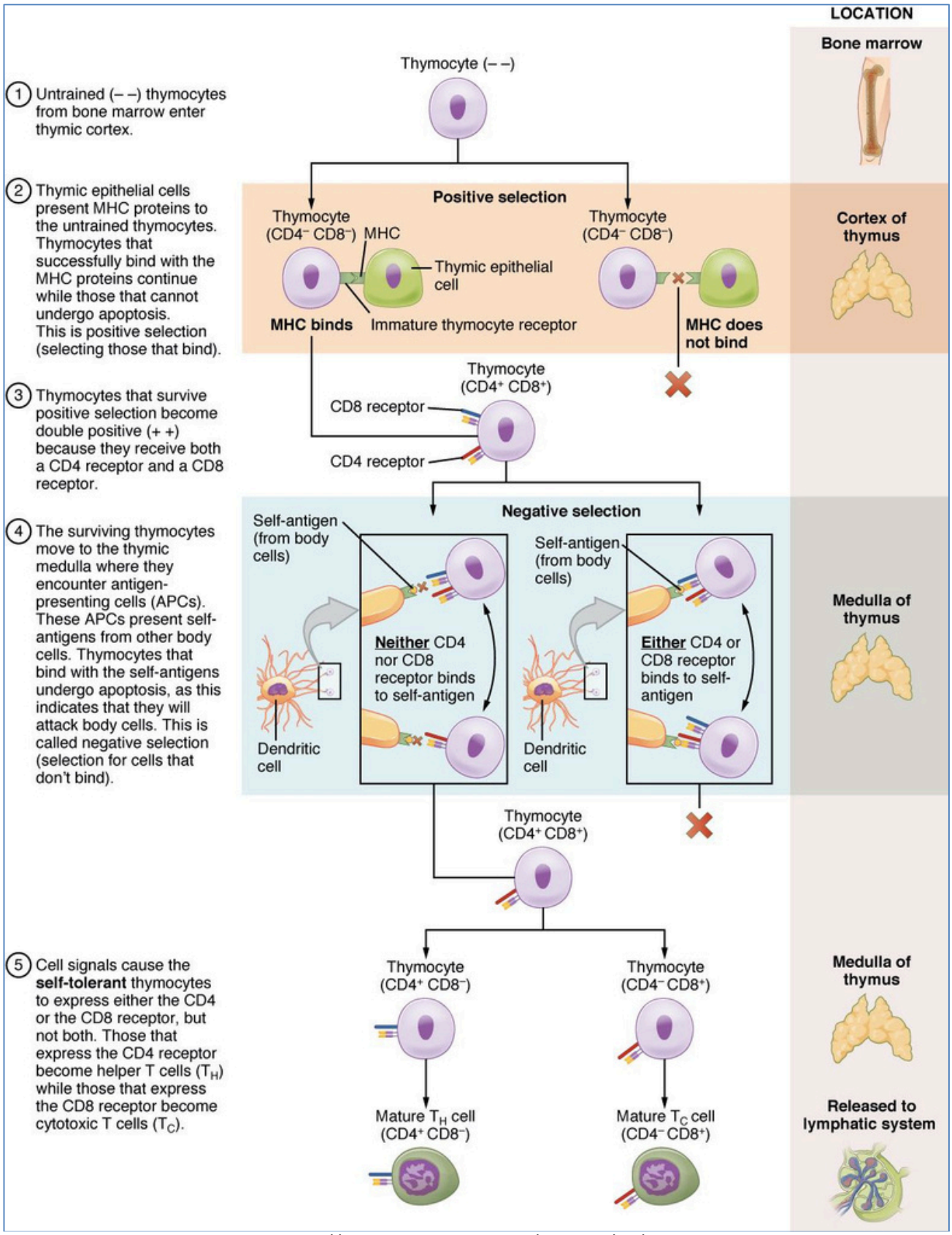
Source: Unattributable

- § **Step 2 – TCR-Gene Rearrangement:**
  - **1st: β** (or δ)**-Chain Gene Rearrangement:**
    - o Random selection of 1xGene from Each of the **V, D & J** –Gene Loci, Then Recombination of these to make a functional gene.
  - **2nd: α** (or γ)**-Chain Gene 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:2 Possible T-Cell *'Lineages';* Depending whether 'αβ' or 'γδ' TCRs:**
      - § *** αβ T-Cells Predominate** →
        - CD4 (helper & regulatory)
        - or CD8 T-Cells.
      - § **γδ T-Cells = Minority** → Mimic cells of the Innate Immune System →
        - Reside in Lymphoid & Epithelial Tissues (Skin/Repro/GIT)
        - Recognise Whole Antigen (as opposed to αβ T-Cells)
  - **(Note: Important Enzymes Involved)**
    - o **RAG-1 Recombinase**
    - o **RAG-2 Recombinase**
    - o **Ligases**
  - **Outcome:** Each TCR has a Different Sequence (Due to different Gene-Fragments & Errors Introduced during Rearrangement) → Recognise Many Different Foreign Ags.



Source: Unattributable

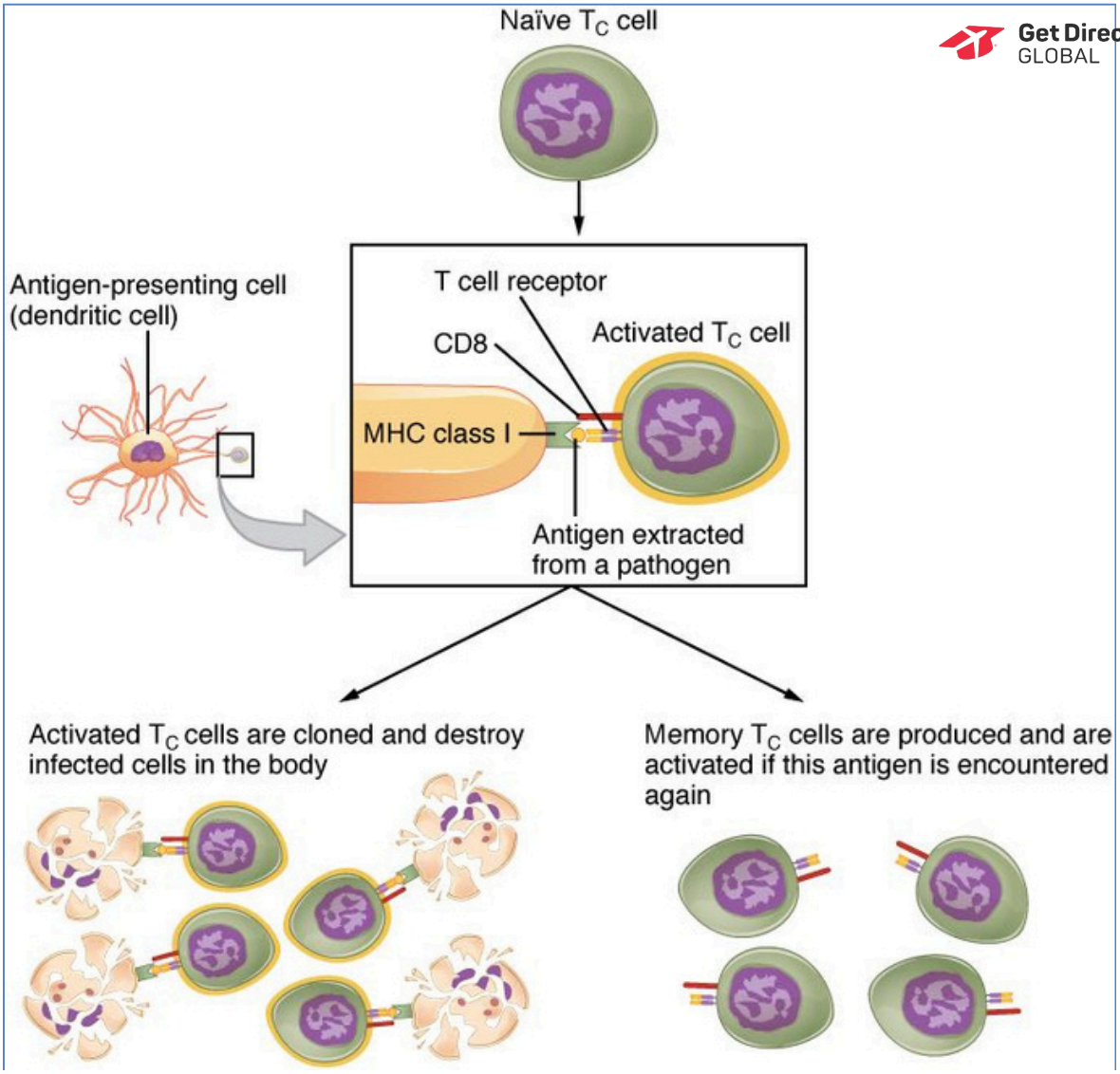
- **Step 3 – TCR Expression:**
  - Thymocytes then express their specific TCRs **(dictated by genes)** on their Membrane.
- **Step 4 – Differentiation into *Double Positive* (DP) Thymocytes:**
  - Double Negative Thymocytes Proliferate & Differentiate into *Double Positive* Thymocytes
    - Ie: They Express ***Both CD4, & CD8* Surface Molecules**.
  - They then Migrate into the **Cortico-Medullary Junction**.
- **Step 5 - Positive Selection (Thymic Cortex):**
  - ***Thymic APCs (Cortical Epithelial Cells, Dendritic Cells & Macrophages)*** **display**
  - **Peptide:MHC-I/II Complexes on their Membranes**.
    These pMHC-I/II Complexes may be recognised by TCRs on the Thymocytes.
    - **Thymocytes with TCRs able to bind pMHC-I Complexes → Receive:**
      - 1- A Survival Signal
      - 2- A Maturation Signal
      - - Eventually, it stops Expressing CD4 & Maintains Expressing CD8 → **Becomes CD8 T-Cell**.
    - **Thymocytes with TCRs able to bind pMHC-II Complexes → Receive:**
      - 1- A Survival Signal
      - 2- A Different Maturation Signal
      - - Eventually, it stops Expressing CD8 & Maintains Expressing CD4 → **Becomes CD4 T-Cell**.
  - **Note: Cells with TCRs that are Unable to Recognise *Either* MHC-I *or* MHC-II, Fail to Receive any Survival Signals, and Die via Apoptosis**.
- **Step 6 – Negative Selection (Medulla):**
  - CD4 & CD8 Thymocytes move into the Medulla where they encounter more APCs.
  - **Thymocytes with TCRs that bind pMHC-I/II *Too Avidly* Receive a Strong Signal that D riv e s th e m in to A p o p to sis**.
    - This eliminates Thymocytes capable of responding to Self-Peptide Antigens.
    - This is Essential for ***Central Tolerance***.
- **Step 7 – Mature Naive CD4/CD8-T-Cells Leave the Thymus:**
  - *Naive Single-Positive* CD4/CD8-T-Cells Leave the Thymus via Venules/Lymphatics.
  - They Migrate to Peripheral 2oLymphoid Tissue (Spleen/Lymph-Nodes/MALT)



- **– In the Periphery (Peripheral 2oLymphoid Organs)**
  - **Step 8 – Antigen Recognition:**
    - **MHCs on APCs Present Specific Ag-Peptide to Respective TCRs on Naive T-Cells:**
      - TCRs on **CD4-T-Cells** Recognise their Specific **Peptide:*MHC-II*** Complexes
        - (Because CD4 has Specific Binding Sites for MHC-II)
      - TCRs on **CD8-T-Cells** Recognise their Specific **Peptide:*MHC-I*** Complexes
        - (Because CD8 has Specific Binding Sites for MHC-I)
      - **Note:** T-Cells do NOT recognise whole antigen (as opposed to B-Cells)
      - **Note:** T-Cells do NOT recognise any peptide which isn't bound to MHC.
        - However, ***Superantigens*** can bind TCR+MHC *Without Processing*. (See Section on MHC for more detail)

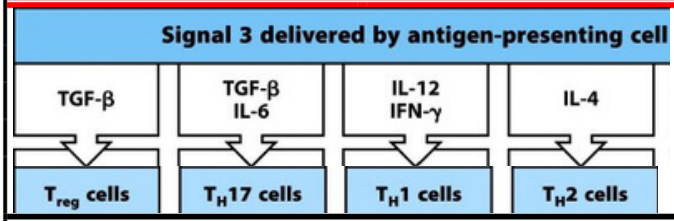
  - **Step 9 – T-Cell Activation (Proliferation & Differentiation):**
    - **Note: T-Cells Require 3 Kinds of Signals From APCs in order to be *fully* Activated:**
      - **1- Activation Signal**
      - **2- Survival Signal (AKA: CO-STIMULATORY SIGNAL)**
      - **3- Differentiation/Proliferation Signal**
    - **1- Activation Signal – Via TCR Binding to pMHC-I or pMHC-II:**
      - MHC-I:
        - (For Binding with TCRs & CD8 Molecules on CD8-T-Cells)
      - MHC-II:
        - (For Binding with TCRs & CD4 Molecules on CD4-T-Cells)
    - **2- Survival Signal – CD28/CD40 Binding to Co-Stimulator Molecules:**
      - CD80 (aka. 'B7'):
        - (For Binding with **CD28** on CD8/CD4 T-Cells)
        - **Note:** Binding of **CD28** to *either* CD80 or CD86 → **Triggers Cell Cycle & Induces IL-2 Synthesis → Drives T-Cell Proliferation**.
      - CD86:
        - (For Binding with **CD28** on CD4 T-Cells)
        - **Note:** Binding of **CD28** to *either* CD80 or CD86 → **Triggers Cell Cycle & Induces IL-2 Synthesis → Drives T-Cell Proliferation**.
      - CD40:
        - (For Binding with **CD40**-Ligand on CD4 T-Cells)

        4-1BB Ligand:
        - (For Binding with 4-1BB on CD8 T-Cells)
      - **Note: Proliferation Signal: CD28-Induced IL-2 → Drives T-Cell Proliferation**
    - **3- Differentiation Signal – Via Cytokines:**
      - **From APCs** - See Table
      - **From Other Innate Immune Cells** - Full T-Cell Activation requires Cytokines from the Innate Immune system, to become fully activated. (Therefore, non-infective Ags, which don't stimulate the Innate Immune System (or release of cytokines), WILL NOT activate T-Cells. → Tolerance)



CNX OpenStax, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons : **Clonal Selection and Expansion of T Lymphocytes** Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

Role of Signal	APC-Surface Molecules	BINDING PARTNERS	
		On CD4 T-Cells	On CD8 T-Cells
1- Activation (Ag Recognition)	**MHC-I**	-	Specific TCR & CD8
	MHC-II	Specific TCR & CD4	-
2- Survival (Co-Stimulatory Molecules)	**CD80 ("B7.1")**	CD28	CD28
	CD86 ("B7.2")	CD28	-
	CD40	CD40-Ligand	-
	4-1BB-Ligand	-	4-1BB
(2- Survival Continued..) (Via a Cytokine)	**IL-2**	IL-2Receptor	IL-2Receptor
3- Differentiation (Cytokines)	**TGF-β**	**Signal 3 delivered by antigen-presenting cell**	
	IL-6		
	IL-12 → Th1		
	IFNγ → Th1		
	IL-4 → Th2		
	IL-2	→ Differentiation of CD8-T-Cells → Cytotoxic **Note:** Most CD8-T-Cell Diff. Requires CD4 Help; but can occur Independently if Stimuli is Strong Enough.	



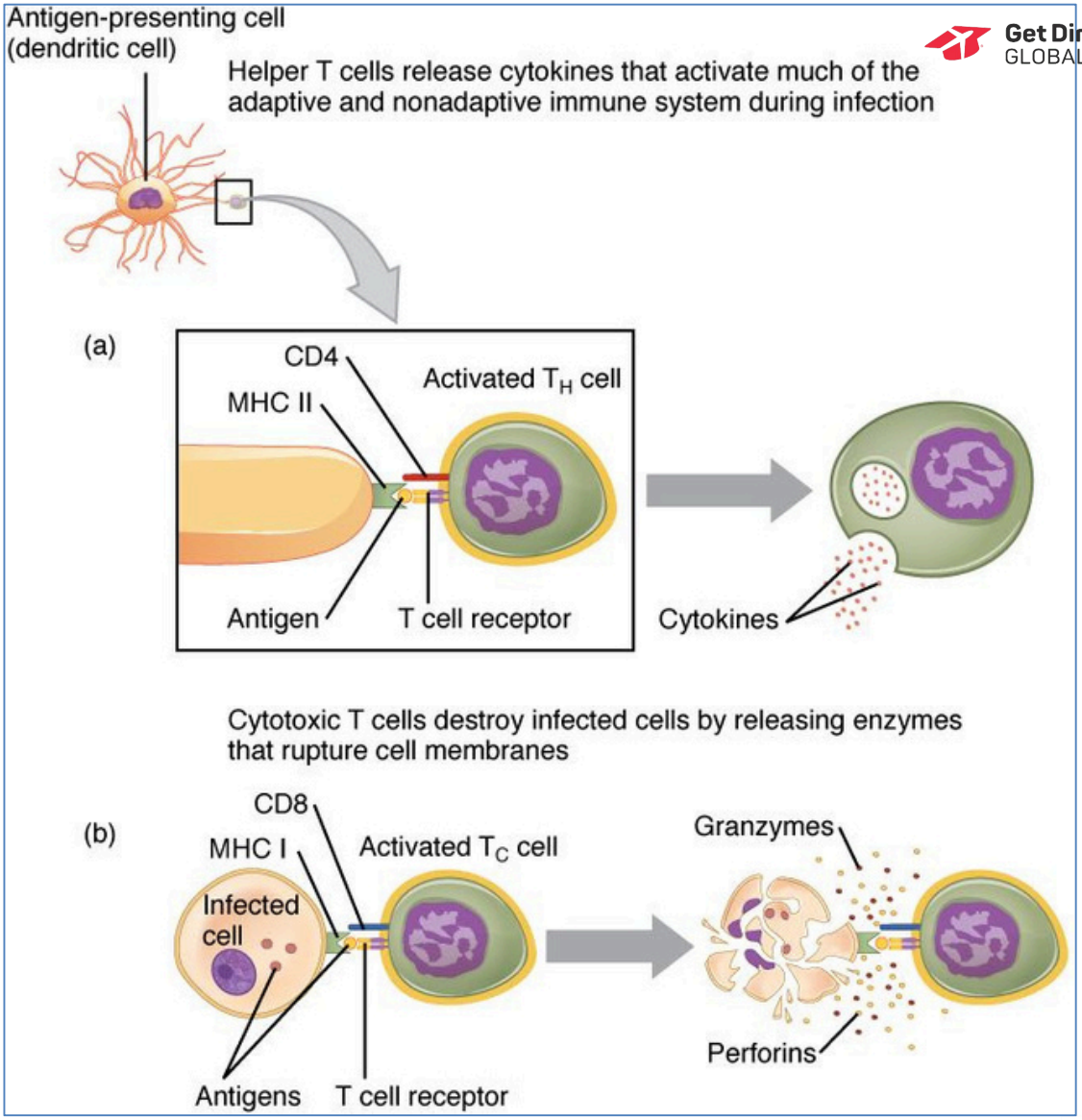
- **Note: Binding of any of these APC-Surface-Molecules to their respective partners on T-Cells → Activates Intracellular Domains of both APC- & T-Cell-Surface-Molecules**.
    - → Activates Intracellular Signalling Cascades → Altered Gene Expression
        - → Altered Gene Expression → Differentiation →
            - Effector Cells
            - OR Memory Cells
- **Note:TCR:Ag Recognition *Alone*, or Co-Stimulation *Alone* Is NOT ENOUGH to Activate T-Cells; and Can Inactivate the Reactive T-Cells → Tolerance**.
    - **Note:** This is a good safeguard in preventing activation of Auto-Reactive T-Cells (See Section on MHC & Central Tolerance for more details)

§ **Step 10 – Effector Functions:**

- **Note: Effector Functions depend largely on the Cytokines that they produce**.
- **CD4-Helper-T-Cells: - Function to Activate Other Cells:**
    - Recognise Bacterial/Antigenic Peptide Presented on MHC-II
    - **Th1-Helper T-Cells:** (Recognise *Bacterial* Peptide)
        - Activate Macrophages **(Via IFNγ & CD40L)** → More Cytotoxic
        - Induces T-Cell Proliferation **(Via IL-2)**
        - Help B-Cells → *Switch* IgM-Plasma-B-Cells → Secrete IgG. **(Via IFNγ)**
    - **Th2-Helper T-Cells:** (Recognise *Antigenic* Peptide)
        - Help B-Cells → *Switch* IgM-Plasma-B-Cells → Secrete IgG/E/A. **(Via IL-4, IL-5 & TGF-β; AND Co-Stimulation from CD40:CD40L)**
    - **(Th17-Helper T-Cells:)**
        - Recruit Neutrophils **(Via IL-17)**

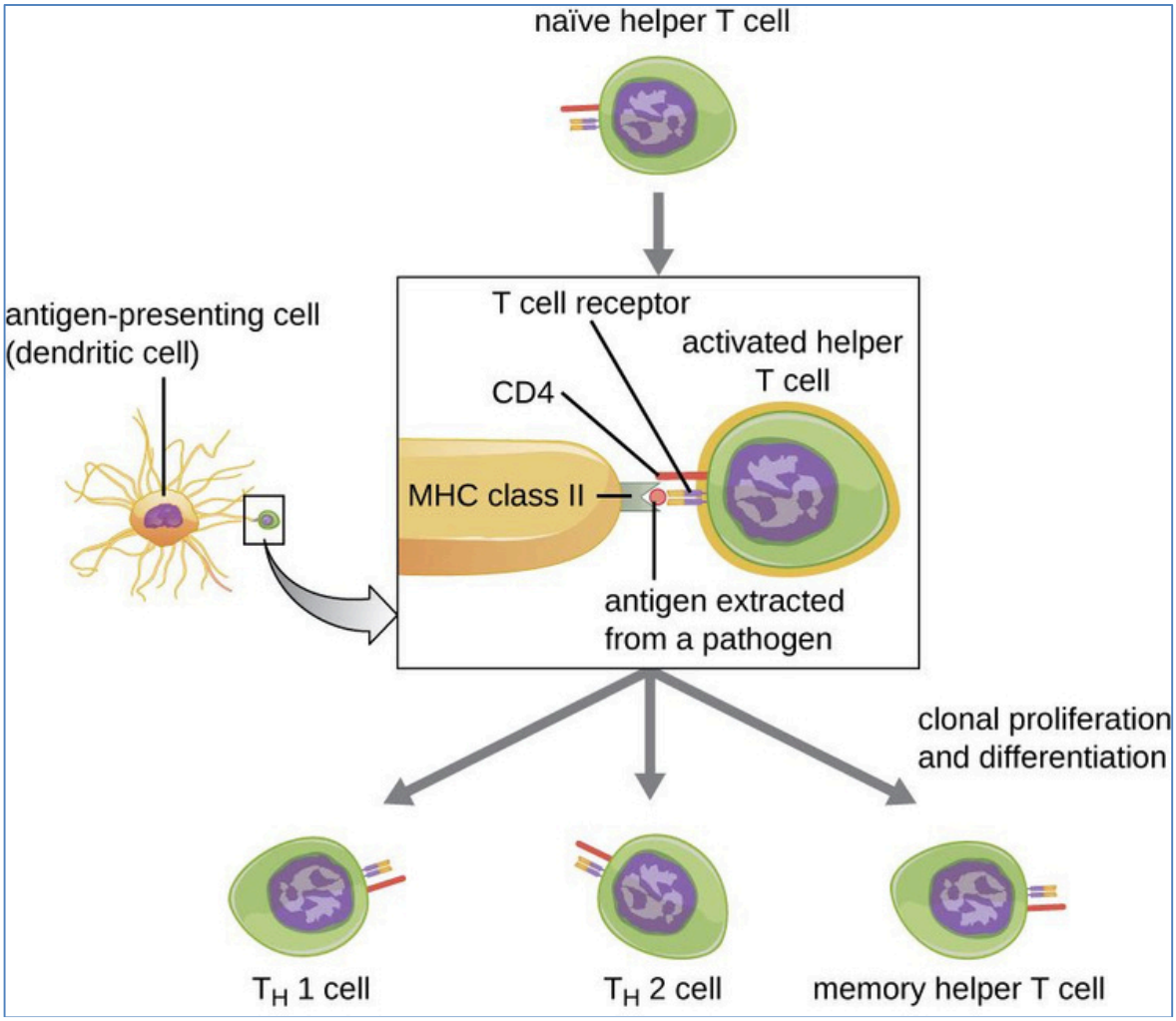
      (T-Regulatory Cells:)
        - Suppress T-Cell Function **(Via IL-10 & TGF-β)**
- **CD8-Cytotoxic-T-Cells: - Function to Eliminate Infected/Abnormal Cells:**
    - **Note:** Help from Th-Cells is Usually Essential for:
        - Differentiation into Cytotoxic T-Cells (Via IFNγ)
        - Enhancing CD8-T-Cell Responses.
    - **Directly Kill Cells Displaying Viral Peptides bound to MHC-I**.
        - **NB:**CTLs also release Cytokines:
            - **IFNγ** → Inhibits Viral Replication
            - **TNFα** → Pro-Inflammatory
        - Also can destroy Tumour Cells
    - **CD8 Cells Kill by *Release of Cytotoxic Granules* → Induce Apoptosis:**
        - Perforin – Aids in delivering Granzymes/Granulysin into Cell.
        - Granzymes
        - Granulysin
    - **The above Chemicals cause Apoptosis by Ether:**
        - Causing Release of Cytochrome-C from Mitochondria &/Or Caspases → Induces DNA Dam age → Apoptosis.

          Or by Activating *'Death Receptors'* (Eg: Fas).



CNX OpenStax, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons : **Pathogen Presentation** (a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by a class I MHC molecule, and CD8 interacts with it.

- **M em ory T-Cells:**
  - o Those that don't become Effector Cells, become Memory Cells.
  - o They are *Long-Lived* & Persist @ Higher Levels than Naive Lymphocytes.
  - o Respond Rapidly to Ag-Challenge.
  - o Can Rapidly Differentiate into Effector Cells.

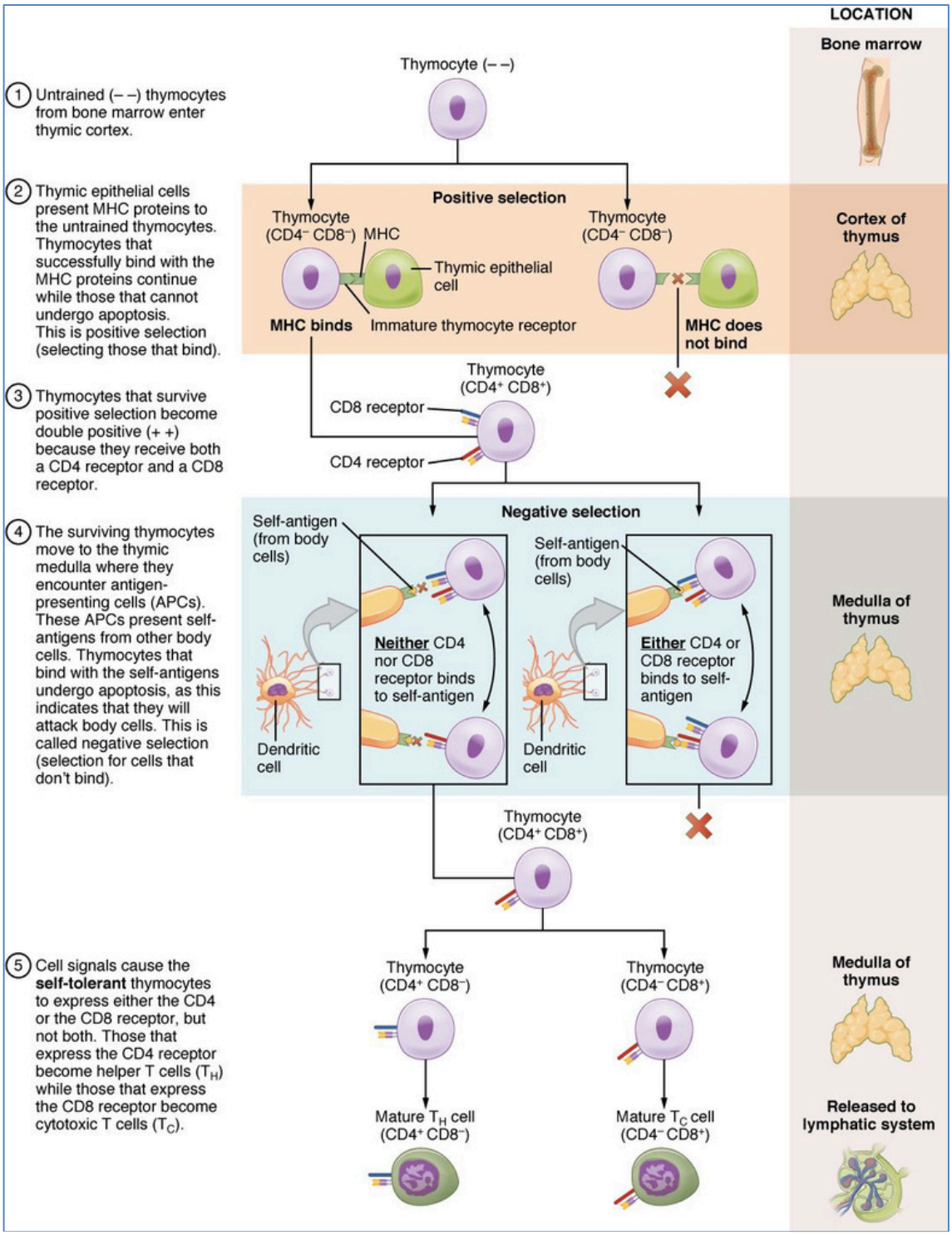


"Tolerance":

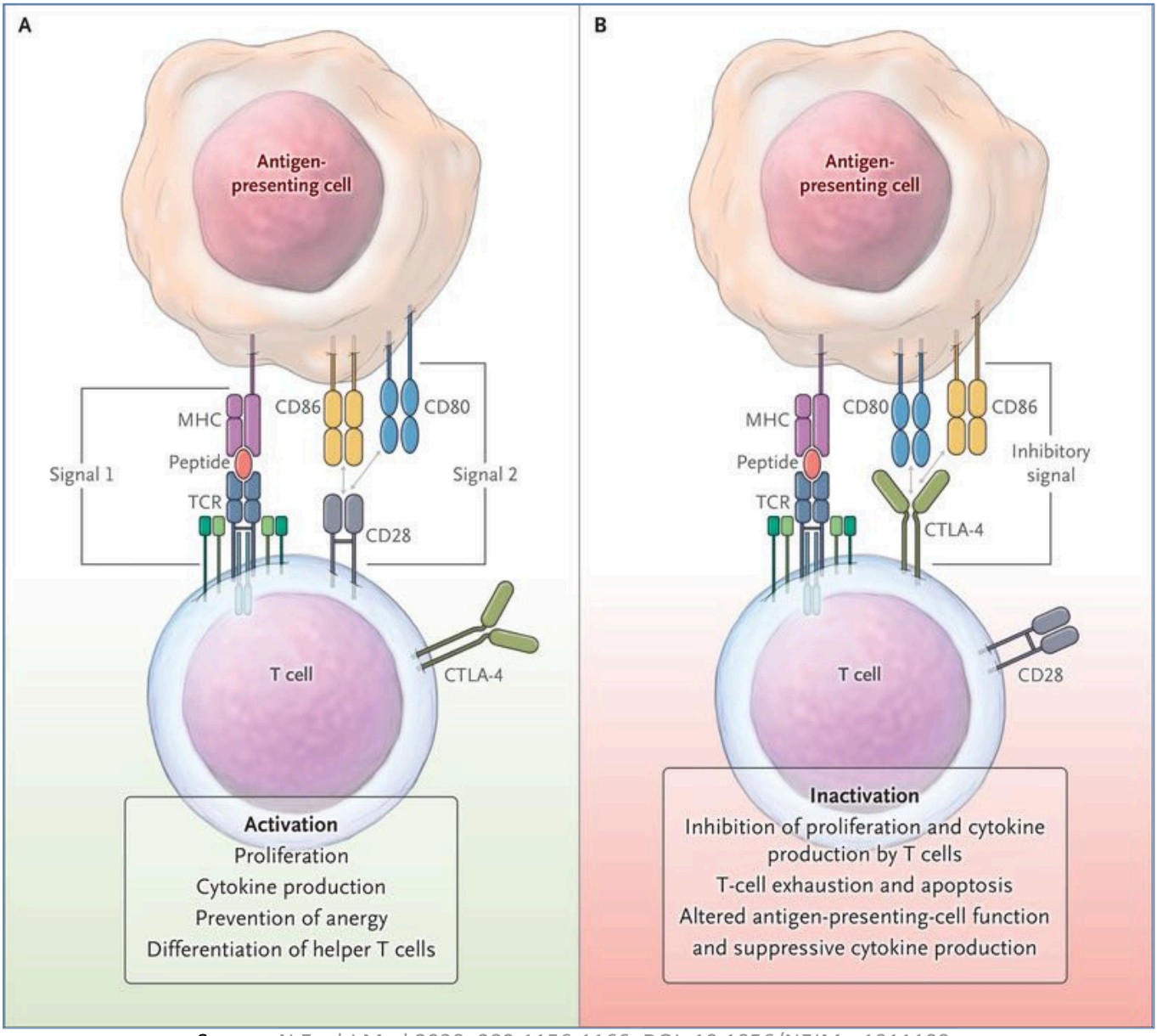
- **What is it?**
  - o "The state of *Immunological* ***Unresponsiveness*** of the *Lymphoid Tissue* to a ***Specific Antigen***"
  - o **Note: Tolerated Antigens = "*Tolerogens*"**
- **Why is it important?**
- o Important in preventing ***Autoimmunity***.

How is it achieved?

- o **1- SELF-TOLERANCE ("CENTRAL TOLERANCE"):**
  - § **Negative Selection of B-Cells & T-Cells in Primary Lymphoid Organs:**
    - Lymphocytes Reactive to Self-Ags are Clonally Deleted during development.
    - **Note:** However, it is impossible to expose all T-Cells to *every Self-Ag* since many of them aren't expressed in the Thymus. (See below for fail-safes)
  - § **Fail-safes:**
    - B-Cells escaping negative selection require TH-Cell Help to produce antibody.
    - T-Cells escaping negative selection are regulated by *other cells* in periphery.



- **2- ACQUIRED IMMUNOLOGICAL TOLERANCE ("PERIPHERAL TOLERANCE"):**
  - **A) - TCR:Ag Recognition *Alone*, or Co-Stimulation *Alone* Is NOT ENOUGH to Activate T-Cells; and Can Inactivate the Reactive T-Cells → Tolerance**.
    - **NB:**This is a good safeguard in preventing activation of Auto-Reactive T-Cells.
  - **B) – Exposure to Exogenous Non-Inflammatory Antigens (Eg: Dust/Pollen/Food) can → Tolerance:**
    - Full T-Cell Activation requires Cytokines from the Innate Immune system to become
    - fully activated.
      Therefore, non-infective Ags, which don't stimulate the Innate Immune System (or release of cytokines), WILL NOT activate T-Cells. → Tolerance

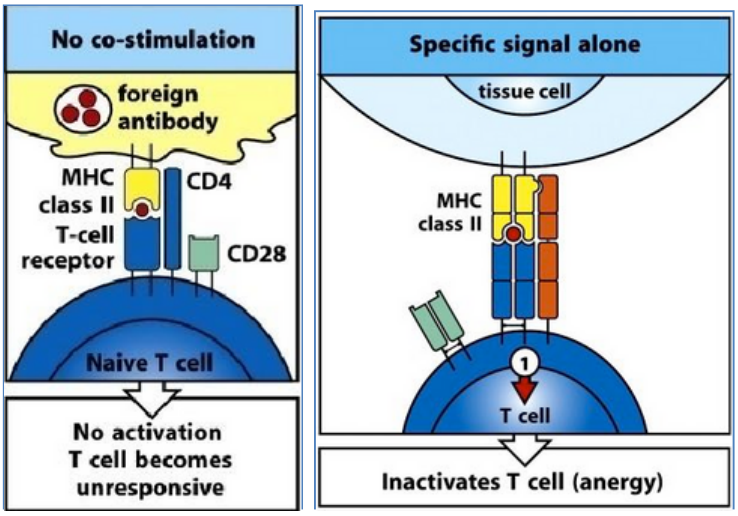


Source: N Engl J Med 2020; 383:1156-1166; DOI: 10.1056/NEJMra1911109;
https://www.nejm.org/doi/full/10.1056/NEJMra1911109

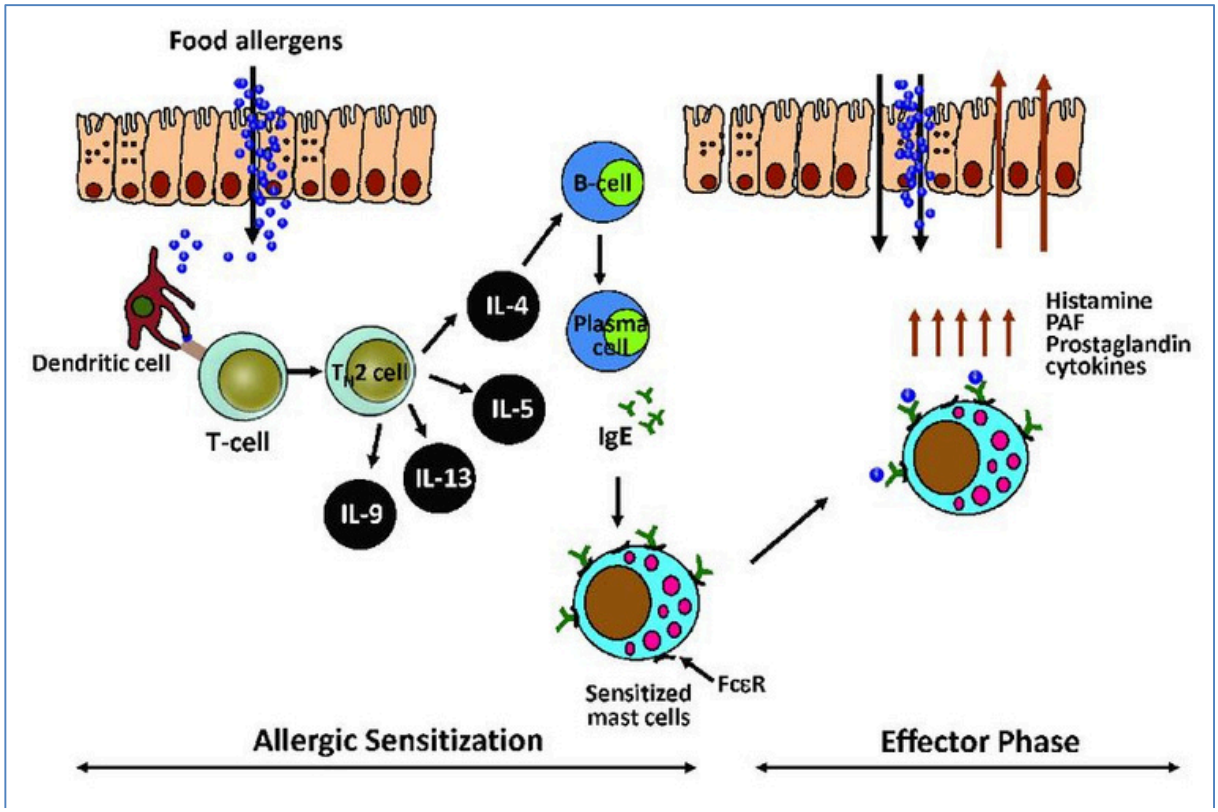
Oral Tolerance

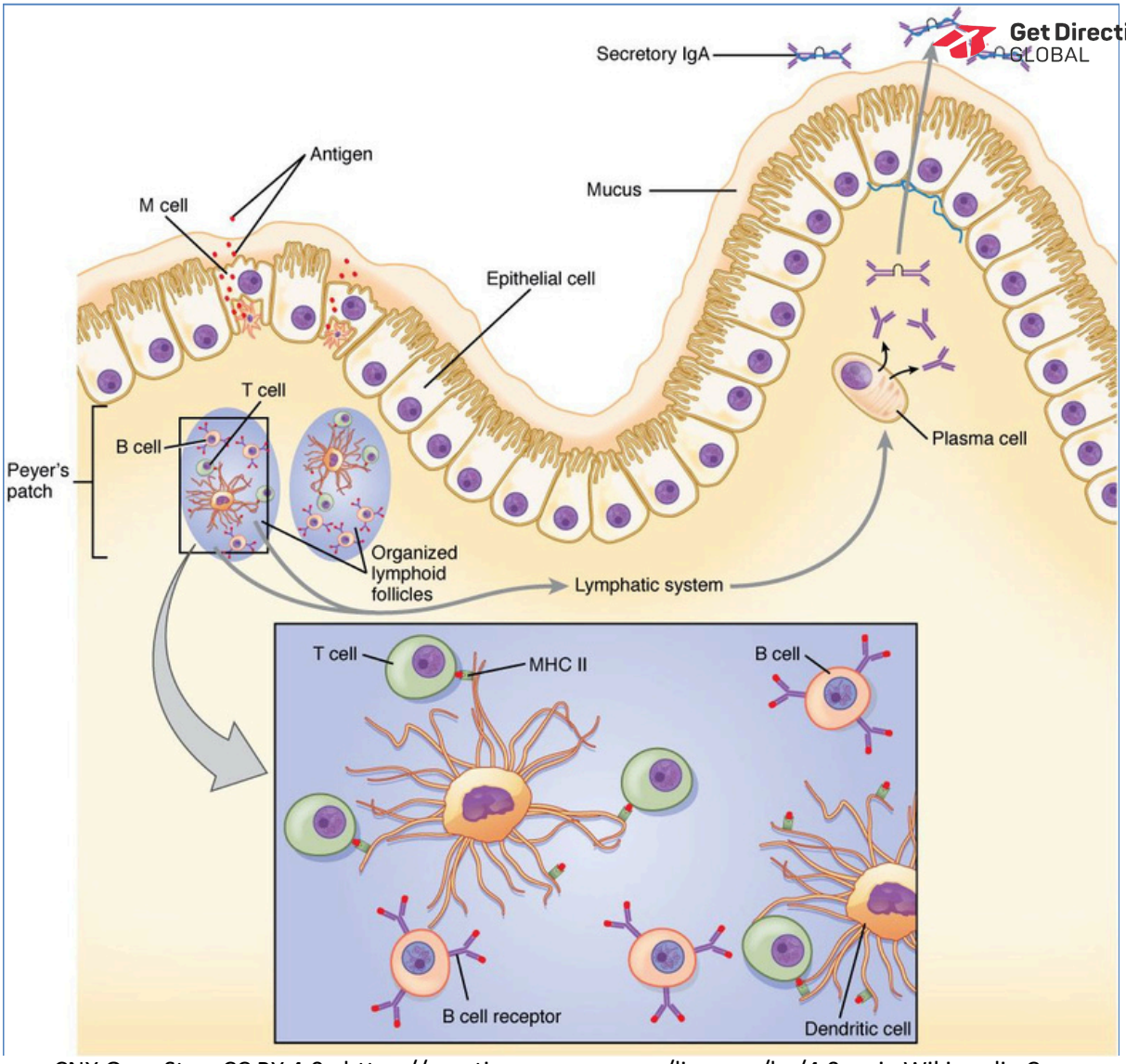
Response to Food Antigens - ('Protective Immunity' *or* 'Oral Tolerance'):

- **Normally, Food Antigens DO NOT stimulate an Immune Response; Instead they Induce *Tolerance*:**
  - o **How? –** Remember, Antigen Presentation *Without Co-Stimulation* is NOT ENOUGH to Activate T-Cells; and actually Inactivates the T-Cells instead → Tolerance.
  - o **Full T-Cell Activation Requires Cytokines** from the Innate Immune system to become fully activated. Therefore, non-infective Ags, which don't stimulate the Innate Immune System (or release of cytokines), WILL NOT activate T-Cells. → Tolerance
  - o **Also, Inflammatory Cytokines cause APCs to express Co-Stimulatory molecules**, so without them, full T-Cell Activation is impossible.



- ***Abnormally*, Food Antigens *may* stimulate an Immune Response → Activating Th-Cells:**
  - o **1st Exposure:** Activated Th-Cells specific to a Food Antigen will then Activate Ag-Specific B-Cells → Produce Antibodies against the Food Ag.
  - o **Subsequent Exposure:** Antibodies bind Food Antigen. Then Ab:Ag-Complexes bind to Mast Cells:
    - § → Mast Cells Degranulate → Release Histamine
    - § Histamine → Vasodilation, ↑Vascular Permeability & Upregulation of Cell Adhesion
    - § M olecules.
      → Crams, Vomiting, Diarrhoea, Angio-Oedema.





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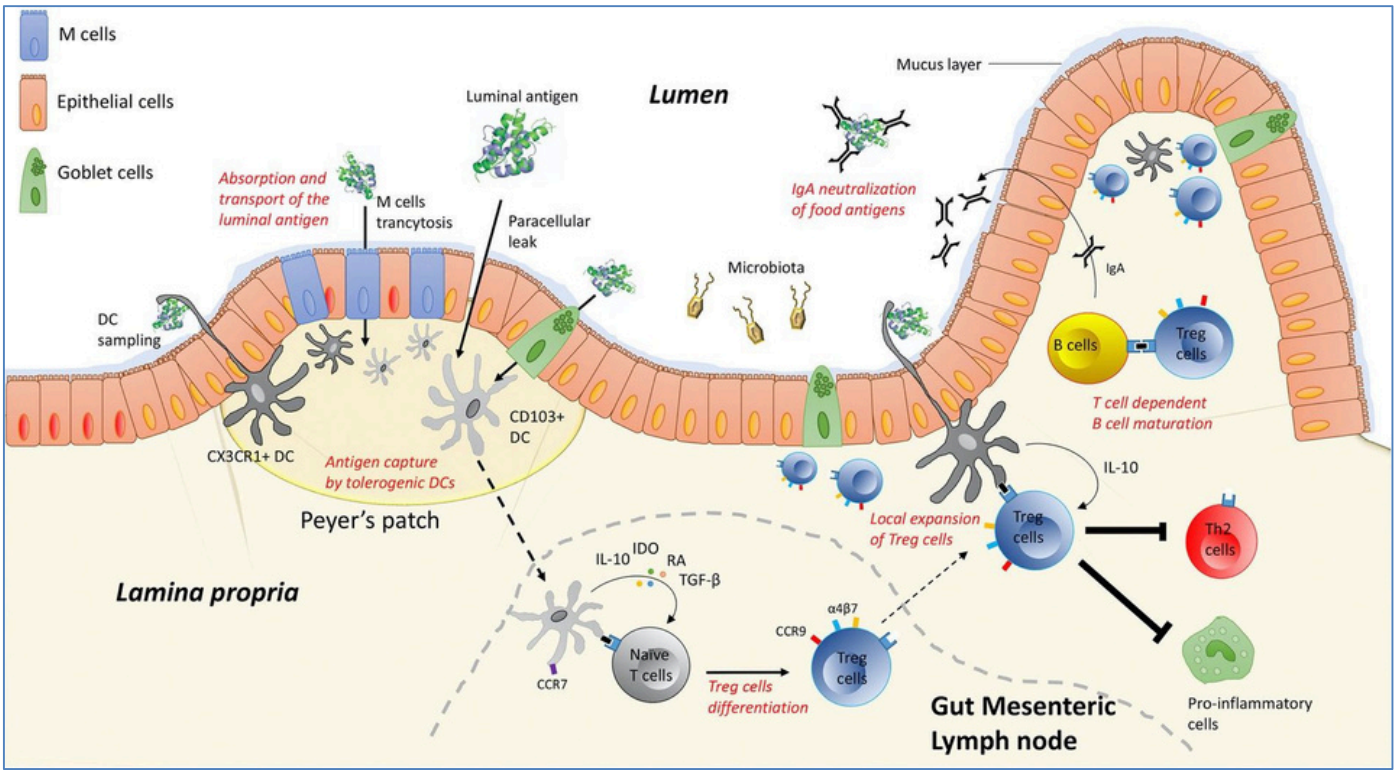
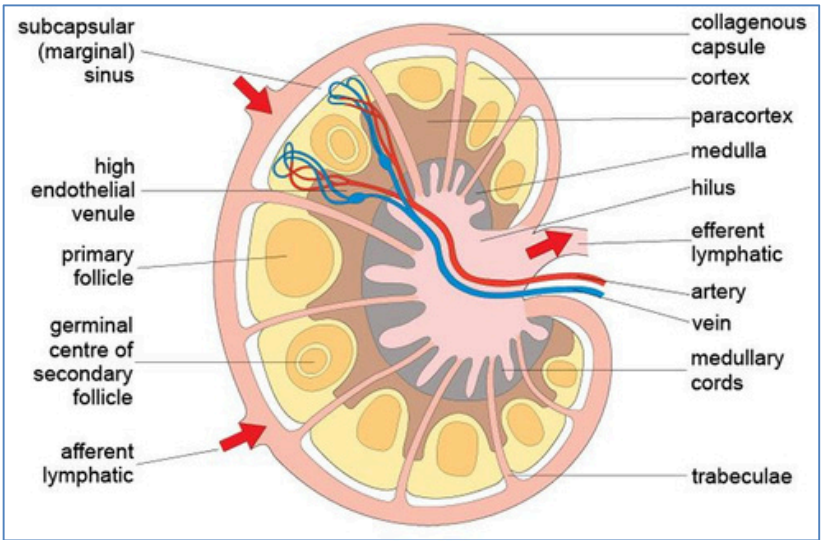


Oral Tolerance Development and Maintenance; Wambre, Erik et al. Immunology and Allergy Clinics, Volume 38, Issue 1, 27 - 37

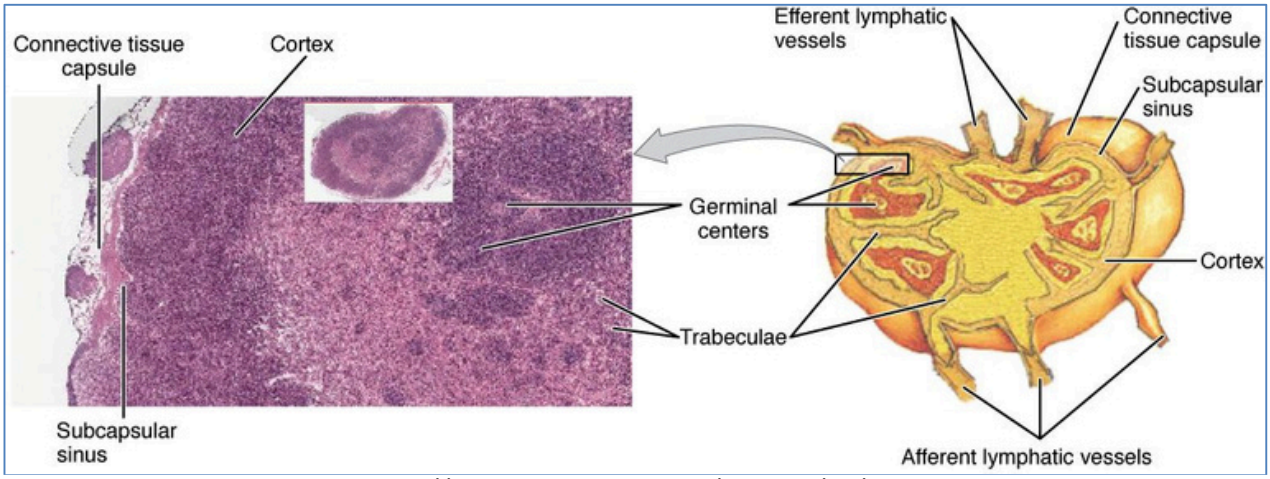
FUNCTIONAL ANATOMY OF THE IMPORTANT SECONDARY LYMPHOID ORGANS:

Lymph Nodes: The *only* Filters of the Lymphatic System: - They Filter out Lymph-Borne Foreign Antigens, & help activate the immune system.

- **3 Regions:**
  - **1- Cortex –**
    - **Outer Cortex –** Mostly B-Cells organised into '**Lymphoid Follicles'** with **'Germinal Centres'** of heavily dividing B-Cells. These Lymphoid Follicles are encapsulated by Dendritic Cells.
      (Note: During an infection, it is these Germinal Centres of proliferating B-Cells that cause the lymph node to expand.)
  - **2- Paracortex –** Mostly circulating T-Cells.
  - **3- Medulla –** (As defined by **Medullary Cords**) Contains Plasma Cells, Macrophages, & B+T-Cells
  - **The Reticular Network -** Fine networks of macrophage-lined reticular fibres that form the main structural support substance of the Lymph Node, as well as provide a surface for adhesion of Dendritic Cells, Macrophages & Lymphocytes, between Lymphoid Follicles & Medullary Cords.
- **Dendritic Cells & Macrophages are the Antigen Presenting Cells** in Lymph Nodes.
- **Circulation in a Lymph Node:**
  - Lymph enters the convex side of a lymph node via numerous **Afferent Lymphatic Vessels**, carrying with it active Antigen-Presenting Cells such as Dendritic Cells, as well as free antigen. (Note: Lymphocytes enter from the blood via HEVs)
  - It then percolates through the **Lymph Sinuses,** the areas of the Reticular Network surrounding the Lymphoid Follicles & Medullary Cords, where Dendritic Cells present their antigens to the surrounding T-Cells, & foreign particles are trapped by Macrophages.
  - The Lymph Sinuses then converge at the **Hilum** & lymph the exits the node via the **Efferent Lymphatic Vessels**, towards either a more central Lymph Node or into the Blood.



Source: Openlearn;
https://www.open.edu/openlearn/mod/oucontent/view.php?id=65373&extra=thumbnailfigure_idm458880948278 0 8



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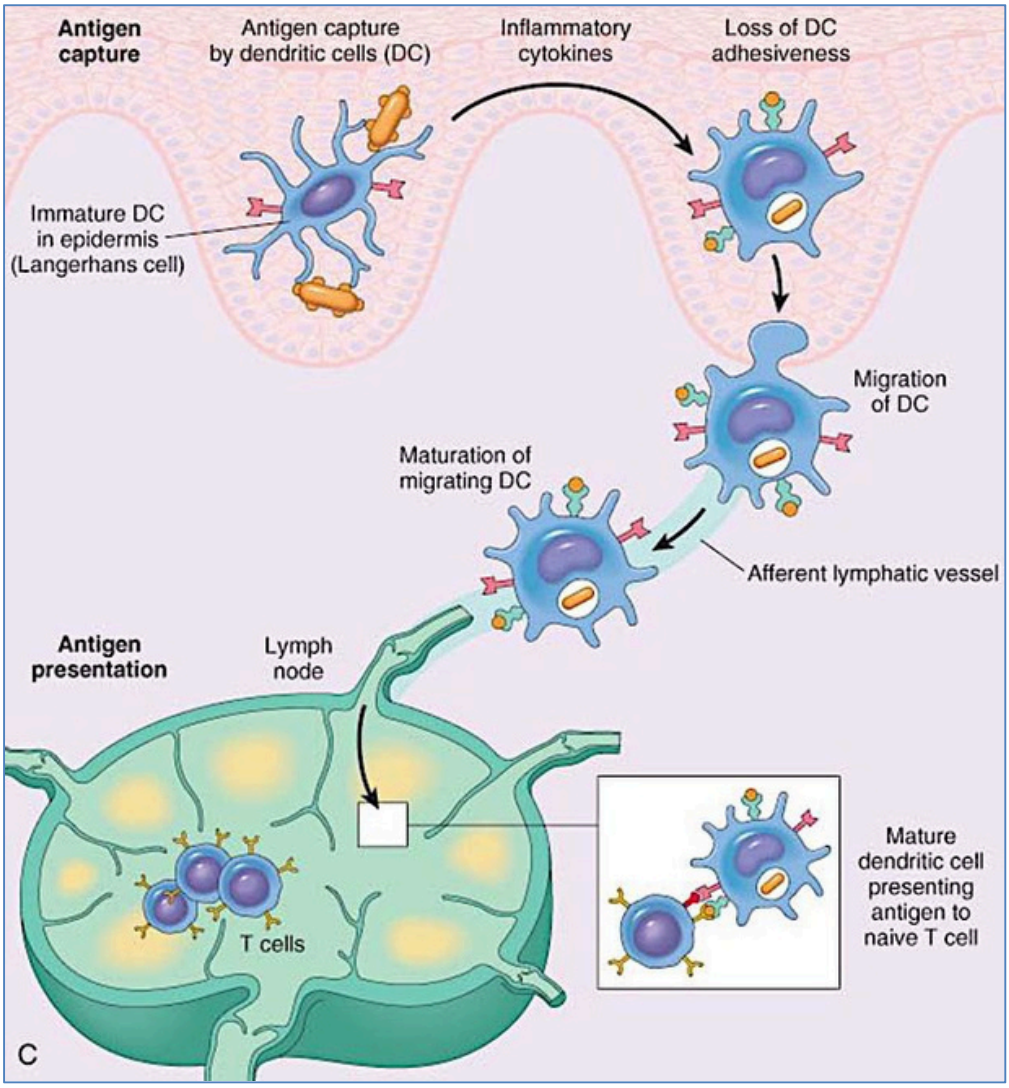
- **Mechanism of Immune Function in a Lymph Node:**
  - **0.** Antigen-Bearing Dendritic Cells & free Antigens enter the Lymph Node via Afferent Lymphatic Vessels. (Note:the dendritic cells actively migrate to the lymph node due to Chemokines.)
  - **1.** Naive B & T-Lymphocytes are also attracted by chemokines to the Lymph Node, and enter via High Endothelial Venules located in the Paracortical Area (T-Cell zone).
  - **2.** Because the above cells are attracted to the Node via Chemokines, they all tend to become localised together in the Paracortical Areas.
  - **3.** Dendritic Cells then present antigens to their respective Naive T-Cells, which proliferate and mature into Effector Cells capable of activating their respective Naive B-Cells.
  - **4.** Effector T-Cells then subsequently activate their respective B-Cells, causing them to proliferate and migrate into nearby Germinal Centres, where they continue to rapidly proliferate.
  - **5.** Effector B-Cells differentiate into plasma cells & begin secreting Ab's. During this time Effector B-Cells undergo a process of selection where their receptors are tested for their ability to bind antigen. (Those that fail, will die)
  - **6.** Ab's & Effector T-Cells leave the lymph node via Efferent Lymphatics & travel via the blood to the site of infection where inflammatory mediators have activated vascular endothelial cells → expression of Adhesion Molecules.
  - **7.** At the site of infection:
    - § CD4-T-Cells Activate Macrophages to make them more cytotoxic.
    - § Antibodies bind to Antigens & recruit complement to: a) Lyse bacteria directly, or b)
    - § Opsonize them to enhance their phagocytosis.

      In the case of a Viral Infection, activated CD8-T-Cells would kill any infected cells present.
- **Note:Lymph Nodes are Important sites for Immunoglobulin Isotype Switching** (or Class Switching), a mechanism that changes a B-Cell's production of Antibody from one class to another. Eg: From IgM to IgG. Note: This process does not affect Antigen Specificity & the Antigen retains Affinity for the same Antigens, but it can now interact with different effector molecules.



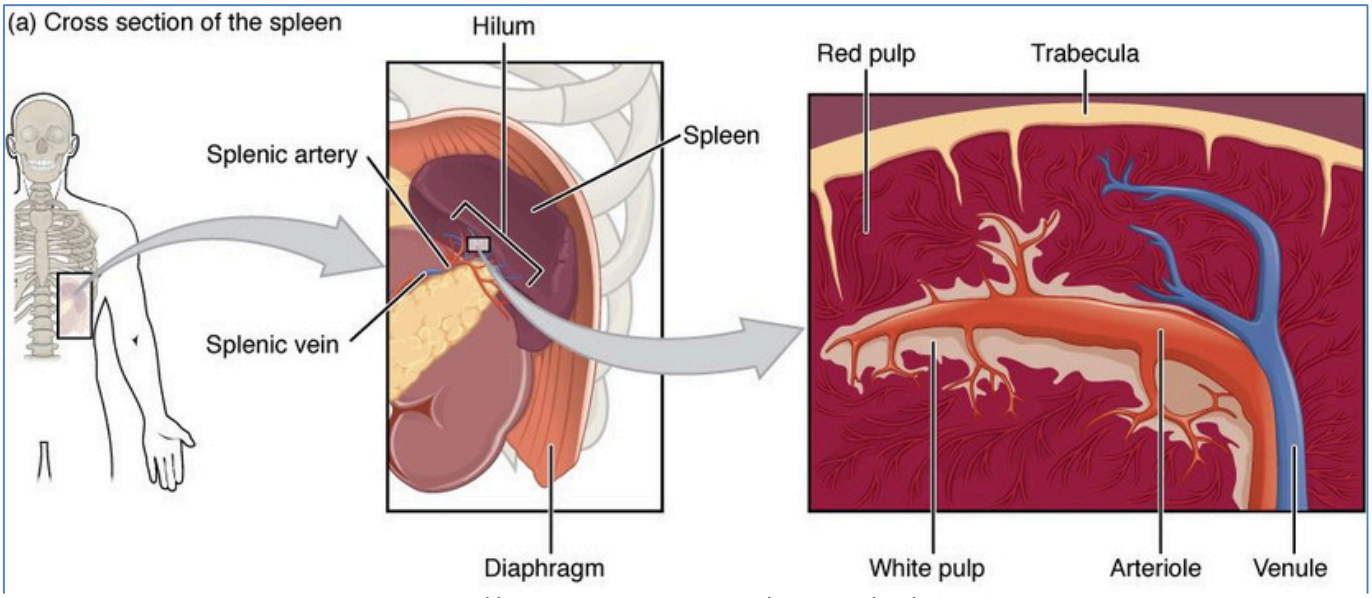
Source: Glycopedia: http://www.glycopedia.eu/e-chapters/chapter-1/article/dendritic-cells-and-adaptive

Spleen: The Filter of the Circulatory System – It is the largest lymphoid organ,

- **Functions:**
  - o It Filters out Foreign **Blood-Borne Antigens**
  - o Filters out **dying RBCs & Platelets** from the Blood (& stores some RBC breakdown products – Eg: Iron from Hb - & releases others to the blood for liver processing).
  - o **Stores blood Platelets**
  - o Providing a site for **Lymphocyte Proliferation**, **Immune Surveillance** & Immune Response. (Contains B+T-Lymphocytes & Macrophages)

- **Anatomy:**
  - o Fibrous capsule with Trabeculae extending inward
  - o Contains B+T-Lymphocytes & Macrophages, as well as huge #s of Erythrocytes (RBCs)
    - § **White Pulp:** Clusters of **B- & T-Lymphocytes,** suspended on Reticular Fibres, which surround the afferent Arterioles. White pulp is divided into 3 areas:
      - **Periarteriolar Lymphoid Sheath (PALS)** - containing mainly T-Cells
      - **Lymphoid Follicles** (mainly B-Cells)
        - o **Germinal Centre –** heavily dividing B-Cells
        - o **B-Cell Corona –** B-Cells
      - **Marginal Zone** – Surrounds the Follicles (Rich in Macrophages; Some T-Cells; Some non-circulating B-Cells called Marginal Zone B-Cells)
    - § **Perifollicular Zone:** Zone surrounding both the Marginal Zone of the Follicles & the
    - § Periarteriolar Lymphoid Sheath. Blood-borne Cells & Antigen enter splenic tissue here.
      Red Pulp: All remaining Splenic Tissue – Composed of Connective Tissue, Venous Sinuses & Splenic Cords. Its primary function is to filter the blood of defective RBCs, Antigens & M icroorganism s.
      (Rich in Macrophages, RBCs, Granulocytes & Platelets)
      - **Venous Sinuses:** Blood Sinusoids
      - **Splenic Cords:** Regions of Reticular Conn.Tissue exceptionally Rich in Macrophages.

- **Blood Flow through the Spleen:**
  - o Blood enters the spleen via the Splenic Artery carrying Lymphocytes & Antigen.
  - o The **Splenic Artery** divides into many Trabecular Arteries.
  - o **Trabecular Arteries** further divide into many **Central Arterioles** (surrounded by White Pulp - PALS) which branch off into terminal capillaries in the Perifollicular Zone.
  - o The **Central Arterioles** then drain into **Venous Sinuses,** which empty into **Trabecular Veins**.
  - o **Trabecular Veins** then merge into the Splenic Vein at the Hilum → Exits the Spleen.



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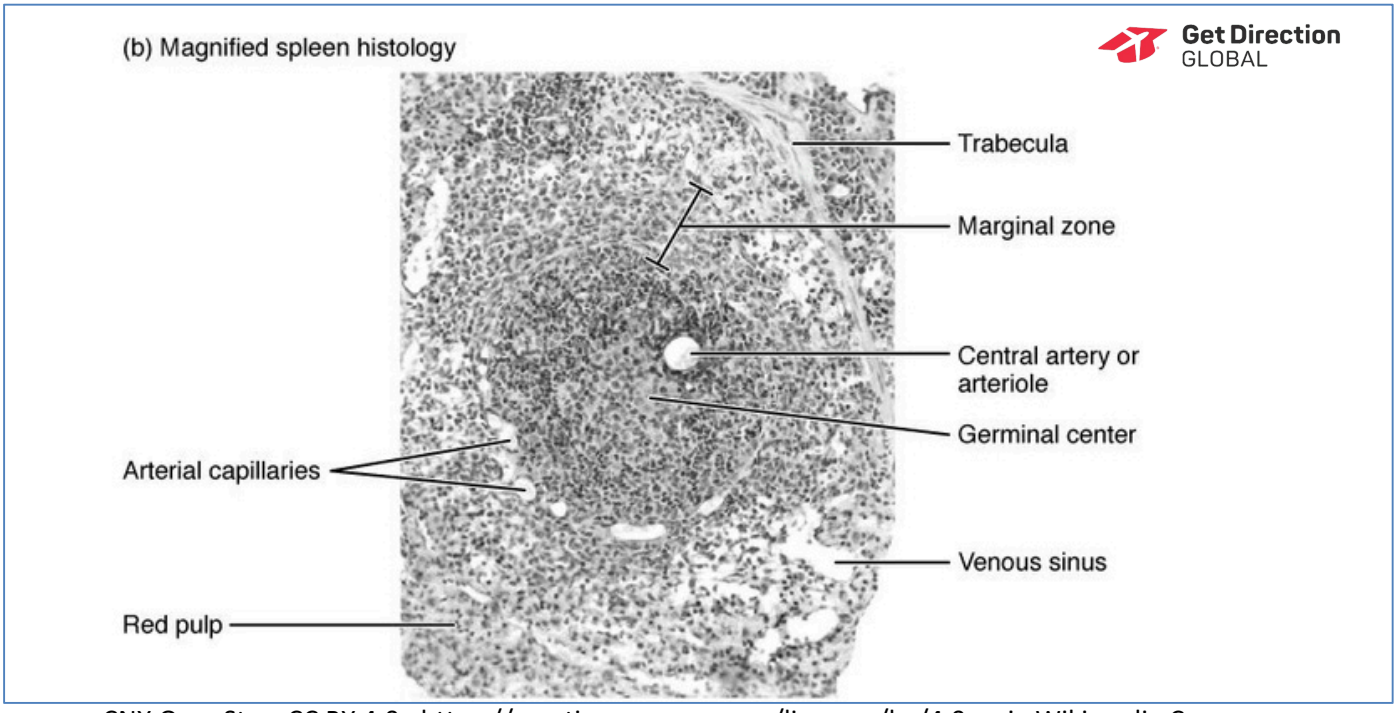

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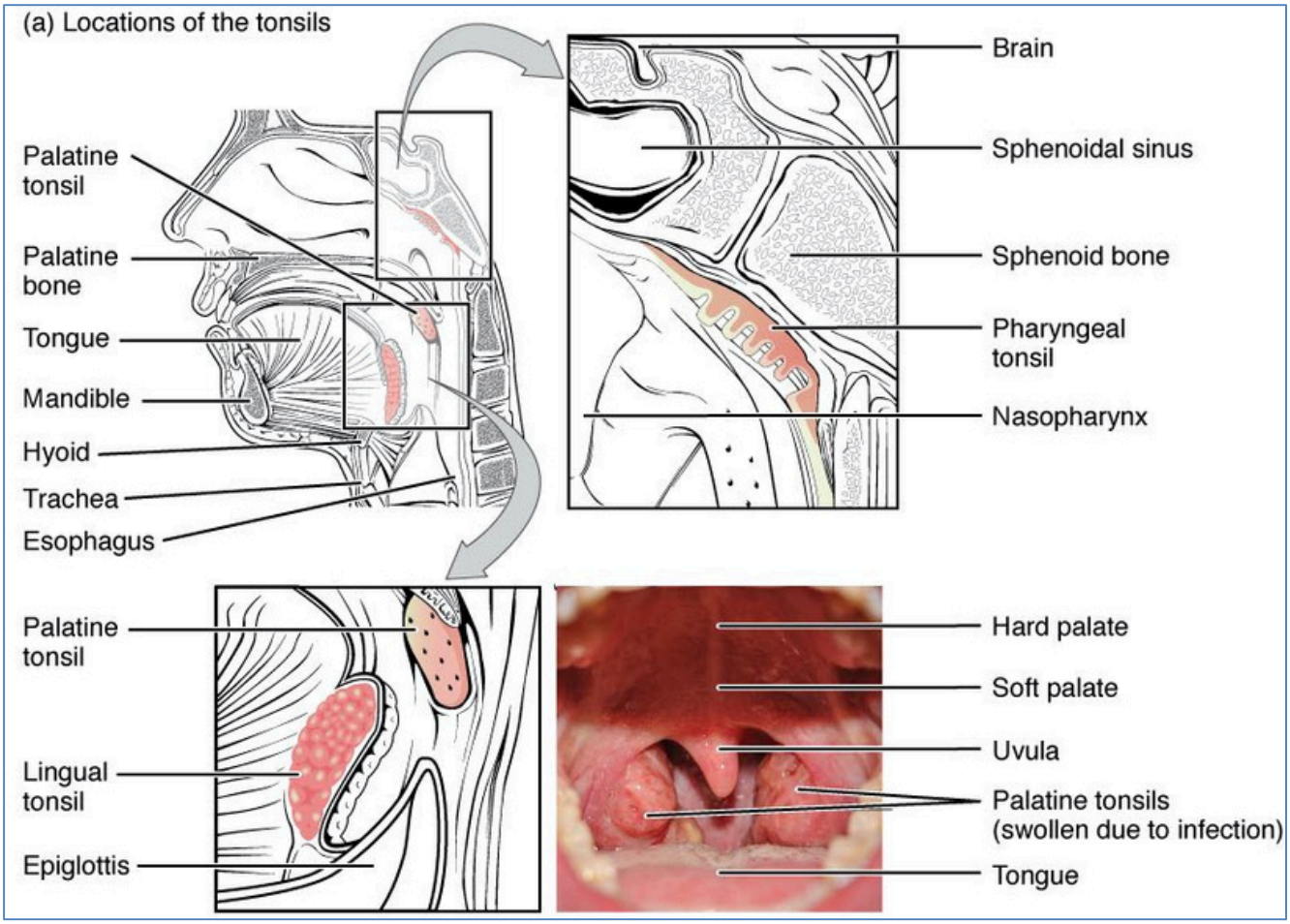
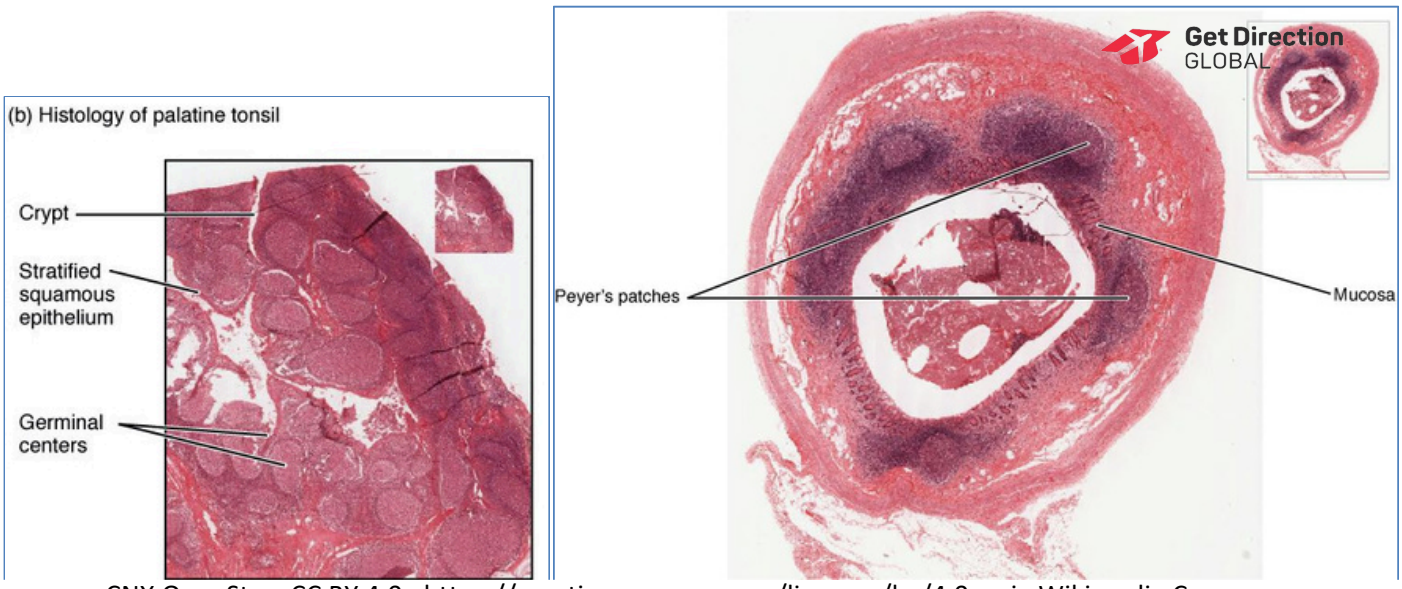
- **M echanism of Im m une Function:**
  1. Antigen-Bearing **Dendritic Cells &** Free-**Antigen** in the Blood enter splenic tissue through capillaries in the Perifollicular Zone.
  2. The blood-borne Microbes, Antigens & Ag:Ab complexes are filtered from the blood by Macrophages + Immature Dendritic Cells in the Marginal Zone.
  3. The already activated Dendritic Cells & the newly activated Dendritic Cells then migrate to the Periarteriolar Lymphoid Sheath, where they present their antigens to their respective Naive T-Cells → Effector T-Cells.
  4. Effector T-Cells then subsequently activate their respective Naive B-Cells (Both circulating B-Cells & B-Cells already in Marginal Zones/Coronas), causing them to proliferate and migrate into nearby Germinal Centres, where they continue to rapidly proliferate.
  5. Effector B-Cells differentiate into plasma cells & begin secreting Ab's. During this time Effector B-Cells undergo a process of selection where their receptors are tested for their ability to bind antigen. (Those that fail, will die)
  6. Ab's & Effector T-Cells leave the Spleen via Venous Drainage and/or Efferent Lymphatics, & end up in the systemic circulation to fight the blood-borne infection.
     - CD4-T-Cells Activate Macrophages to make them more cytotoxic.
     - Antibodies bind to Antigens & recruit complement to: a) Lyse bacteria directly, or b) Opsonize them to enhance their phagocytosis.
     - In the case of a Viral Infection, activated CD8-T-Cells would kill any infected cells present.

- **Asplenia – Clinical Significance:**
  - o Impaired clearance of Opsonised particles
  - o Susceptible to (Bacteraemia) blood-borne bacterial infections. (Primarily Encapsulated Bacteria)
  - o **Treatment:**
    - § Prophylactic Antibiotics
    - § Immunisation
    - § Aggressive treatment of Infection.

M ucosal Associated Lym phoid Tissue (M ALT):

- **Functions:**
  - o **Protects the Internal Mucosal Surfaces. (Ie: The Interfaces between External & Internal):**
    - § ***Gastrointestinal Associated Lymphoid Tissue [GALT]**
    - § Bronchus Associated Lymphoid Tissue [BALT]
    - § Genitourinary Tract.
  - o **"Common" Mucosal Immunity:**
    - § Ag-Priming in One Mucosal Tissue confers Immunity @ Other Mucosal Surfaces.
    - § Also confers Systemic Immunity.
  - o **Why do Mucosal Surfaces require a specialised immune system?**
    - § Because most Mucosal Surfaces have a ***One-Cell-Thick Epithelium*** → Vulnerable.
    - § Because mucosal functions involve ***High Exposure to External Environment***:
      - Ie: Gas Transfer (lungs)
      - Ie: Food Absorption (GI)
      - Ie: Reproduction
      - Ie: Sensory Activities (Nose, Eyes, Throat, Mouth)
- **Anatomy:**
  - o **Consist of Distinct 'Accumulations' of Lymphoid Tissue within the mucosa:**
    - § **Eg: GALT – (Gut Associated Lymphoid Tissues):**
      - Tonsils & Adenoids – surrounding entrance to GI & Respiratory Tract.
      - ***"Peyer's Patches"*** – in the Small Intestines.
      - Solitary Lymphoid Nodules
      - Appendix
    - § Smaller lymphoid patches exist in other mucosal surfaces.





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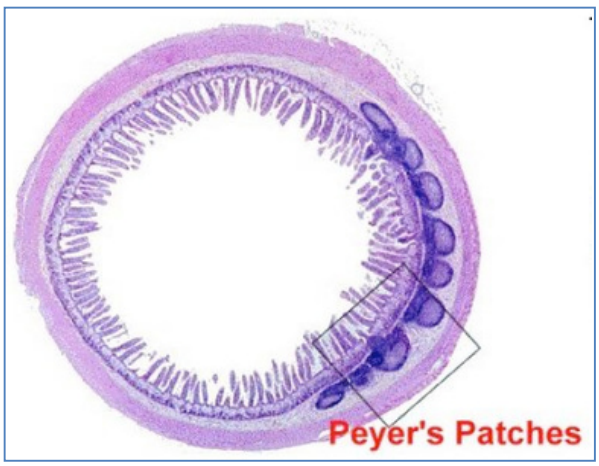
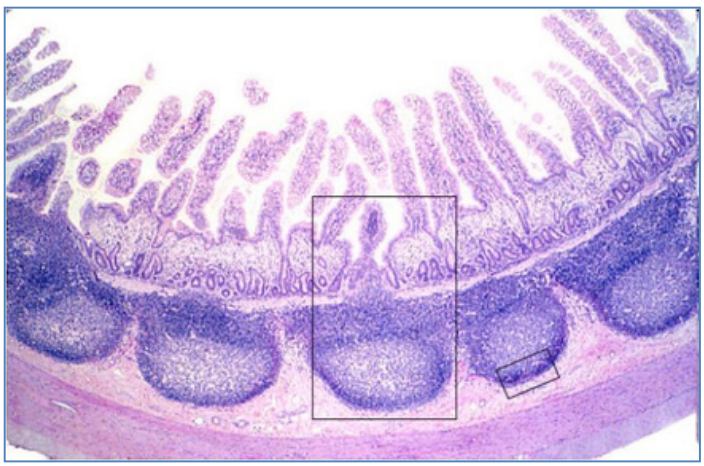
- **Protective Components of the GIT Mucosa:**

Non-Immune Components	Immune Components
Cell Barrier	Secretory Antibody
Mucous	Cell-Mediated Immunity
Gastric Acid	T-Cells (CD4, CD8 & γδ T-Cells)
Microflora	Dendritic Cells
Proteolytic Enzymes	Macrophages & NK Cells
Motility	

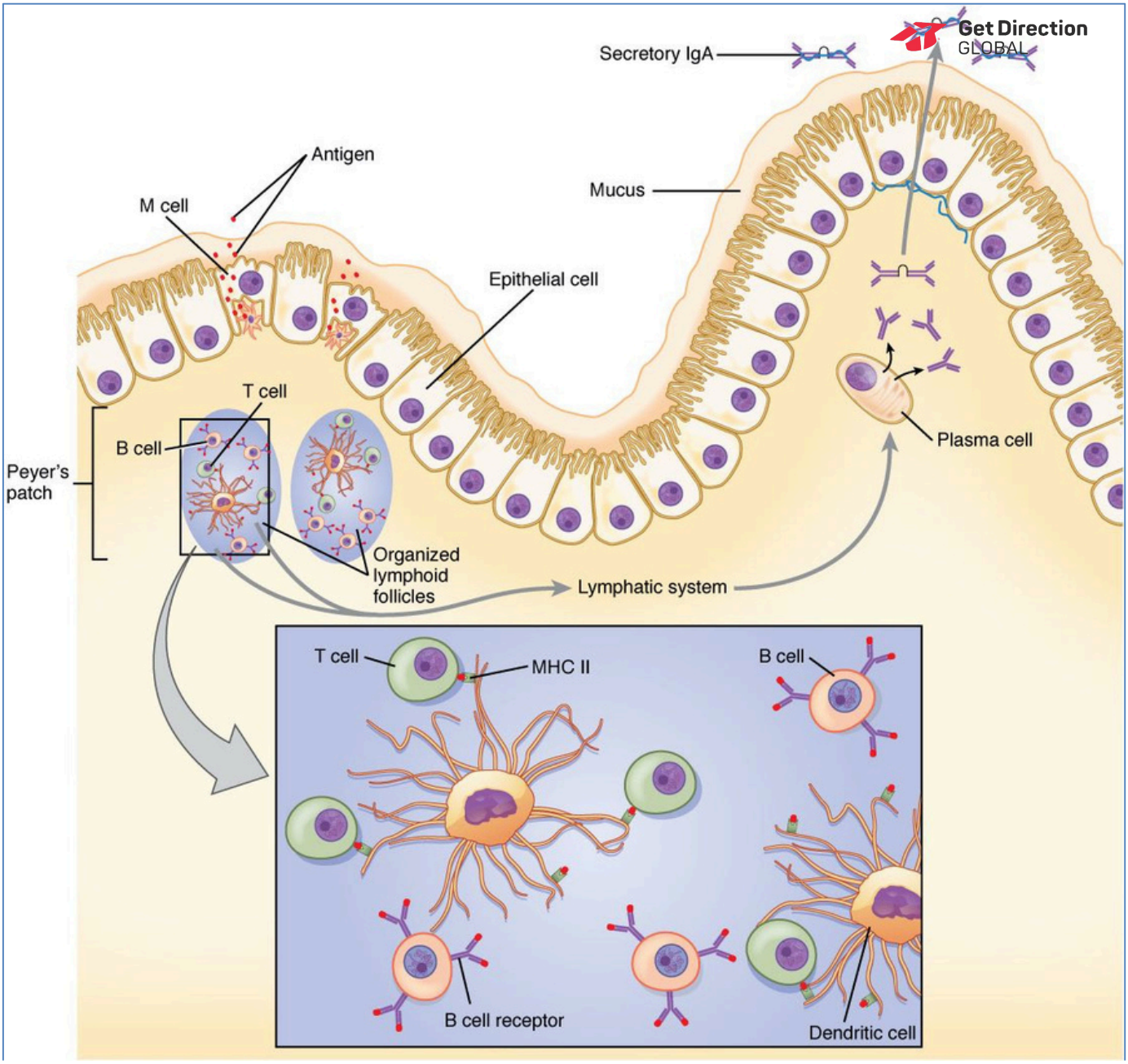
- **Tw o O rganisations of the M ucosal Im m une System :**
  - o **1) Organised Lymphoid Tissues (Ie: Peyer's Patches):**
    - § **- Sites of *Induction* (Ag-Presentation & Activation of Naive Lymphocytes)**
      - **- Peyer's Patches are Like *mini* Lymph Nodes**.
    - § Dome-like Structures extending into the Intestinal Lumen.
    - § Epithelial Layer Contains ***'M'*-Cells (*Microfold-Cells*)** which transport Ag into Lamina Propria.
    - § Contain Resident Dendritic Cells in the Lamina Propria.
    - § Contain Constantly Re-Circulating Naive B- & T-Cells.
  - o **2) Scattered Lymphoid Cells:**
    - § **- Sites of *Effector Function* (Cell-Mediated & Humoral Adaptive Immunity)**
    - § Effector T-Cells. (Including Intraepithelial CD8 T-Cells)
    - § γδ-T-Cells
    - § Effector B-Cells (Plasma Cells) – *IgA-Secreting*.
    - § Resident Innate Immune Cells (Macrophages/Mast-Cells/etc)





- **Lymphocyte Circulation – From Peyer's Patches → Blood/Lymph → Scattered MALT:**
  - o Circulation of Lymphocytes between the Mucosal Immune System & blood/lymph is controlled by Tissue-Specific Adhesion Molecules & Chemokines.
  - o Note:'CCR9' = a Chemokine receptor on T-Cells which aids in Migration back to MALT.

- **Peyer's Patches – Mechanism of Immune Function:**
  1. **M-Cells (microfold cells)** take up Antigens/Pathogens by Endocytosis *or* Phagocytosis, and then release Antigen Fragments at their *Basal Surface*, where Naive B-Cells & Dendritic Cells are waiting:
     - **i.** Specific Naive B-Cells bind & internalise their Ags; and then display them on MHC-II.
     - **ii.** Dendritic Cells below the M-Cells ingest the antigens and display them on MHC-I & MHC-II.
  2. **CD4-T-Cells** specific to the Ags displayed on Dendritic Cells are Activated to Th-Cells by Dendritic Cell.
  3. **CD8-T-Cells** specific to the Ags displayed on Dendritic Cells are Activated to Tc-Cells by Dendritic Cell.
  4. **Effector Th-Cells** then find their Ag-Specific B-Cells and Activate them to start differentiating into IgA-Secreting Plasma Cells.
  5. **Effector CD4, CD8 & B-Cells** leave the Peyer's Patches via the Lymphatics → Lymph Node.
  6. These activated Effector CD4, CD8 & B-Cells proliferate and finish differentiating in the Lymph Node.
  7. Thousands of CD4, CD8 & B-Cell Clones leave the Lymph Node → Blood.
  8. **Once in the blood**, these effector clones migrate back to the Mucosal Tissue through HEVs.
     - **i.** Note: Lymphocytes activated in Peyer's Patches express a special Chemokine Receptor called CCR9, which is specific to a Chemokine expressed only on mucosal HEVs (Especially when inflamed).
  9. **Effector CD8 T-Cells** which return to MALT kill any virally-infected Enterocytes or become intraepithelial cells.
  10. Once **Effector B-Cells** (Now Plasma Cells) are back in the MALT, they begin secreting IgA.
      - **i.** Note:IgA is a Dimer joined by a '***J-Chain***'.
      - **ii.** Note:IgM may also be secreted by some B-Cells; and *also* has a '***J-Chain***'.
  11. **Antibodies** secreted within the Lamina Propria can do different things:
      - **i.** Activate Complement by the Alternative Pathway
      - **ii.** Neutralise Antigens in the Lamina Propria
      - **iii.** Opsonise Antigens for Phagocytosis
      - **iv.** Bind to Phagocytic Cells → Initiates Oxidative Burst & Release Inflammatory Cytokines.
      - **v.** Can be Transported across the epithelium...see below:
  12. '***J-Chain***' on IgA (or IgM) binds to the ***'Poly-Ig* Receptor'** on the basal membrane of the epithelial cell.
      - **i.** IgA (or IgM) is then ***Transcytosed*** across the epithelium and into the intestinal lumen.
      - **ii.** Note: Antibodies can also be transported into the Bile Canaliculi & Mammary Glands (Breasts).
      - **iii.** Note:IgA (or IgM) in its ***secreted form*** = **s**IgA (or **s**IgM)
  13. **sIgA** Antibodies (in the intestinal lumen) can ONLY Neutralise Antigens.
      - i. Why? – Because all other antibody functions require either *Complement* or *Phagocytes*, which don't exist in the intestinal lumen. (As the lumen is an *'Immune Privileged*' site)
      - § **Note:IgA-Deficiency – Why are most people affected asymptomatic?**
        - Due to IgM's ability to replace IgA as the predominant antibody in secretions.
        - Note:IgM is the only other Antibody with a J-Chain, & hence the only other able to be transcytosed.

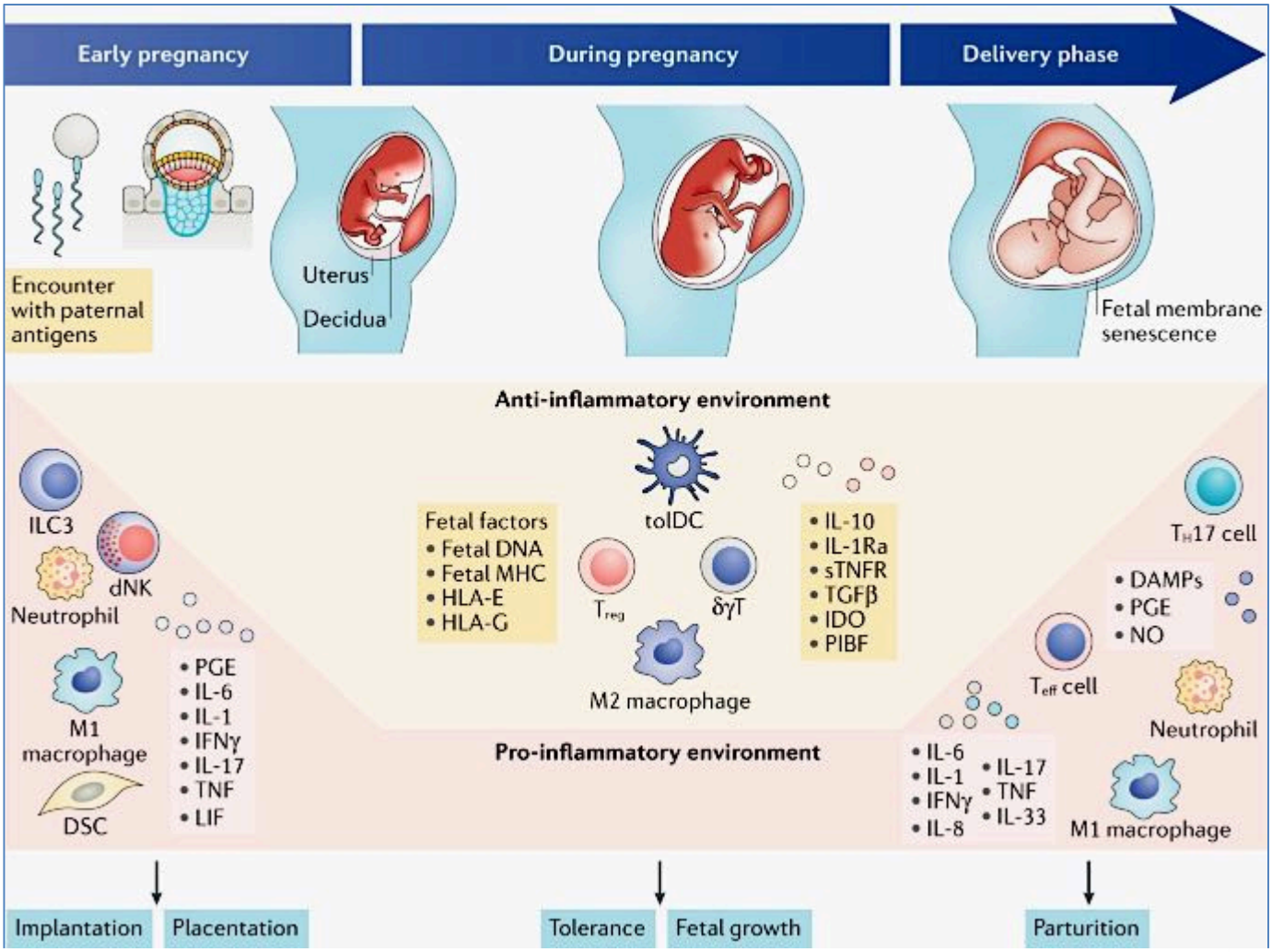


CNX OpenStax, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons : **IgA Immunity** The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that im m une responses can be m ounted .

REJECTION IMMUNOLOGY

Placental Immunology: (How the Foetus Avoids Immune Rejection):

- **Foetuses are 50% Foreign to the Mother and would usually lead to Immune Rejection via T-Cells.**
- **However, the Foetus can Survive; But the Mechanisms behind this are still largely unknown:**
  - **Note:** Self-immunosuppression of the mother is pointless, as this would leave the mother & foetus vulnerable to infection.
- **Medawar's 3 Strategies for Foetal Survival:**
  - **1- Reduced/Modified MHC Antigen Expression on Trophoblasts:**
    - Foetal Trophoblasts DO NOT express Classical MHC-I molecules (Ie: Neither HLA-A or HLA-B).
      - They DO, however, express ***HLA-G*** (A NON-Polymorphic, NON-Classical MHC-I).
      - *HLA-G* is thought to prevent NK-Cell Attack
      - Also express ***HLA-C*** & ***HLA-E*** which aren't recognised as foreign.
        - *HLA-C* & *HLA-E* also bind to NK-Cells & prevents NK-Cell Attack.
    - → Lack of Antigen-Stimulation of Maternal Lymphocytes.
  - **2- Modulation of Maternal Immune System:**
    - Immune cell functions change during pregnancy.
      - Trophoblast Secretions → *Cytokines* that Suppress *Local* T-Cells (Local)
      - High Progesterone & HCG → Immunosuppressive (General)
  - **3- Placenta is a Physical Barrier which Can't be crossed by Lymphocytes:**
    - Although placenta is a Foetus-Derived tissue, its outer layer (Trophoblasts) is the only
    - interface between Foetal & Maternal Tissues.
      There is NO Vascular Continuity between Mother & Foetus.

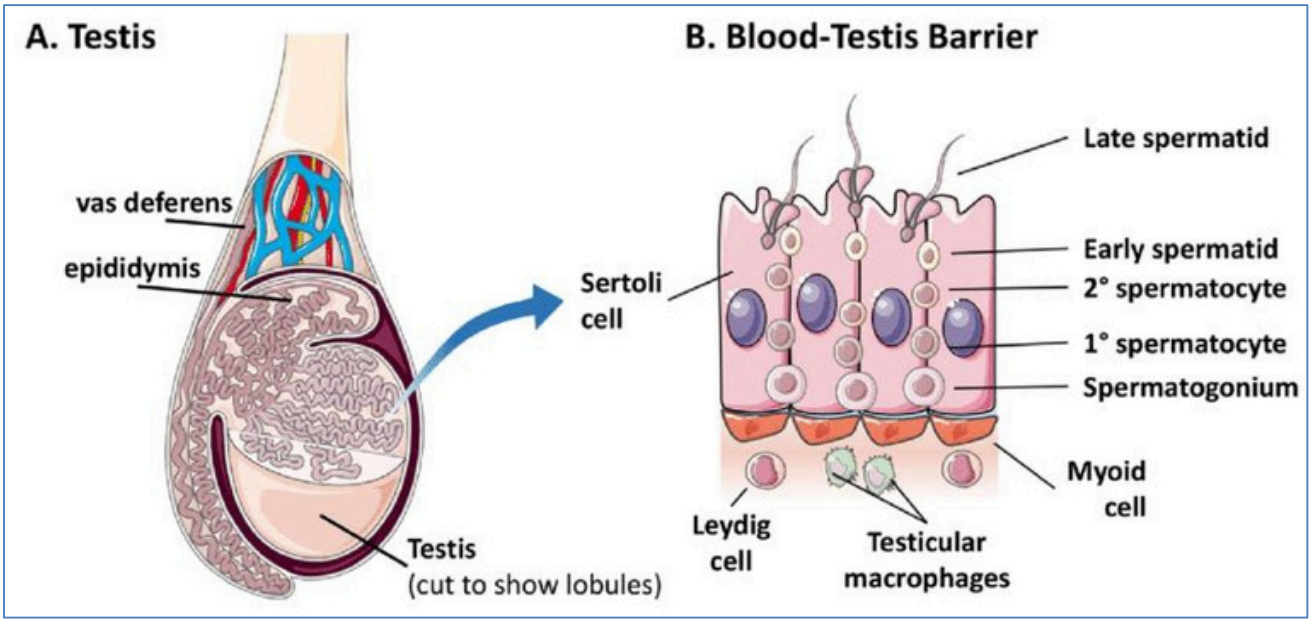


Förger, F., Villiger, P.M. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. *Nat Rev Rheumatol* **16,** 113–122 (2020). https://doi.org/10.1038/s41584-019-0351-2

Testicular Immunology: (How the Sperm Avoids Immune Attack):

- **Sperm are highly Antigenic (since they are genetically unique)**.
- **(In Males) – The *'Blood-Testes Barrier'* Protects the Sperm from the Immune System:**
  - o Epithelial Barrier in Epididymis (joined by Tight Junctions) separate sperm from immune system.
  - o **Abnormalities of the Blood-Testes Barrier can expose Sperm to the Immune System:**
    - § (Eg: Malformation, Trauma, Infection, Obstruction)
    - § → Production of Anti-Sperm Antibodies → Possibly Infertility

- **(In Females) – Sperm in Female Repro-Tract → Intense Inflammatory Response:**
  - o Functions to remove excess sperm & microbes (≈24hrs post coitus)
  - o However, can → Production of Anti-Sperm Antibodies → Possibly Infertility.



Persistence and Sexual Transmission of Filoviruses - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Localization-of-the-blood-testis-barrier-within-the-male-reproductive-tract-A_fig1_329384250

TRANSPLANT BASICS:

- **Terminology of Transplant:**

Types of Tissue and Organ Grafts and Their Complications		
Graft	**Procedure**	**Complications**
Autograft	From self to self	No rejection concerns
Isograft	From identical twin to twin	Little concern of rejection
Allograft	From relative or nonrelative to individual	Rejection possible
Xenograft	From animal to human	Rejection possible

Principles of Transplant Immunology:

- **Alloantigens =** "Antigens that differ between members of the same species."
  - o MHC is the most obvious Alloantigen & is the most potent trigger of rejection.
  - o However, other alloantigens include Minor Histocompatibility Antigens, which are self-proteins which have been broken down into peptides & displayed on MHC-I Molecules.

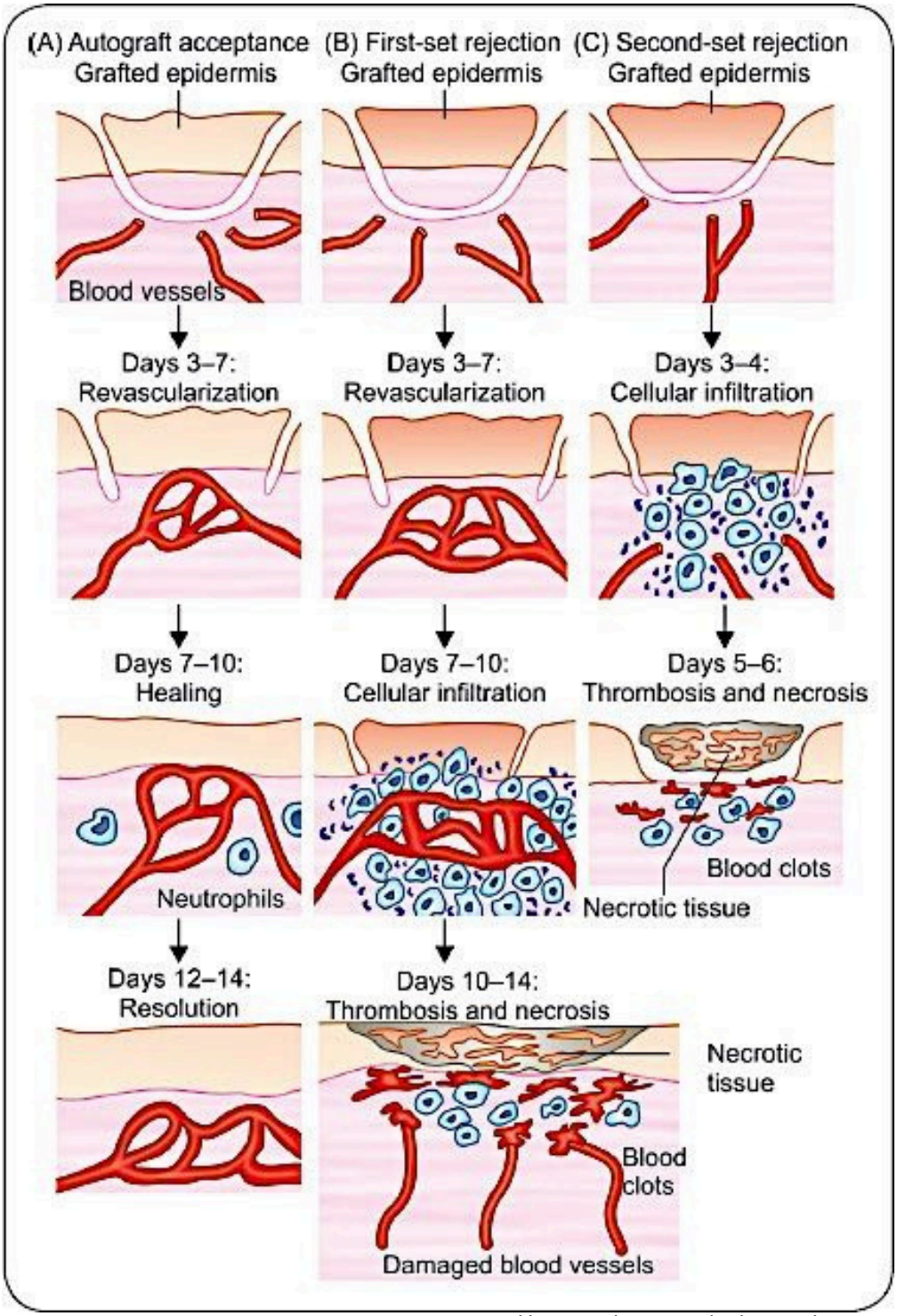
- **"1st-Set" & "2nd-Set" Graft Rejection:**
  - o **1st Set Rejection:**
    - § Allogenic graft is given to Unsensitised Individual. (Without Immunosuppressants)
    - § Graft is Rejected fairly rapidly once Host Sensitisation has occurred.
  - o **2nd Set Rejection:**
    - § Allogenic graft from the *Same Donor* is given to a *Pre*-Sensitised Individual (Without Immunosuppressants)
    - § Graft Rejection is *Accelerated* → Rejection is much more rapid.
    - **(Note:2nd-Set Rejection is *Specific*** – Ie: It will only occur if the Recipient is *Pre*-Sensitised to *That Specific Donor*)
  - o **Note: Transfer of "2nd-Set" Rejection by Lymphocyte Transfusion:**
    - § Transfusion of Lymphocytes from a Pre-Sensitised Individual to a Naive Individual confers In s ta n t A llo im m u n ity (2nd-S e t R e je c tio n).

- **Even Matching just the MHC 'Type', Doesn't Guarantee Graft Survival:**
  - o (Ie: MHC genes may be the same, but other *Minor* Histocompatibility genes may be different.)
  - o **Minor Histocompatibility Antigens** ('Minor H Antigens') are cell-proteins which have been broken down into peptides & displayed on MHC-I Molecules of all cells.
    - § Minor H Antigens will be different between Graft & Host (unless genetically identical).
    - § Note: Most minor H antigens are encoded by autosomal genes, & most are unknown.
  - o **Matching MHC-Type @ the HLA Locus will Prolong Graft Survival, but NOT Guarantee Survival**

- **"The Alloimmune Response" → 2 Pathways to Rejection:**
  - o **1- Direct Allorecognition (AKA. Direct Sensitisation):**
    - § **Note:** Organ grafts contain APCs of *Donor Origin*.
    - § These Donor Dendritic Cells migrate to Local Lymph Node via Lymph & expose their MHC or Minor-H-Antigen → Directly stimulates *Alloreactive* Host T-Cells.
      - (These T-Cells have TCRs specific for the allogenic MHC-I/II:Peptide Complexes)
    - § Alloreactive Effector T-Cells are carried back to the graft → Attack the graft directly.
    - § **Note:Direct Allorecognition is thought to be largely responsible for Acute Rejection**.
  - o **2- Indirect Allorecognition (AKA. Indirect Sensitisation):**
    - § Uptake & Processing of Allogenic Graft-Proteins by the Host's Dendritic Cells → Presents Peptide bound to self-MHC → Stimulates Ag-specific T.Cells.
    - § Alloreactive Effector T-Cells are carried back to the graft → Attack the graft directly.
  - o **(Note: During the Alloimmune Response, the Regional Lymph Nodes become enlarged due to m asses of Proliferating Effector T-Cells.)**

- **Afferent & Efferent arms of Alloimmune Rejection:**
  - o **Afferent =** Sensitization phase of the immune response (Direct/Indirect Allorecognition)
  - o **Efferent =** Lymphocytes differentiate into Effector Lymphocytes → Initiate an Immune Response.

- **The Central Role of T-Cells in Rejection:**
  - o Direct Cytotoxic T-Cell attack on graft cells occurs when the T-Cells recognise the Graft-MHC directly.
  - o If MHC-Restriction occurs (Ie: T-Cells don't properly recognise graft-MHC), the T-Cells may still contribute to Graft-Rejection by:
    - § a) Activating Macrophages → Tissue Injury & Fibrosis
    - § b) Activating B-Cells to Produce Allo-Antibodies → Ab/Compliment -Mediated Graft Destruction.



Source: Transplant and Cancer Immunology, https://doi.org/10.5005/jp/books/12637_20

CLINICAL TRANSPLANTATION:

Get Direction GLOBAL

Ischaemic Times:

- **Cold Ischaemic Time:**
  - o Begins when the organ is Clamped & Cooled during Removal.
  - o Ends when the organ is Returned to Physiological Temperature.
- **Warm Ischaemic Time:**
  - o Starts when the organ is Returned to Physiological Temperature.
  - o Ends when Surgical Anastomoses are complete → Reperfusion.

Organ Transplant (Eg: Kidney):

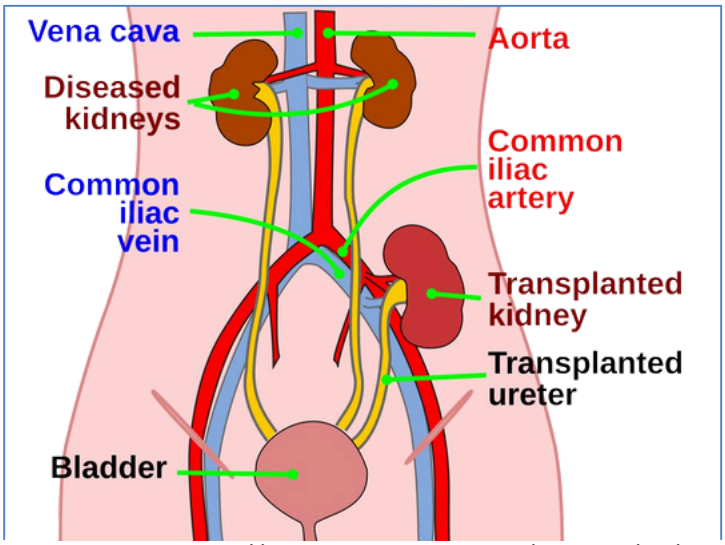
- **Indication:**
- o Chronic Kidney Failure

Requirements:

- o **Absolute Requirements:**
  - § ABO blood group must be Identical OR Compatible.
  - § Negative T-Cell Cross match (Ie: Incubate donor T-Cells with Recipient's Serum → No
  - § Reaction)
  - § No Previous Antibodies against Donor HLA.
    No shared incompatibilities with previous donors.
- o **Other Considerations:**
  - § *Degree* of HLA Match
  - § Viral Status
  - § Previous blood transfusion?

- **Factors Affecting Graft Survival:**
  - o *ABO blood group identity
  - o *Negative Cross Match
  - o *Degree of HLA match
  - o **Immunosuppressive Therapy.
- **Complications of Kidney Transplants:**
  - o Transplant Rejection (See below)
  - o Infections (Due to Immunosuppressant drugs)
  - o Post-Transplant Lymphoproliferative Disorder (Eg: Immune Suppressant Induced Lymphoma)
  - o Electrolyte Imbalances (Ca/Ph) which can lead to ↓Bone Density.
  - o Side Effects of Immunosuppressive Medications.
- **Signs of Kidney Rejection:**
  - o **Histological (Ie: By Biopsy):**
  - o § Abundant Infiltration of Inflammatory Cells in Renal Tubules

    Functional:
    - § ↓EPO (Erythropoietin Release) → Anaemia & Hypoxia
    - § ↑BP – Due to ↓GFR
    - § ↑Uraemia



Bone Marrow Transplant:

- **Note:BM Transplants are dangerous because they require the recipient's bone marrow to be destroyed.**
- o **Therefore, Assessment of Risk/Benefit Ratio is essential.**

Indications:

- o **Any Abnormality of Bone-Marrow (Myeloid) Stem Cells:**
  - § Ie: Malignancies (Leukaemia/Lymphomas)
  - § Ie: Immunodeficiencies
  - § Ie: Acquired Abnormalities (Eg: Thalassaemia/Sickle Cell Disease/Aplastic Anaemia)

- **Requirements:**
  - o **HLA Matching:**
    - § **MHC-I/II matching is Essential (To Prevent Graft Rejection or Graft Vs. Host Disease)
    - § This is done by Genetic Techniques to match HLA Genes.
  - o **Cross Matching:**
    - § Incubate Donor Cells in Recipient Serum.
    - § To Determine whether Antibodies in Recipient's Serum will *Cross-React* with Donor Cell Ags.
    - § (To Avoid hyperacute rejection)
  - o **Mixed Lymphocyte Culture (MLC):**
    - § To detect level of reactivity between Donor & Recipient Lymphocytes
    - § (Detects subtle differences in MHC-II that aren't detectable by standard techniques)
    - § (To Avoid GVHD & Rejection)

- **Considerations:**
  - o **Relating to the Disease:**
    - § Is it *Curable* by Transplant?
    - § Is there an *Alternative*?
  - o **Relating to the Procedure:**
    - § Recipient Age
    - § General Health
    - § Infection
    - § Donor Availability.

- **(Note: Umbilical *'Cord Blood'* can be used as BM Transplants**, because ↑[Stem Cell] & Non-Invasive
- extraction procedure**)**

BMT Procedure:

- o **1- Elimination of Recipient BM Stem Cells:**
  - § By High-Dose Chemotherapy/Total-Body Irradiation.
  - § Why? – To Eliminate the Pt's *Immune System* → ↓Risk of Graft-Rejection.
- o **2- BM Donation:**
  - § 500-1200ml of BM is extracted from donor. (Usually 1st degree relatives)
  - § • BM Donation is treated with Anti-T-Cell-Antibodies to leave only Stem Cells. OR Umbilical Cord Blood.
- o **3- BM Transplant:**
  - § Transfusion of Donor Marrow into Recipient's Bone.

- **Complications of BMT:**
  - o **Graft Failure:**
    - § Rejection...OR
    - § Insufficient # of BM Cells in Post-Transplant Period. (Treated by stimulatory Cytokines)
  - o **Infection:**
  - o § High rates despite preventative measures.

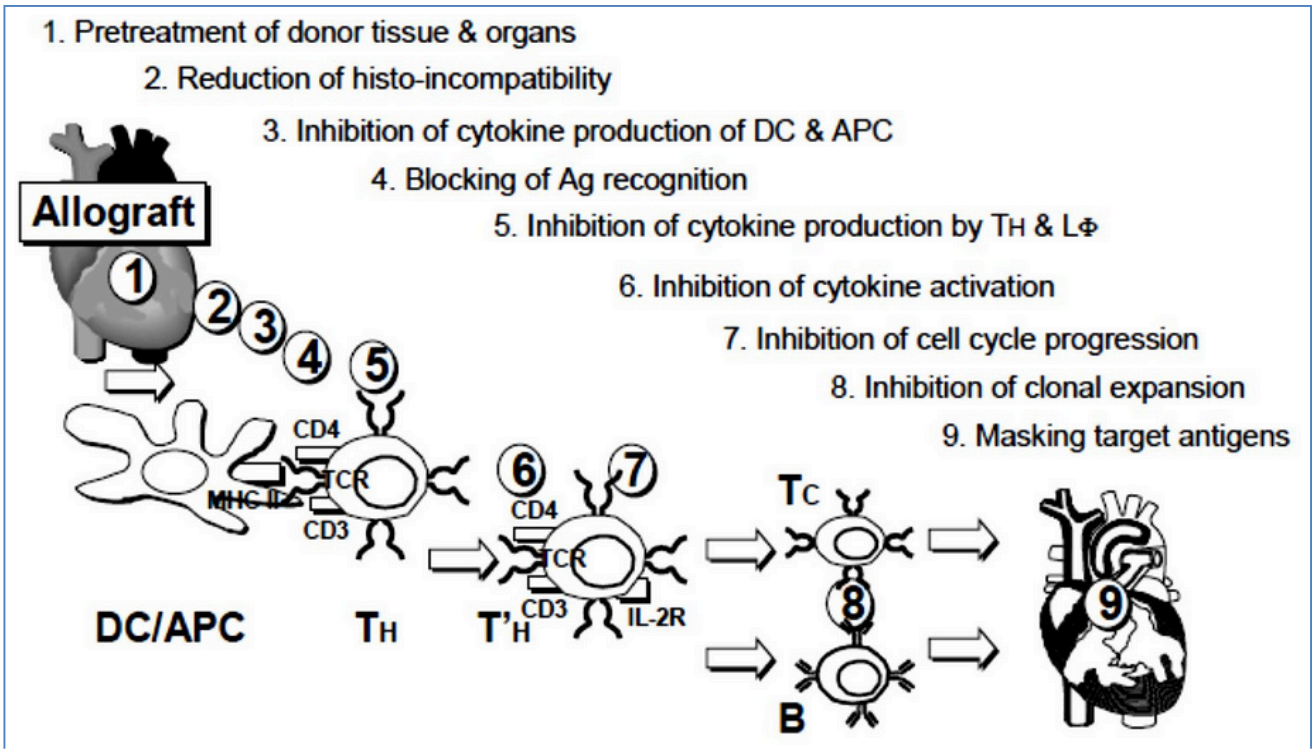
  Graft Vs. Host Disease:
    - § Where the Immunologically-Mature Graft Cells *Attack the Host*! (Ie: Reverse Rejection)
      - Can occur even if donor & recipient are HLA-identical because the immune system can still recognise differences in Minor-H-Antigens.
      - Therefore, it is necessary to select donors with a *Similar Genotype* for Minor-H-Ags.
    - § Occurs 7-10 days post-op.
    - § Symptoms: - Skin Rash/Fever/Hepatosplenomegaly/Bloody Diarrhoea/Breathlessness.
    - § *70% Mortality Rate*

IMMUNE INTERVENTION IN TRANSPLANTATION:

- **Types of Immune Intervention:**
  - **Immunosuppression of Recipient:**
    - Most Common
    - Currently drugs are *Non-Specific* → *General* Immunosuppression → Immunocompromise.
    - (However, more specific drugs are being developed)

      Note: The *Strength* of Immunosuppressants is a fine balance between Rejection & Infection.
      - Too much immunosuppression → Infections / Cancer risk
      - Too little immunosuppression → Rejection
  - **Induction of Specific Tolerance:**
    - Impossible in humans
  - **Pre-treatment of Allograft Prior to Transplant:**
    - Ie: Removal of Donor APCs from graft tissue

- **Potential Sites for Immunomodulation:**
  - Drug development could target any one of the following processes.



IMMUNOSUPPRESSION:

- **Requirements of Immunosuppressive Agents:**
  - o Induction must be at/before *Initial Exposure* to the Allograft.
  - o Maintenance to prevent Allograft Rejection
  - o Treatment of Rejection Episodes.
- **Current Immunosuppressive Agents:**
  - o **Non-Specific:**
    - § *Corticosteroids
    - § *Cyclosporin
    - § Irradiation
    - § Cytotoxic Agents
    - § Antibodies
  - o **Specific:**
    - § NONE.

- **Corticosteroids:**
  - o **(Eg: Prednisone)**
  - o **Mechanism of Action:**
    - § **Anti-Inflammatory Effects:**
    - § • ↓- Oedema/Cap.Dilation/Angiogenesis/Diapedesis/Phagocytosis/Fibrosis.

      ***Immunosuppressive Effect:**
      - • Inhibit gene transcription for the Inflammatory Cytokines (IL-1 to IL-8), Particularly
      - • IL-1 & IL-2 → (↓ Antigen-Induced B & T Lym phocyte Proliferation)
      - • →↓Circulating Lymphocytes & Monocytes (Macrophages)
      - →↓Antigen Presentation
  - o **Side Effects:**
    - § ↑Risk of Infection
    - § Growth Suppression in Children
    - § Diabetes
    - § Gastric Ulcer
    - § Hypertension
    - § Cushings Syndrome (Hyper-cortisolism)

- **Cytotoxic Agents (AKA. Cytostatics):**
  - o **(Primarily used in Chemotherapy for Cancer)**
  - o **Mechanism of Action:**
    - § Blocks DNA Synthesis (S-Phase) → Inhibits Cell Division →Kills Rapidly Dividing Cells.
    - § Note: Since Lymphocytes rapidly divide, they are susceptible → Bone Marrow Suppression.

- **Cyclosporin & Tacrolimus:**
  - o **(A Fungal Metabolite)**
  - o **Mechanism of Action:**
    - § Inhibits IL-2 Receptors → (↓Antigen-Induced Lymphocyte Proliferation)
    - § Inhibition of Cytokine Production by Lymphocytes
  - o **Side Effects:**
    - § Renal Toxicity

- **Antibodies as Immunosuppressants:**
  - o **Mechanism of Action:**
    - § The aim is to *Inhibit Lymphocyte Function* by giving Abs directed against Lymphocytes.
    - § Eg: IL-2-Receptor Antibodies → Inhibit the function of IL-2 Receptors.
  - o **Problems:**
    - § Selection of Relevant Antigens specific to Lymphocytes.
    - § Avoiding Antibodies against blood products.
  - o **Monoclonal Antibodies:**
    - § Specific Antibodies manufactured to bind to Specific Antigens.

INFLAMMATION

INFLAMMATION

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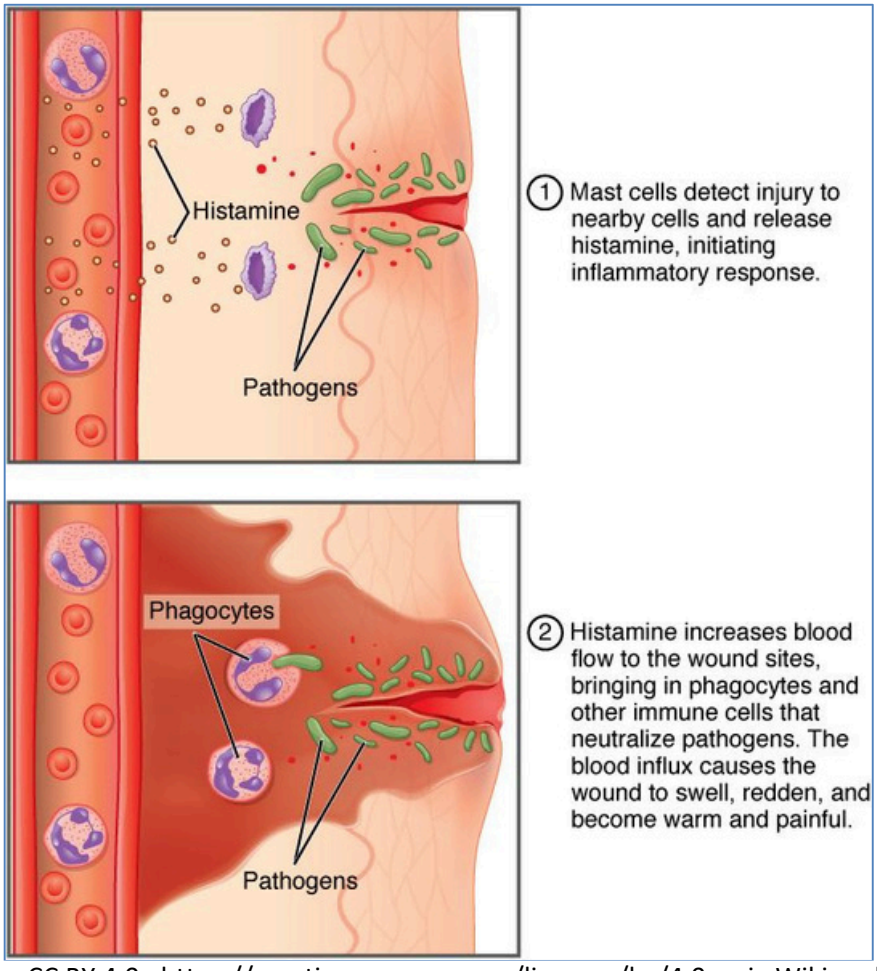
General Features of Inflammation:

- **What is it?**
- o The complex reaction of Vascularised Tissue to Injury/Microbes.

5 Cardinal Signs:

- o o Pain (Dolor)
- o Swelling (Tumor)
- Redness (Rubor)
- o Heat (Calor)
- o Loss of Function

- **What is its Purpose?**
  - o The Body's First *Active* Defence against Invading Microbes.
    - § Neutralize
    - § Destroy
    - § Limits the Spread of Harmful Agents.
  - o Sets the stage for *Tissue-Repair*.
- **Major Players in Inflammation:**
  - o **Vessels**: (Endothelial Cells)
  - o **Connective Tissue Cells Involved:**
    - § Mast Cells (Histamine Release)
    - § Fibroblasts (Scarring & Tissue Repair)
    - § Macrophages (Phagocytosis & Cytokine Secretion)
    - § Lymphocytes (Cell-Mediated & Humoral Immunity)
  - o **Blood Cells Involved:**
    - § Monocytes (→ Macrophages)
    - § Neutrophils (Phagocytosis)
    - § Eosinophils (Parasitic Infections & Allergy)
    - § Basophils (Allergy)

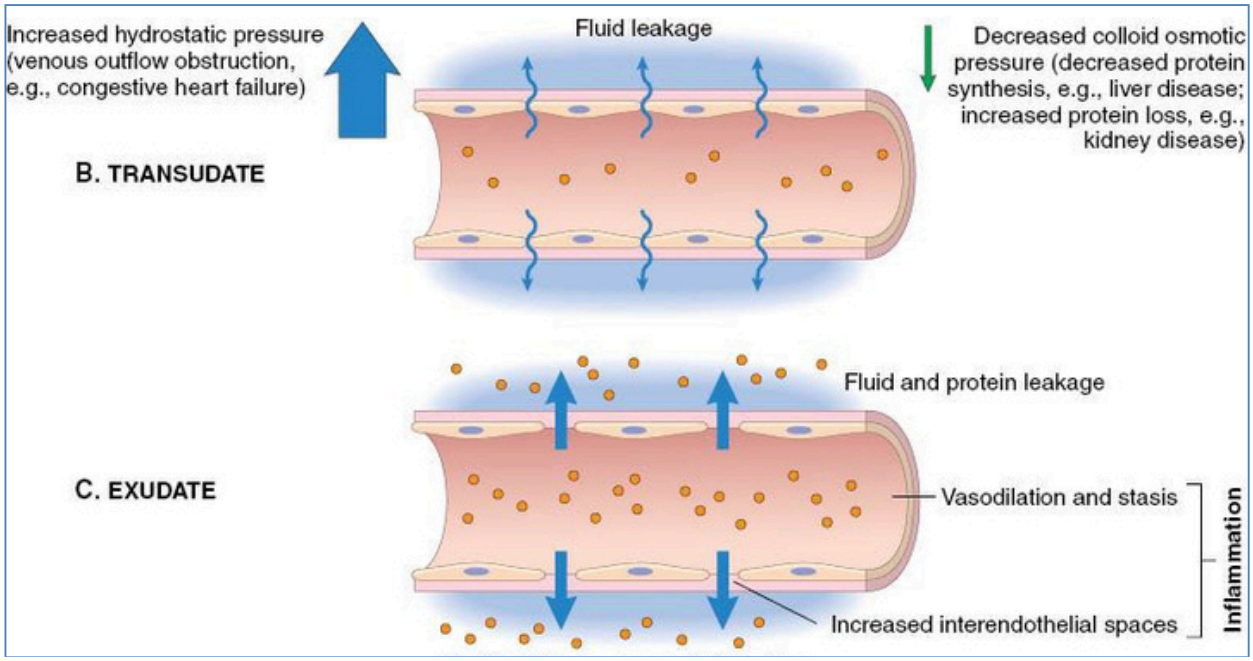


Acute Vs. Chronic Inflammation:

- **Acute Inflammation:**
  - Ie: Minutes/hours/days after Trigger.
  - **Primary Characteristics:**
    - Vasodilation → ↑ Blood Flow
    - *Exudation* (Fluid & Plasma Protein accumulation in local tissues)
    - *Neutrophil Migration* (into tissues)
- **Chronic Inflammation:**
  - Ie: Weeks→Years after Trigger. (Or Continuous trigger)
  - **Primary Characteristics:**
    - High Numbers of Inflammatory Cells:
      - Macrophages
      - Lymphocytes
    - Angiogenesis
    - Fibrosis
    - Necrosis

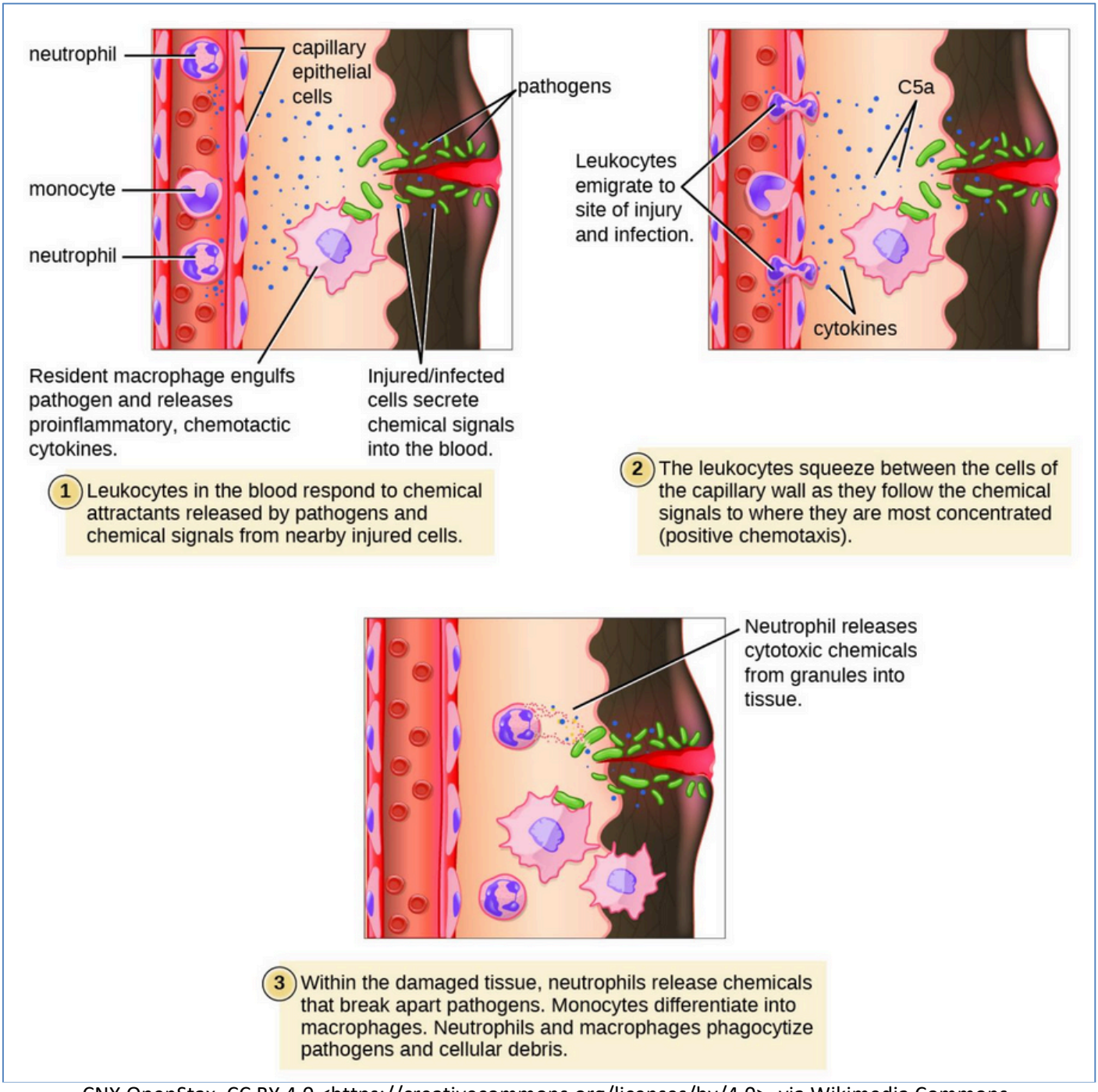
The Primary Inflammatory "*Responses*" (Vasoactivity & Leukocyte Migration):**

- **Vasoactivity:**
  - **- Vasodilation:**
    - Increase in Vascular Calibre → ↑Blood Flow
    - **Mechanism:** Relaxation of Vascular Smooth Muscle
  - **- &/OR ↑Vascular Permeability:**
    - Structural Changes in Endothelium → Allows Plasma Proteins & Leukocytes to Leave the
    - Circulation.
      Mechanism: By Endothelial Cell Contraction → Creates Gaps Between Cells.
  - **Triggered By:**
    - **Histamine (Directly), or Indirectly by Histamine-Releasing Factors:
    - Platelet-Activating Factor (PAF):
    - Bradykinin
    - Nitric Oxide
  - **Effects:**
    - ↑Blood Flow
    - → ↑Mucus Production
    - Transudate (Leakage of Fluid from Circulation → Tissues)
      Exudate (Leakage of Fluid, Cells & Plasma Proteins from Circulation → Tissues)
      - → Easier Leukocyte Emigration from Blood →Tissues.



Unattributable

- **Leukocyte Migration:**
  - o ↑ **WBCs in Extravascular Space:**
    - § Neutrophils/Eosinophils/Basophils
    - § Macrophages
    - § Lymphocytes
  - o ↑**Cell-Mediated Immune Responses**
    - § Innate – Granulocytes/Macrophages
    - § Adaptive – Lymphocytes & NK-Cells



HYPERSENSITIVITY & ALLERGY

HYPERSENSITIVITY & ALLERGY.

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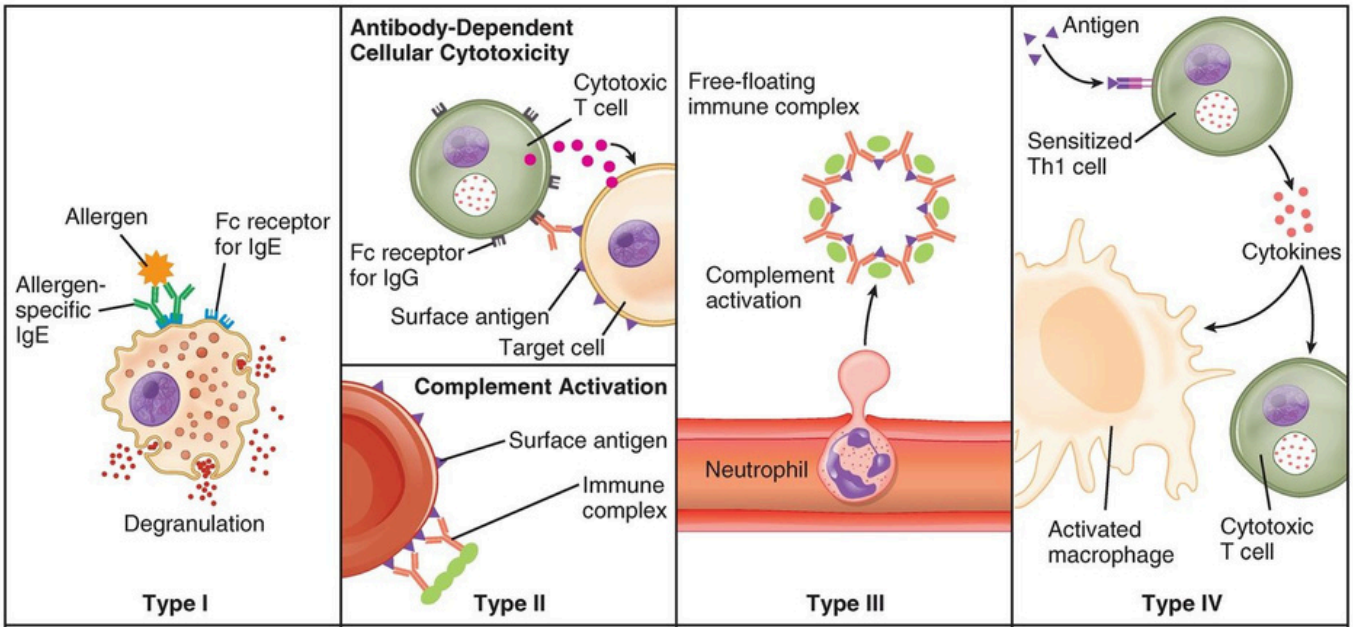
Hypersensitivity:

- **= an *Abnormal state of Immune Reactivity* with *Deleterious Effects* on the Host.**
- (Note: Often the immune response is to an otherwise innocuous antigen.
- **(Atopy = "Tendency to produce Immediate Hypersensitivity Reactions (usually IgE-Mediated) against Innocuous Substances)**

There are 4 Types of Hypersensitivity:

- **I - Anaphylactic**
- **II – Antibody Dependent Cytotoxicity**
- **III – Immune Complex**
- **IV – Cell Mediated Disease**

Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

	Hypersensitivity Types and Their Mechanisms Get Direction GLOBAL			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
Mechanism of activation	Allergen-specific IgE antibodies bind to mast cells via their Fc receptor. When the specific allergen binds to the IgE, cross-linking of IgE induces degranulation of mast cells.	IgG or IgM antibody binds to cellular antigen, leading to complement activation and cell lysis. IgG can also mediate ADCC with cytotoxic T cells, natural killer cells, macrophages, and neutrophils.	Antigen-antibody complexes are deposited in tissues. Complement activation provides inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue.	T_H1 cells secrete cytokines, which activate macrophages and cytotoxic T cells.
Examples of hypersensitivity reactions	Local and systemic anaphylaxis, seasonal hay fever, food allergies, and drug allergies	Red blood cell destruction after transfusion with mismatched blood types or during hemolytic disease of the newborn.	Post-streptococcal glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Contact dermatitis, type I diabetes mellitus, and multiple sclerosis

TYPE-I HYPERSENSITIVITY:

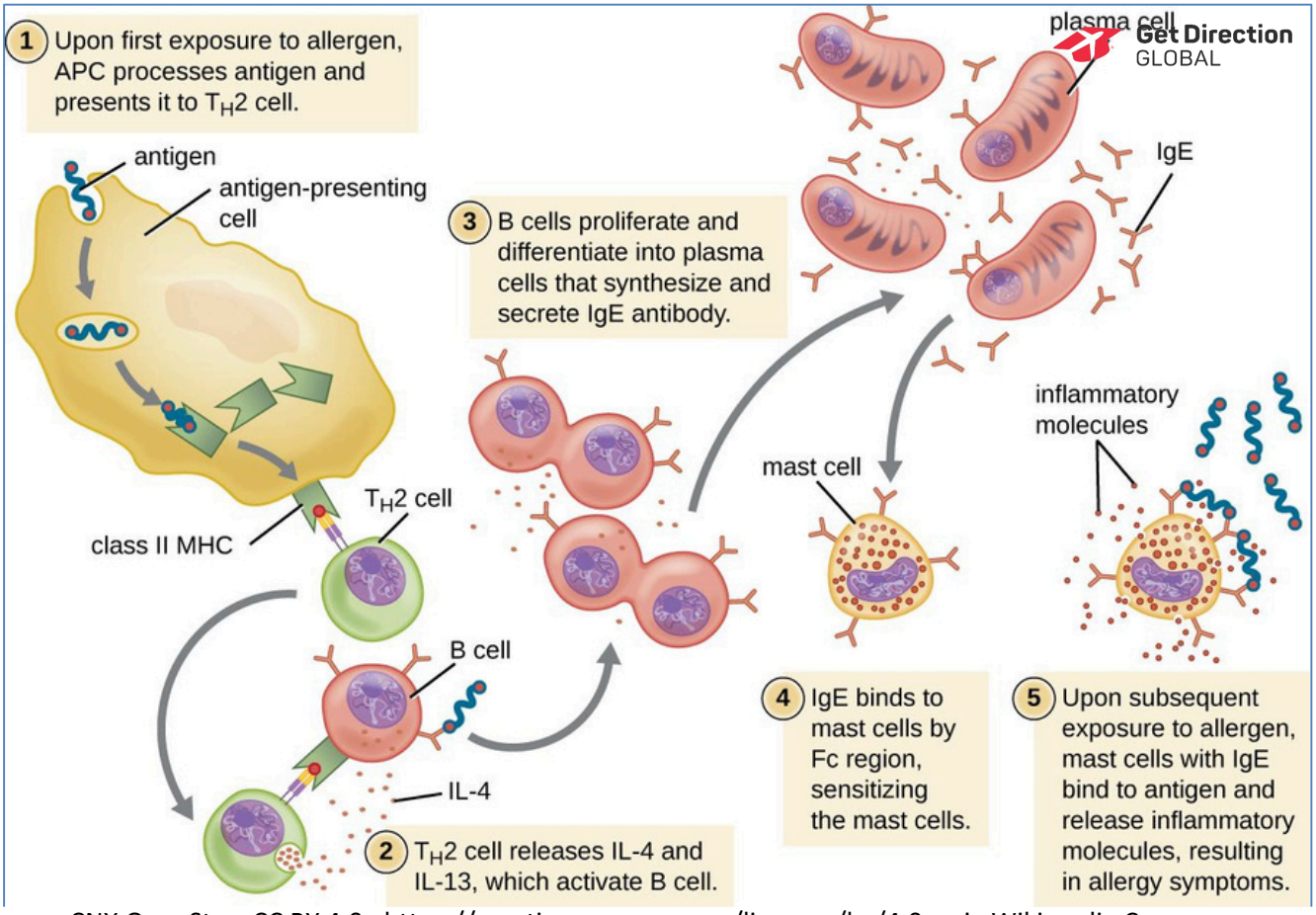
- **(*Anaphylaxis/Allergy*) - *IMMEDIATE***
- **– A Function of Th2-Cells, IgE-Antibodies & Mast Cells**
- **Common Type-I Hypersensitivities:**

Type I Hypersensitivities		
Common Name	**Cause**	**Signs and Symptoms**
Allergy-induced asthma	Inhalation of allergens	Constriction of bronchi, labored breathing, coughing, chills, body aches
Anaphylaxis	Systemic reaction to allergens	Hives, itching, swelling of tongue and throat, nausea, vomiting, low blood pressure, shock
Hay fever	Inhalation of mold or pollen	Runny nose, watery eyes, sneezing
Hives (urticaria)	Food or drug allergens, insect stings	Raised, bumpy skin rash with itching; bumps may converge into large raised areas

- **M echanism :**
  - **Rapid immune reaction to a Previously-Sensitised Antigen**
  - **- Antigen is Re-Exposed to a sensitized Mast-Cell/Basophil →*Degranulates* IgE-Bound 'Mast Cells':**
    - § → Releasing Inflammatory Mediators of Type-1-Hypersensitivity Reactions.
  - **Sensitization:**
    - § 1- Allergen enters the body.
    - § 2- APCs Presents the Allergen to Ag-Specific Th2-Cells
      - (Note: Allergens preferentially stimulate a Th2-Cell response → Drives IgE production)
    - § 3- Th2-Cells → Activate Ag-Specific B-Cells to secrete IgE (**Via IL-4, IL-13 + Co-Stimulation**)
      - (Remember that Ig-Switching from IgM to IgE is Mediated by IL-4 from Th2-Cells.)
    - § 4- B-Cells Produce **IgE**-Antibodies against the Allergen.
    - 5- Fc-Portion of IgE-Antibodies attach to *High-Affinity*-Fc-Receptors on Mast-Cells.
      - (Ie: Mast cells effectively become primed against the specific allergen.)
  - **Re-Exposure:**
    - § 6- Re-Exposure of Antigen →Antigen binds Antibody on Mast-Cell → Mast-Cell Degranulates:
      - →Releases Inflammatory Mediators → Vasodilation & Smooth Muscle Contraction.
        - Mediators Include:
          - § Histamine
          - § Leukotrienes
          - § Prostaglandins

          } →Cause Symptoms of Allergic Reaction.
      - →Releases IL-4 → Potentiates & Amplifies IgE Production by Plasma Cells.

(↑ IgE = ↑ Mast cell Activation = ↑ Inflammatory Mediators & Inflammatory cells = ↑ IgE)



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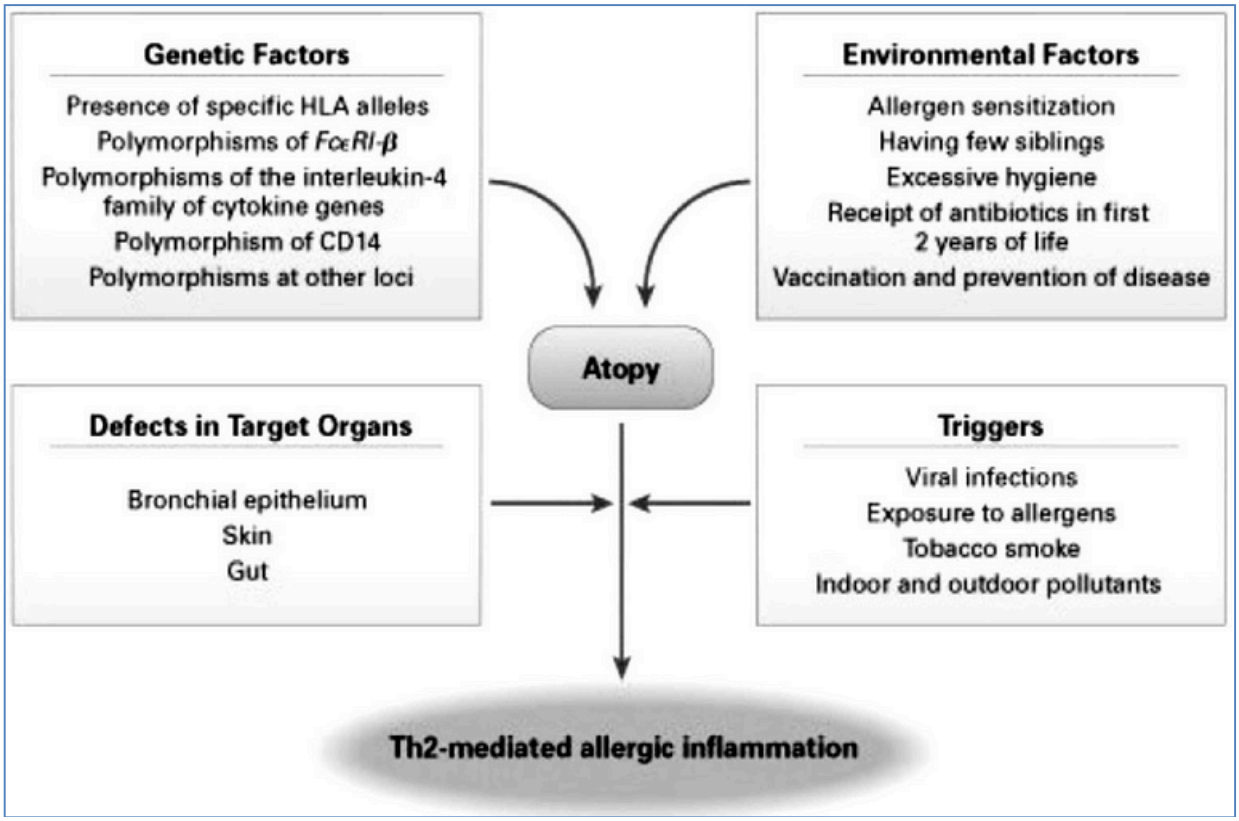
- **M ast Cells in Type-I Hypersensitivity:**
  - o **Mast Cells line *Body Surfaces*** → Alert the immune system to local infection.
  - o **Have *High-Affinity* Fc-Receptors** → Allow mast cells to bind Ag-Specific IgE Antibodies.
  - o **Binding of Ag to IgE:FcRs** →**Degranulation** of basophilic granules.
  - o **Molecules Released in Degranulation:**
    - § ****Histamine:**
      - Vasodilation
      - ↑Vascular Permeability
      - Bronchial Smooth Muscle Contraction.
    - § ****IL-4:** Stimulates & Amplifies Th2-Cell Response.
    - §
      - ***Prostaglandins & Leukotrienes → Trigger further Histamine Release →:**
        - Vasodilation
        - ↑Vascular Permeability
        - Bronchial Smooth Muscle Contraction
        - ↑Mucus Secretion.
    - § **TNFα:** Proinflammatory Effects
      - Activates Endothelium.
      -
    - § **CCL3 Chemokine:**
      - Attracts Phagocytes (Monocytes, Macrophages & Neutrophil).

- **Allergic Responses are *'Bi-Phasic'* – (Immediate- & Late- Phase Responses in Allergy):**
  - o **Immediate Phase Response:**
    - § Occurs within seconds of Exposure.
    - § Due to *Release of Preformed* Mediators by Mast-Cells. (Ie: Histamine, Prostaglandins)
  - o **Late Phase Response:**
    - § Occurs 8-12hrs after Exposure → Oedema.
    - § Due to *Synthesis* of Mediators by Mast-Cells. (Ie: Cytokines, Leukotrienes & Chemokines)

- **Clinical Effects of Mast Cell Degranulation:**
  - **Effects Depend On:**
    - **1-** Specific Allergen **2-**
    - Dose of Allergen **3-**
    - **Route of Entry (Antigen Location)**
      - **Blood Stream →** Systemic anaphylaxis → Anaphylactic shock
      - **Airborne →** Allergic conjunctivitis/ rhinitis/ asthma
      - **Skin →** Wheel and flare reaction/ urticaria/ atopic dermatitis (eczema)
      - **Food →** GIT transepithelial fluid loss → Diarrhoea/ bloating/ etc.

- **Determinants of Allergic Diseases (Incl: Asthma):**
  - **Genetic Susceptibility:**
    - 'Atopy' has a strong familial basis.
    - Ethnic differences in susceptibility for Atopy.
    - There are distinct *Susceptibility Genes* for Allergic Diseases.
  - **Environmental:**
    - **'The Hygiene Hypothesis' – A decrease in exposure to microbes in early childhood** is a possible cause of the increase in allergies in high SES populations & Developed Countries.
      - Proposes that *Less Hygienic* Environments & Minor Infections during early childhood are protective against Atopy & Asthma.
      - Implies that Th2 (atopic) responses in early childhood are *Reprogrammed* to Th1 (non-atopic) responses by cytokines from early infections.
      - (Remember that Ig-Switching from IgM to IgE is Mediated by IL-4 from Th2-Cells.)
    - Allergen Levels
    - Environmental Pollution
    - Dietary Changes (Eg: food allergies)



- **Question – *What is the Immunological Basis for Hypo-Sensitisation?*:**
  - (AKA: Allergen Immunotherapy)
  - = Involves giving *Gradually-Increasing* quantities of specific allergens to people with IgE-Mediated (Type-I Hypersensitivity) Conditions. The *Aim* is to divert the Th2-Cell (IgE) Response to a Th1-Cell Response → Decrease in IgE Production.

EXAMPLES OF COMMON TYPE-I HYPERSENSITIVITY DISEASES:

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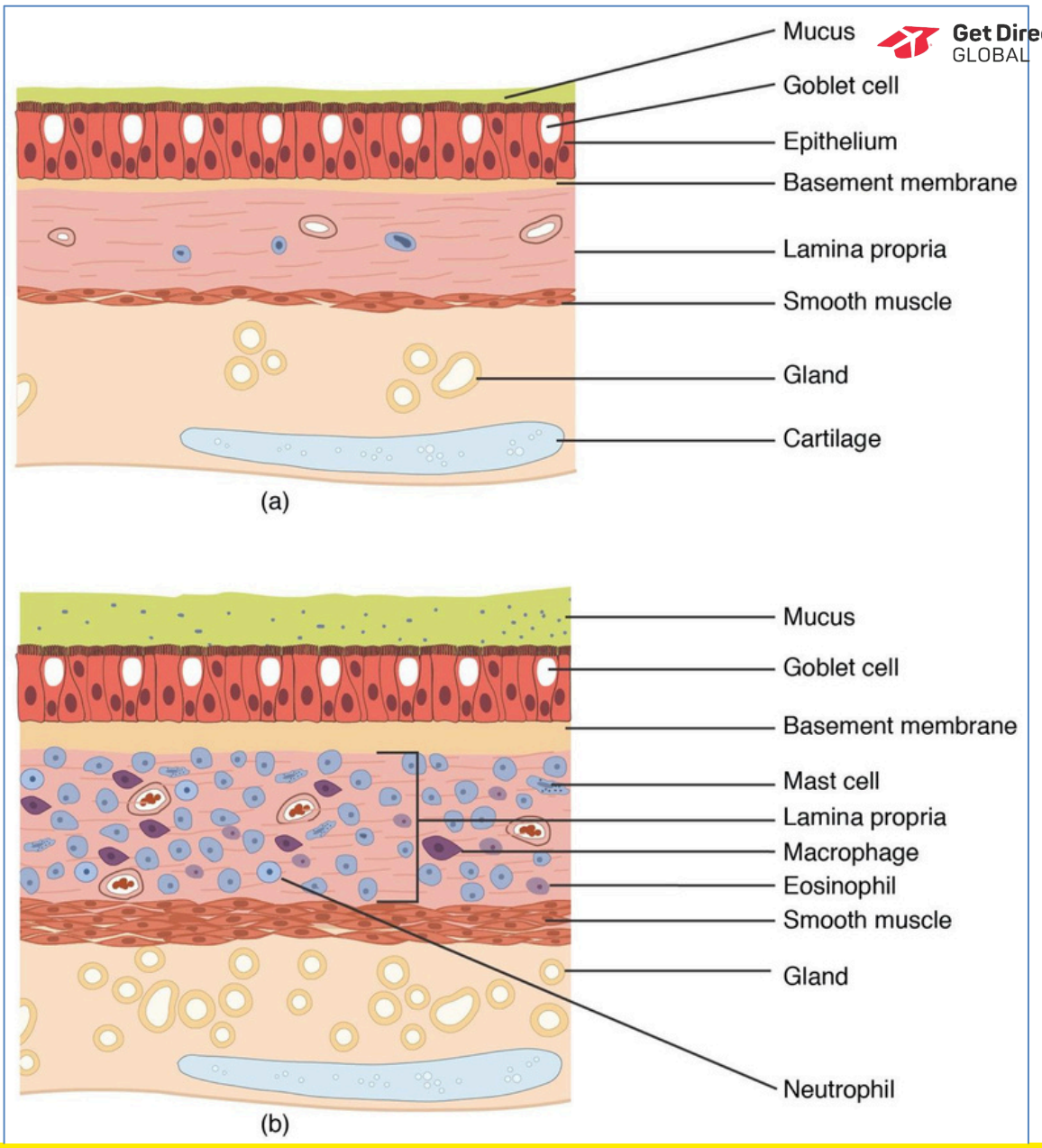
**Eg: Allergic (Atopic) Asthma:

- **Exposure of Respiratory Sub-Mucosa to Allergen → Local Mast Cell Degranulation:**
  - o →Local Histamine, Prostaglandin & Leukotriene Release
  - o →Airway Vasodilation, ↑Vascular Permeability & **Constriction of Airway Smooth Muscle**. **(Bronchoconstriction)**
    - § →Life-Threatening *Airway Obstruction*.
- **Triggers:**
  - o o Exposure to Allergens
  - o Tobacco Smoke Viral Infections
  - o Pollutants
  - o Exercise
  - o Cold Air
  - o Drugs – (β-Blockers, Aspirin, NSAIDs)
- **Biphasic Response:**
  - o **Immediate Phase Response – The "Attack":**
    - § Occurs within seconds of Exposure.
    - § Due to *Release of Preformed* Mediators by Mast-Cells:
      - (Ie: Histamine, Prostaglandins)
  - o **Late Phase Response:**
    - § Occurs 8-12hrs after Exposure → Oedema, SM Contraction, SM Hyperplasia, SM
    - § Hypertrophy.
      Due to *Synthesis* of Mediators by Mast-Cells:
      - (Ie: Cytokines, Leukotrienes & Chemokines)
- **Pathophysiological Features:**
  - o Airflow limitations → Wheezing & Hyperinflated Chest.
  - o Over-distended lungs.
  - o Airway hyper-reactivity – (Exaggerated broncho-constriction to non-specific stimuli)
  - o Remodelling of Airway due to Inflammation:
    - § ↑Inflammatory Cells
    - § Oedema
    - § SM Hypertrophy
    - § ↑Mucous
  - o (Often associated with Eczema, Urticaria/hives, Rhinitis, or Nasal Polyps)
- **Diagnosis:**
  - o *Obstructive Spirometry – (Responsive to Bronchodilators)
  - o IgE Levels – (Measurement of Allergic Status)
- **Treatment:**
  - o **Symptomatic –** Bronchodilators (β-Agonists. Eg: Salbutamol)
  - o **Immunosuppressants –** Inhaled Cortico-Steroids (ICS)
- **(*Note:Other Types of Asthma*):**
  - o **Episodic Asthma:**
    - § Pt is often asymptomatic but suffers attacks of asthma during URTI or after exposure to certain aeroallergens.
      - Common in older patients.
  - o **Occupational Asthma:**
    - § Variable airway obstruction caused by workplace exposures - (Fumes/Gases/Chemicals/Dust)
    - § Due to hypersensitivity reaction to a substance at work.
      - Eg: Heavy exposure to Gas/Fumes/Vapour.



Normal and Bronchial Asthma Tissues (a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Eg: Allergic Bronchopulmonary Aspergillosis (ABPA):

- **What is it?**
- An Allergic (Type-I Hypersensitivity) Reaction to Aspergillus Fungus.

Mechanism – Same as Asthma:

- **Exposure of Respiratory Sub-Mucosa to Aspergillus → Anti-Aspergillus IgE Antibodies → Bind to M ast C ells**.
- **Re-Exposure → Local Mast Cell Degranulation:**
  - →Local Histamine, Prostaglandin & Leukotriene Release
  - →Airway Vasodilation, ↑Vascular Permeability & Bronchoconstriction.
    - → Intense Bronchial Inflammation with high IgE & Eosinophilia.

- **Diagnostic Features:**
  - Asthma (majority of cases)
  - Mucus Plugging
  - Proximal Bronchiectasis
  - Positive Skin-test to an extract of Aspergillus Fungus.
  - Elevated serum IgE – (Specific to Aspergillus)
  - Shadows on Chest XR.
  - Presence of Aspergillus in Sputum Microscopy.
- **Treatment:**
  - Prednisolone (Oral Corticosteroid) → Immunosuppressant avoids further tissue damage.
  - High dose *Inhaled* Corticosteroid → (As above)

Eg: Allergic Rhinitis:

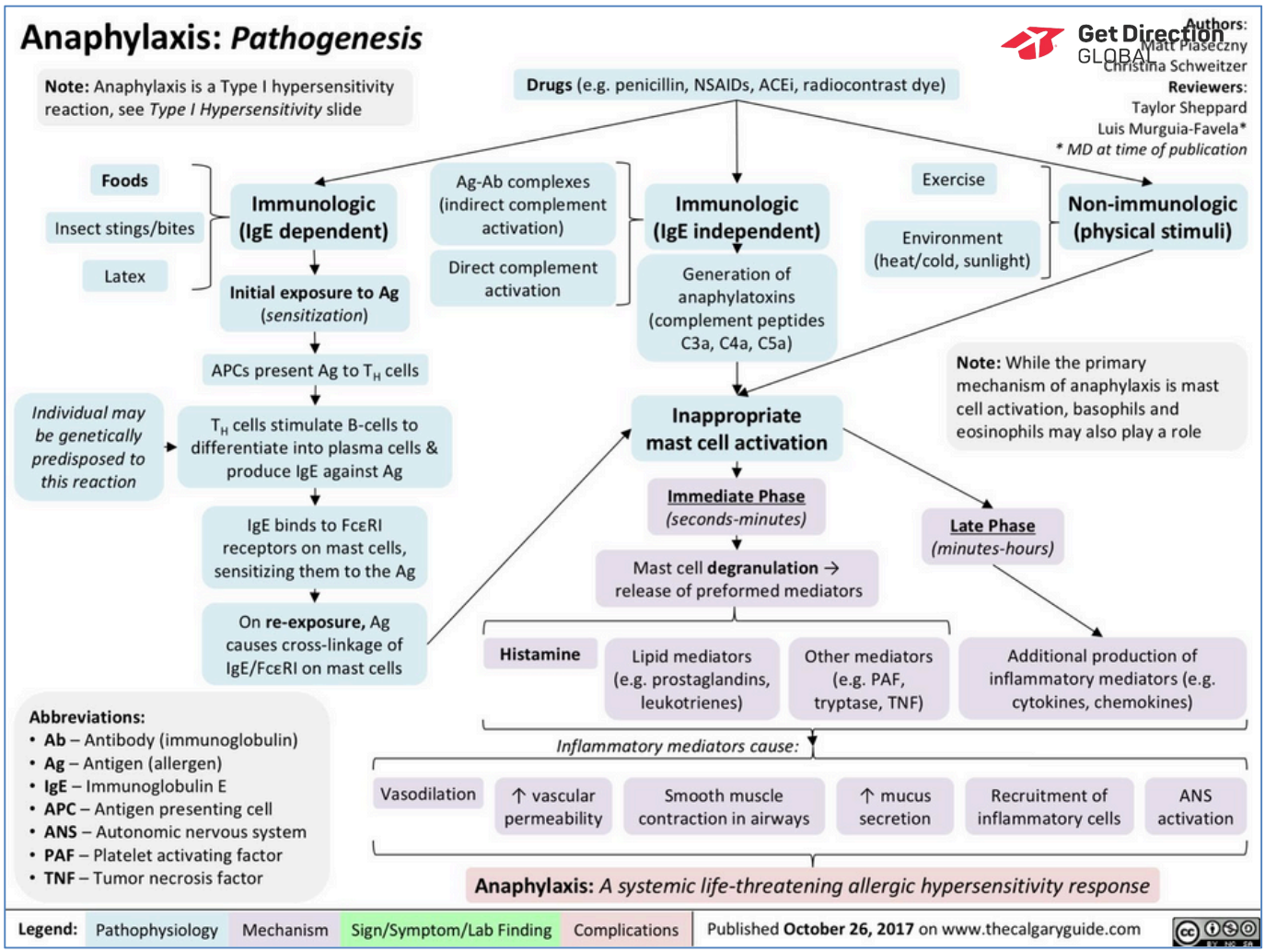
- **What is it?**
- Characterised by Episodes of Sneezing/Itching/Rhinorrhoea/Nasal Obstructions.

Treatment:

- Allergen Avoidance
- Anti-Allergic Meds
- Immunotherapy for specific allergens.

****Eg: Anaphylaxis (& Anaphylactic Shock):**

- **Blood-Borne Antigen → Systemic Mast-Cell Degranulation:**
  - →Systemic Histamine, Prostaglandin & Leukotriene Release
  - →Systemic Vasodilation & ↑Vascular Permeability
    - →Life-Threatening *Fluid Shifts*, *Oedema* & *Hypotension* →Anaphylactic Shock:
- **Features of Shock – (The result of Hypoperfusion of Vital Organs):**
  - Low Blood Pressure
  - Cool Extremities
  - ↓Cerebral Perfusion → Altered Mental Status
  - ↓Renal Perfusion → ↓Urine Output
  - ↓Coronary Perfusion → Ischaemic Chest Pain
  - ↓General Tissue Perfusion → Lactic-Acidosis
- **Treatment:**
  - *Adrenaline – (A Vasoconstrictor, Antihistamine, Bronchodilator & Cardiostimulator)
  - Remove Causative Agent
  - Volume Replacement
- **Q: How does Penicillin Cause Anaphylaxis?**
  - **- Penicillin forms Conjugates with Self-Proteins → Essentially *Modifying* them:**
  - →APCs can take up Penicillin-Modified Self-Peptides → Present them to Th2-Cells:
    - →Th2-Cells Activate Penicillin-Binding B-Cells → IgE against Penicillin.
      - →IgE binds to High Affinity Fc-Receptors on Mast-Cells
  - **– Binding of Penicillin to IgE-Bound Mast-Cells → Degranulation → Anaphylaxis:**
    - →Systemic Histamine, Prostaglandin & Leukotriene Release
    - →Systemic Vasodilation & ↑Vascular Permeability
    - →→Causes Life-Threatening *Fluid Shifts*, *Oedema* & ↓*BP* →Shock.



Source: The Calgary Guide

Type-II Hypersensitivity:

- **(*Autoimmune Diseases & Drug Allergies*) - *DELAYED***
- **– Antibody-Mediated Attack against *Altered* Cell-Surface Antigens:**
  - o **Eg: Drug-Induced Haemolytic Anaemia** (Drugs bind to surface antigens of RBCs)
  - o **Eg: Autoimmune Thrombocytopenia** (Drugs bind to surface antigens of Platelets)
  - o **Eg: Rheumatic Heart Disease**. (Anti-*M-Protein*-Abs cross react with Cardiac Myosin)
  - o **Eg: Blood Transfusion Reactions**

Common Type II Hypersensitivities		
Common Name	**Cause**	**Signs and Symptoms**
Hemolytic disease of the newborn (HDN)	IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction	Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases
Hemolytic transfusion reactions (HTR)	IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction	Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

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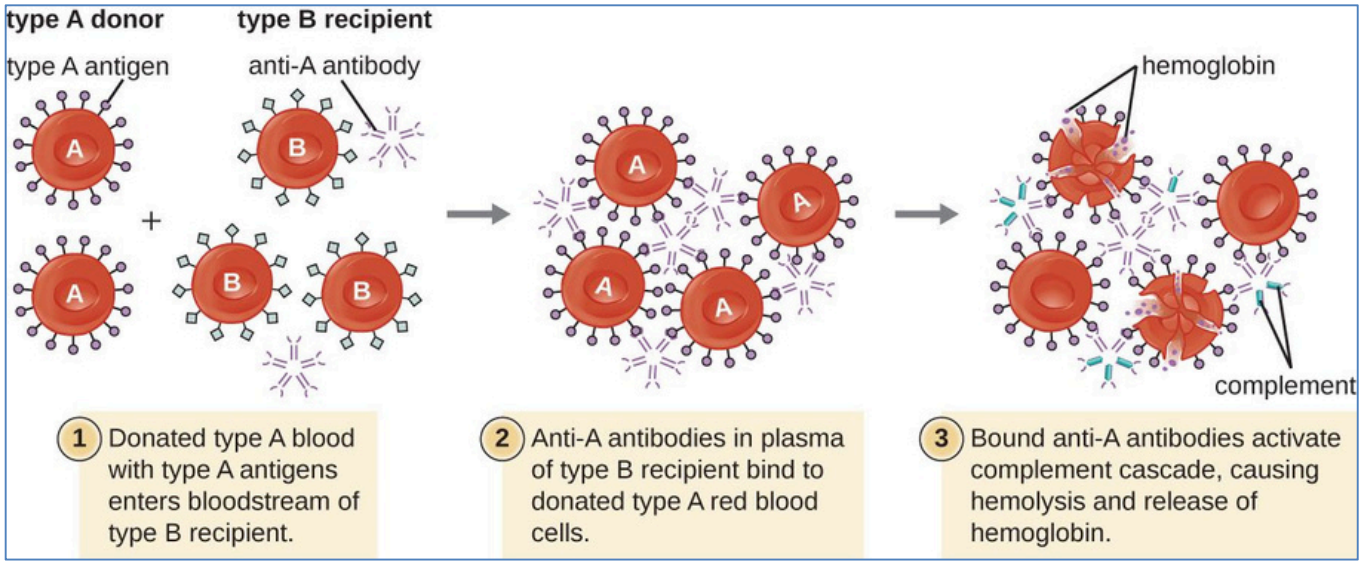

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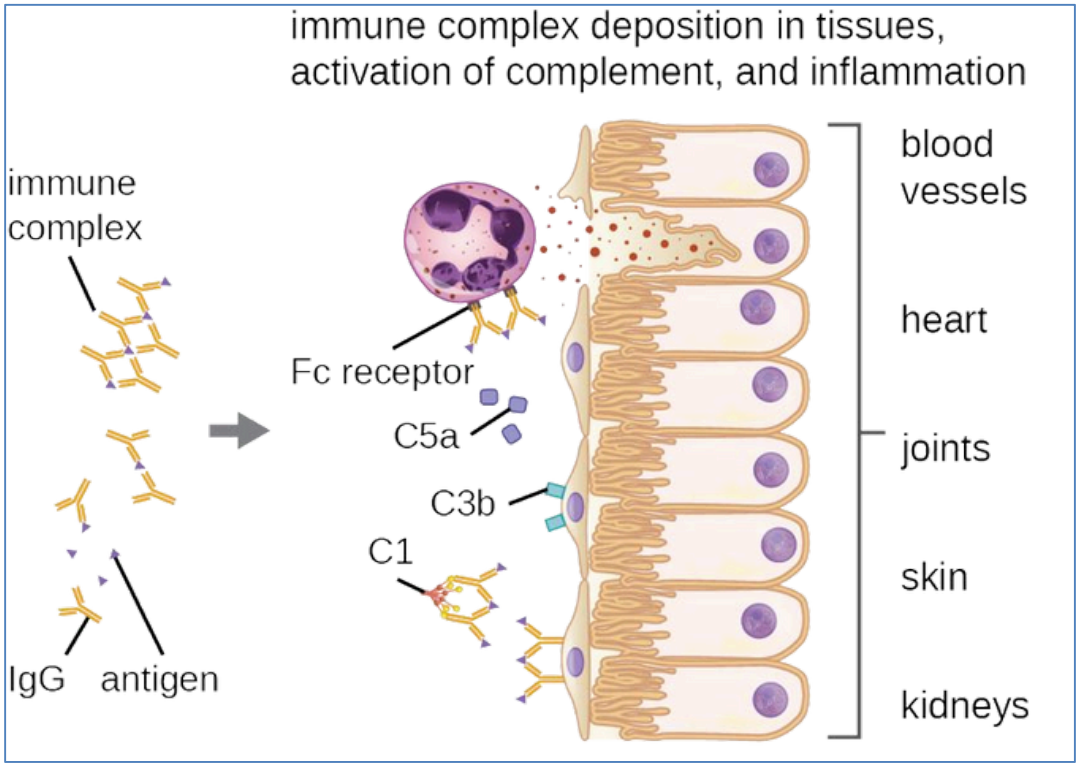
- **M echanism :**
  - o **IgG Antibodies against specific Host Cell-Antigens bind to Cells & Opsonise them for Phagocytosis:**
    - § → Altered Blood-Borne cells targeted are cleared by Macrophages in the Spleen.
      - (Eg: Drug-Induced Haemolytic Anaemia)
      - (Eg: Autoimmune Thrombocytopenia)
    - § → Tissue-Cells targeted are destroyed by *Resident* Macrophages in that tissue.
      - (Eg: Rheumatic Heart Disease)
  - o **Note: Drug-Induced Haemolytic Anaemia/Thrombocytopenia:**
    - § Specific Drugs bind to the Surface of RBCs/Platelets → Are Targeted by Anti-Drug IgG.
    - § → Anti-Drug IgG binding to RBCs/Platelets → Opsonises them for Phagocytosis in Spleen.

Type-III Hypersensitivity:

- **(*'Arthrus Reaction', 'Serum Sickness' & Some Autoimmune Diseases*) - *DELAYED***
- **– Immune-Complex (Ag:Ab) Deposition → Activate Fc-Receptor+ & Complement :**
  - o **Eg: 'Arthrus Reaction' → Vasculitis**.
  - o **Eg: 'Serum Sickness'**
  - o **Eg: Rheumatoid Arthritis**

- **Mechanism:**
  - o **Deposition of *Small* Immune-Complexes (Ag:IgG) in Vessel Walls:**
    - § → IgG binds to Fc-Receptor on **Mast Cells** → Degranulation.
      - → Local Inflammation → Vasodilation, ↑Vascular Permeability.
      - → Local Oedema → Vessel Occlusion.
    - § → Activation of **Complement** & Recruitment of Granulocytes.
    - § →→**Vasculitis**.



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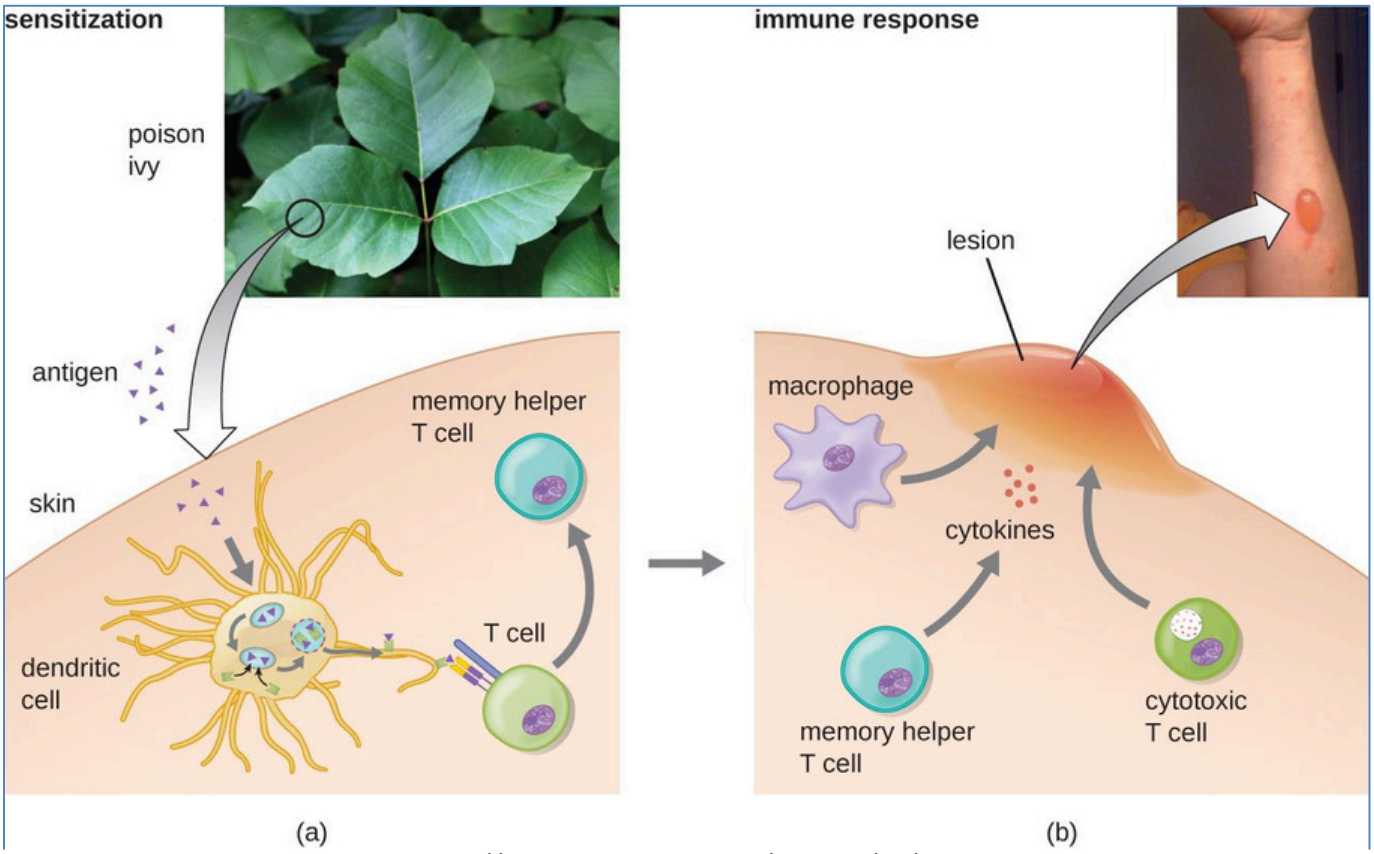
  - o **Eg: 'Arthrus Reaction' → Vasculitis:**
    - § Intradermal Injection of Antigen → In Situ formation of Ag:IgG Complexes:
      - Local Deposition of Ag:IgG in dermal Blood Vessels →Manifests as local Vasculitis.
  - o **Eg: 'Serum Sickness' → Vasculitis/Glomerulonephritis/Arthritis**.
    - § IV Injection of Foreign Antigen (Eg: Tetanus Antiserum) → formation of Ag:IgG Complexes:
      - Systemic Deposition of Ag:IgG in Blood Vessels:
        - o →Manifests as Vasculitis/Glomerulonephritis/Arthritis. (Self-Limiting)

    (Note: Rarely seen anymore due to advent of *Monoclonal* Antibodies.)

Type-IV Hypersensitivity:

- **(*Autoimmune Diseases*) - *DELAYED***
- **– Function of Th1, Th2 & Cytotoxic T-Cells:**
  - o ***Th1 – Eg: Contact Dermatitis, Tuberculin Reaction (Mantoux Test) – *OUR FOCUS!***
  - o **Th2 – Eg: Chronic Asthma, Chronic Rhinitis**.
  - o **CTL – Eg: Type-1-Diabetes Mellitus**
  - o **Eg: Multiple Sclerosis**
  - o **Eg: Coeliac Disease**

- **Mechanism:**
  - o **Pre-Primed Ag-Specific Th-1-Cells *Recognise and Bind* Macrophages displaying Ag:MHC-II**
    → *Activates* M acrophages → Secretion of Cytokines, Chem okines & Cytotoxins:
    - § IFNγ & TNFβ → Activates Endothelium & ↑Vessel Permeability → inflammation.
    - § • →Visible Swelling
      →→Tissue Damage → ***Granulomas***



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IMMUNODEFICIENCY

IMMUNODEFICIENCY

Get Direction GLOBAL

***Immuno-Deficiency – (Host Defences are Abnormal)*:**

Primary Immune Deficiency:

- **(Ie: Host defences are *Inherently/Genetically* Defective)**
  - Most have Genetic Aetiology.

- **Secondary Immune Deficiency:**
  - **(Ie: Physically/Chemically/Infectively –Induced Immune Deficiency)**
  - **Physically-Induced Immune Deficiency:**
    - Eg: Radiation
  - **Chemically-Induced Immune Deficiency:**
    - Eg: Drugs – Corticosteroids/Immunosuppressants.
  - **Infectively-Induced Immune Deficiency:**
    - Eg: HIV

Primary and Secondary Immunodeficiencies

Disease		Effect on Immune Function	Outcomes
Primary immunodeficiencies	Chronic granulomatous disease	Impaired killing of bacteria within the phagolysosome of neutrophils and macrophages	Chronic infections and granulomas
	Selective IgA deficiency	Inability to produce secretory IgA	Predisposition to lung and gastrointestinal infections
	Severe combined immunodeficiency disease (SCID)	Deficient humoral and cell-mediated immune responses	Early development of severe and life-threatening opportunistic infections
	X-linked agammaglobulinemia	Flawed differentiation of B cells and absence of specific antibodies	Recurrent infections almost exclusively due to pathogens that cause pyogenic infections
Secondary immunodeficiencies	Immunosuppressive therapies (e.g., chemotherapy, radiotherapy)	Impaired humoral and/or cell-mediated immune responses	Opportunistic infections, rare cancers
	Malnutrition	Impaired humoral and/or cell-mediated immune responses	Opportunistic infections, rare cancers
	Viral infection (e.g., HIV)	Impaired cell-mediated immune responses due to CD4 T-cell lymphopenia	Opportunistic infections, rare cancers

"Red-Flags" for Immunodeficiency:

- **History:**
  - **1- History of Unusual *Number* of Infections**
  - **2- History of *Severe/Unusual TYPES* of Infections:**
    - Eg: Overwhelming Infections *without* a predisposing cause.
    - Eg: Recurrent Infections with *Low Virulence Organisms* – (Ie: Commensals/yeasts/Staph
    - Epi)
    - Eg: Infections with *Unusual Organisms* – (Eg: PCP, Serratia)
      Eg: Infections in *Unusual Sites* – (Eg: Nails)
  - **3- History of a *Predisposing Event* Compromising the Immune System:**
    - Malnutrition
    - Nutrient Deficiencies – (Eg: ↓Vit- A)
    - Specific Viral Infections – (Eg: HIV, Measles)
    - Immunosuppressive Therapy – (Eg: Asthma Corticosteroids)
    - Cancer Chemotherapy/Radiotherapy.
    - Adverse Drug Reactions
    - Autoimmune Disorders
    - Splenectomy/Thyroidectomy/Tonsillectomy
- **Examination:**
  - **Syndromes Associated with Immunodeficiency:**
    - Eg: Down's Syndrome
    - Eg: Ataxia Telangiectasia
    - Eg: Kwashiorkor – (→Severe Malnutrition)
    - Eg: DiGeorge Syndrome
  - **Skin Manifestations:**
    - **Eczema & Petechiae** (Eg: Wiskott-Aldrich Syndrome
    - **Telangiectasia** (Eg: Ataxia-telangiectasia)
    - **Oculocutaneous Albuminism** (Eg: Chediak-Higashi Syndrome)
    - **Chronic Dermatitis** (Eg: Hyper-IgE Syndrome)
    - **Extensive Molluscum, warts, candidiasis** (Eg: T-Cell Deficiency)
  - **Sites & Nature of Infection:**
    - Eg: Fungal Infection of Nail Beds.
    - Eg: Multiple Abscesses
  - **Absence of Tonsils**
  - **Lymph Nodes:**
    - Eg: Obvious infection, but no Lymph Node Swelling.
  - **Nutritional State**.
  - **Gingivostomatitis:**
    - Inflammation of the Oral Mucosa and Gingiva.

Laboratory Investigations – Confirming your Suspicion:

- **Blood Count:**
  - Full Blood Count
  - Specific Count of Cell Types:
- **White Cell Morphology:**
  - **B-Cells:**
    - Number
    - Phenotyping
  - **T-Cells:** Number
    - Phenotyping
    - Cytokine Production
    - Response to Mitogens – (Ie: Lymphocyte Proliferation Assays)
    -
  - **NK-Cells – Cytotoxicity**
  - **Phagocytic Function:**
    - Adhesion
    - Killing
- **Immunoglobulin Count:**
  - **Specific Ig-Isotype Titres:**
  - (IgG, IgA, IgM)

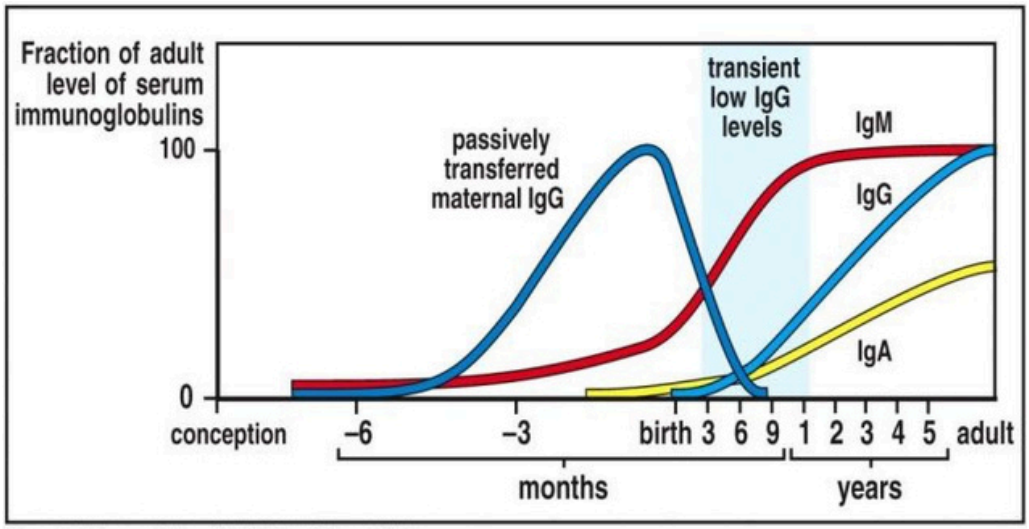
    Antibody Response to Disease:
    - Immunisation response.
- **Complement Count:**
- o Eg: In Glomerulonephritis/Nephrotic Syndrome – Complement proteins can be lost in urine.
- **Skin Tests**
  - For Delayed Hypersensitivity (Eg: Type-IV For TB)

Molecular Genetics:

o Looking for genetic mutations associated with known Immuno-Deficiencies.

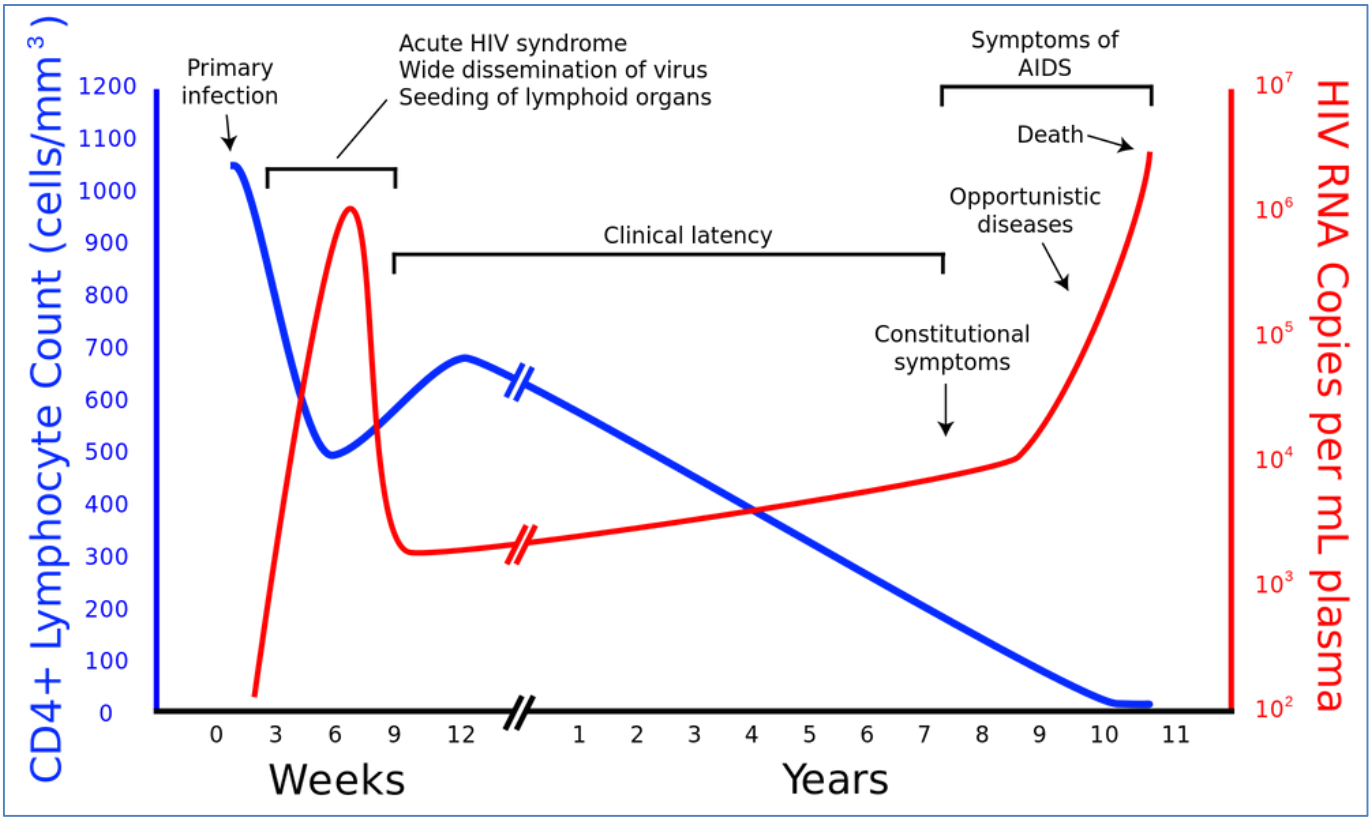
Clinical Categories for Understanding Immunodeficiency:

- **PID – Primary Immunodeficiency:**
  - **Primary B-Cell Diseases:**
    - **↓Antibodies →Inability to Clear *Extracellular* Organisms → Recurrent Infections:**
      - Eg: IgG Deficiency Eg: IgA Deficiency
      - Eg: **Bruton's X-linked Agammaglobulinaemia – (X-Linked Recessive)**
      - Eg: **Common Variable Immune Deficiency – (Abs are present, but non-functional)** Eg: **Transient Hypogammaglobulinaemia of Infancy. (THI)** – Around 6-12mths; between when Maternal IgG wanes and when infants begin to make their own IgG.



  - **Primary T-Cell Diseases:**
    - **Presents as Severe Infections in Infancy**
      - (Or Chronic Thrush (Mucocutaneous Candidiasis)
    - **Often Presents as Recurrent Viral/Fungal Infections**
    - **Often Associated with B-Cell Defects:**
      - Eg: Thymic Hypoplasia – (Ie: DiGeorge Syndrome)
      - **Eg: Hyper IgM Syndrome – (T-Cells fail to direct B-Cells in Isotype Switching)**
      - Eg: Defective Cytokine Receptors
      - Eg: Defective Cytokine Production
  - **Combined B- & T-Cell Diseases:**
    - **Presents as Severe, Frequent, Opportunistic Infections → Early Death.**
      - ***Eg: SCID – Severe Combined Immuno-Deficiency – (X-Linked Recessive)**
  - **Disorders of Phagocytic Function:**
    - **Inability to contain Local Infections → Chronic Abscesses.**
    - **2 Major Categories:**
      - **Eg: Leukocyte Adhesion Deficiency**
      - **Eg: Defects of Intracellular Killing – (Ie: '*Chronic Granulomatous Disease*')**
  - **Disorders of the Complement System:**
    - **Defective Humoral Immune Function → Chronic Infections:**
      - Eg: Classical Pathway Deficiency – (C2,3,5,6,7,8,)
      - Eg: Alternative Pathway Deficiency – (Properdin Deficiency)
      - Eg: C1-Esterase Deficiency → Angioedema

- **SID – Secondary Immunodeficiency:**
  - ***HIV:**
    - **Why does it lead to Acquired Immunodeficiency?:**
      - Directly – Via killing of infected cells.
        - *Killing of Infected CD4 Cells by CD8-Cytotoxic-T-Cells
        - (Low CD4 count → Loss of Cell-Mediated Immunity)
      - Increased Susceptibility to Apoptosis of Infected Cells
    - **6 Stages of HIV & AIDs:**
      - 1- Acute Seroconversion Illness
      - 2- Asymptomatic HIV Infection – (CD4 count >500)
      - 3- Early Symptomatic HIV Infection – (CD4 count >500)
      - 4- Middle Symptomatic HIV Infection – (CD4 count 200-400)
      - 5- Late Symptomatic HIV Infection – (CD4 count <200)
      - 6- Advanced HIV Disease.
    - To successfully reproduce itself, HIV must convert its RNA genome to DNA via ***Reverse Transcriptase***, which is then imported into the host cell's nucleus and inserted into the host genome through the action of ***HIV integrase***. Because HIV's primary cellular target, CD4+ T-Cells, functions as the memory cells of the immune system, integrated HIV can remain dormant for the duration of this cell's lifetimes.



https://www.wikidoc.org/index.php/HIV_AIDS_natural_history,_complications,_and_prognosis

- (Others – Malnutrition, Immunosuppressive Therapy, Splenectomy, Etc)

Treating Immunodeficiency:

- **Treating B-Cell Defects:**
  - Antibiotics
  - IV Immunoglobulins
- **Treating T-Cell & Combined Immunodeficiencies:**
  - Quarantine
  - Antibiotics
  - Bone Marrow Transplant
  - Thymic Transplant (in DiGeorge Syndrome)
- **Treating Phagocytic Dysfunction:**
  - Antibiotics
  - Bone Marrow Transplant
- **Treating Complement Deficiency:**
  - Plasma Infusion
  - Treatment of Infections
- **Treating Secondary Immune Deficiencies:**
  - Prevention
  - Aggressive Treatment
  - Antiretroviral Agents (In HIV)

IMMUNITY AGAINST INFECTIOUS ORGANISMS & EVASION OF THE IMMUNE RESPONSE

General Terminology:

- **Normal Flora:** ("Commensal") Bacteria consistently associated with an animal.
- **Pathogen:** A microorganism able to produce disease
- **Pathogenicity:** Ability of a Microorganism to cause disease
- **Virulence:** The *Degree* of Pathogenicity
- **Opportunistic Pathogens:** Bacteria which cause disease in a compromised host.
- **Infection:** When an organism breaches a body surface into an area where it shouldn't.
- Note: Infection doesn't *necessarily* mean Disease.

Disease **– Depends on:**

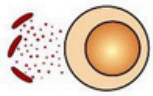
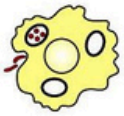
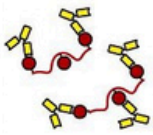
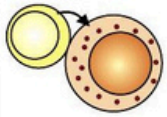
- o Route of entry. (→Spleen/nodes/MALT/etc)
- o Number of Infectious Bacteria
- o Immune status of the host.

How Pathogens Cause Tissue Damage:

- **Exotoxins:**
  - o – Released by microorganisms
  - o → Act at the Surface of Host Cells (Ie: Binding to Host Receptors).
  - o Eg: Superantigens → Toxic Shock (Due to mass release of cytokines)
- **Endotoxins:**
  - o – Are Intrinsic Components of the Microbial Structure
  - o Eg: LPS → Trigger Phagocytes to release Cytokines → Septic Shock.
- **Direct Cytopathic Effect:**
- o Many pathogens are Cytopathic → Directly damage Infected Cells.

Immune Complexes:

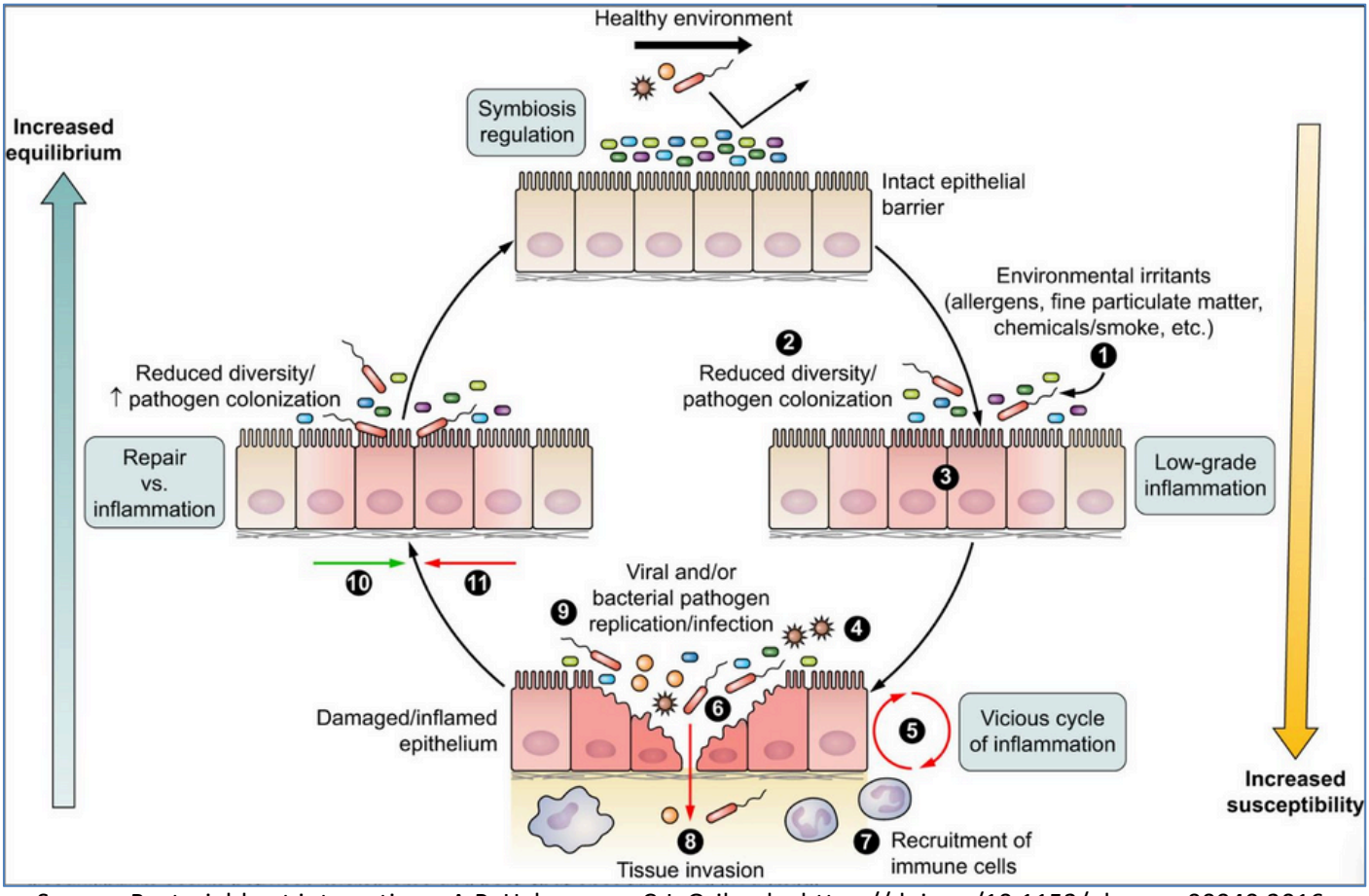
- o Eg: Ag:Ab Complexes deposit in the Kidneys/Microvessels/etc. → Disease.
  - § Eg: Glomerulonephritis
- **Anti-Host Antibodies:**
  - o Some Bacterial Antigens (Eg: M-Protein on Streptococcus) are very similar to Host Antigens.
    - § Therefore, the resultant Antibodies will cross-react with Host-Cells → Cell Damage.
- **Cell-Mediated Immunity:**
  - o Ie: T-Cells which kill infected cells.
  - o Note: Neutrophils can also cause tissue damage by Degranulation & Respiratory Bursts.

	Direct mechanisms of tissue damage by pathogens			Indirect mechanisms of tissue damage by pathogens		
	Exotoxin production	**Endotoxin**	**Direct cytopathic effect**	**Immune complexes**	**Anti-host antibody**	**Cell-mediated immunity**
Pathogenic mechanism						
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridium tetani* *Vibrio cholerae*	*Escherichia coli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)	Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*	*Mycobacterium tuberculosis* *Mycobacterium leprae* Lymphocytic choriomeningitis virus *Borrelia burgdorferi* *Schistosoma mansoni* Herpes simplex virus
Disease	Tonsilitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid fever Bacillary dysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles,subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma	Kidney disease Vascular deposits Glomerulonephritis Kidney damage in secondary syphilis Transient renal deposits	Rheumatic fever Hemolytic anemia	Tuberculosis Tuberculoid leprosy Aseptic meningitis Lyme arthritis Schistosomiasis Herpes stromal keratitis

Source: Unattributable

The Process of Infection:

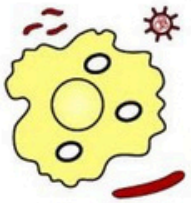
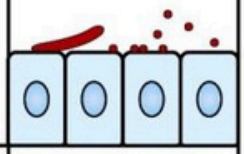
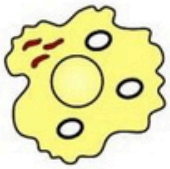
- **1- Commensals (Normal Flora) are where they're meant to be.**
- **2- Passive, Protective Barrier is broken → Local Infection**
- **3- Innate Immune Response & Afferent Adaptive Immune Response:**
  - o (Afferent Adaptive = The sensitisation phase – APCs stimulate respective T-Cells; and Th-Cells stim ulate their respective B-Cells)
- **4- Efferent Adaptive Immune Response:**
  - o (Efferent Adaptive = Lymphocytes differentiate into Effector Cells → Clear the Infection)



Source: Bacterial-host interactions, A.P. Hakansson, C.J. Orihuela, https://doi.org/10.1152/physrev.00040.2016

Effector Immune Functions Depend on Pathogen Location:

- **Extracellular:**
  - **Note: Virtually all Pathogens have an *Extracellular* Phase, during which they are vulnerable to the circulating molecules & cells of the Immune System (Innate & Adaptive):**
    - Complement
    - Antibodies
    - Phagocytes (Macrophages, Neutrophils, Dendritic Cells)
  - Note: These primarily aim to eliminate the Microorganism via Lysis or Promoting Phagocytosis.
- **Intracellular:**
  - **Pathogens are *Not* accessible to humoral mechanisms. Instead the Infected Cell is Attacked by:**
    - Natural Killer (NK)-Cells (Innate Immune System)
    - Cytotoxic-T-Cells (Adaptive Immune System)
    - Note: Activation of Macrophages by NK/Tc-Cells induce the Macrophage to Kill their intracellular pathogens.

	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Mycoplasma* spp. *Streptococcus pneumoniae* *Vibrio cholerae* *Escherichia coli* *Helicobacter pylori* *Candida albicans* Worms	Viruses *Chlamydia* spp. *Rickettsia* spp. *Listeria monocytogenes* Protozoa	*Mycobacterium* spp. *Salmonella typhimurium* *Yersinia pestis* *Listeria* spp. *Legionella pneumophila* *Cryptococcus neoformans* *Leishmania* spp. *Trypanosoma* spp. *Histoplasma*
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA	NK cells Cytotoxic T cells	T-cell and NK-cell dependent macrophage activation

Source: Unattributable

VIRUSES:

Properties of Viruses:

- Relatively Small compared to bacteria.
- Grow *Intracellularly*
- Many are *Totally Dependent* on the cell to provide Enzymes for Nucleic Acid Replication
- Some have sophisticated mechanisms for *Avoiding the Immune System*.

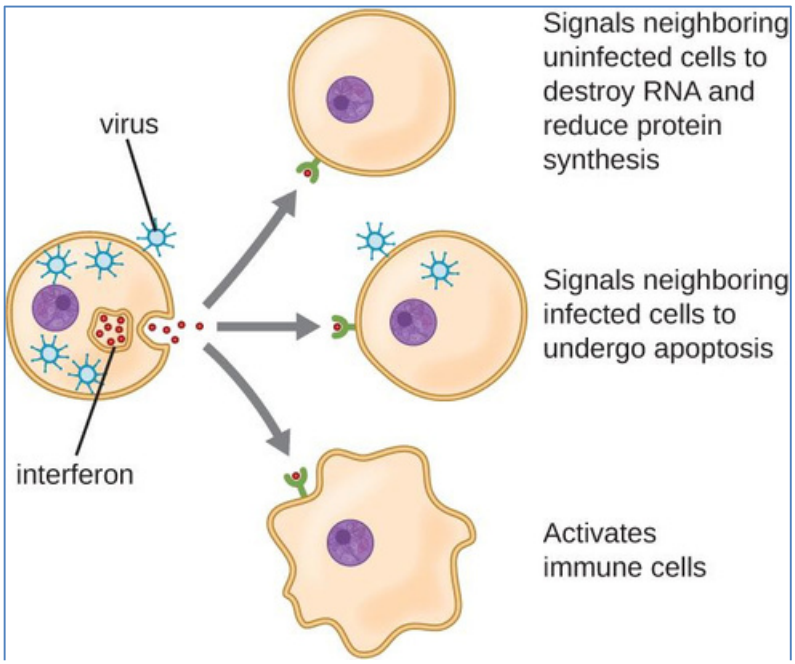
Viral Antigens:

- **May be Structural of Non-Structural:**
  - o Envelope Glycoproteins (AKA. Matrix Proteins)
  - o Capsid Antigens
  - o Nucleoproteins

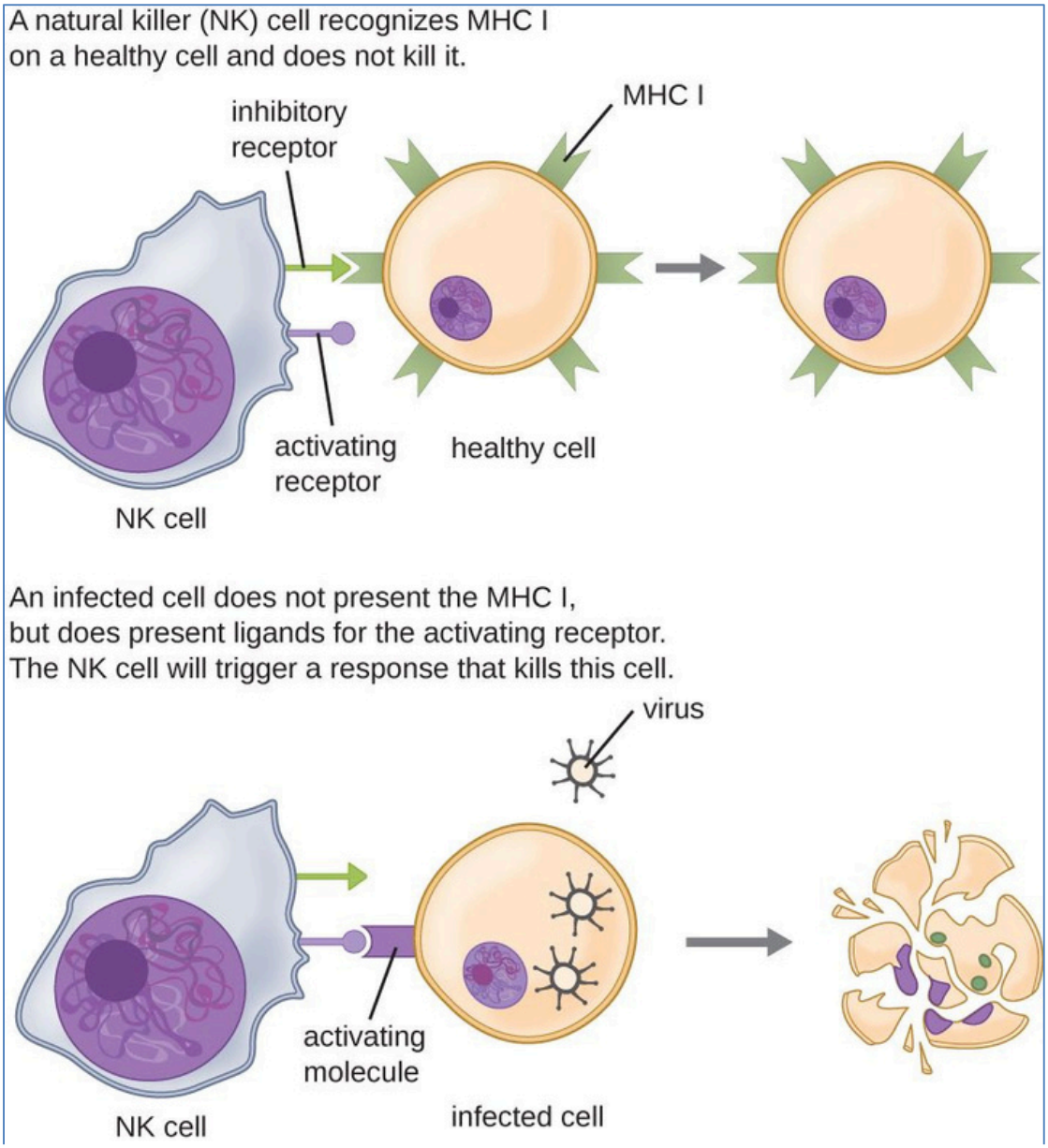
Immunity Against Viruses:

- **Innate Immunity:**
  - o ***Interferons (IFNs):**
    - § **(Four Major Classes):**
      - IFNα – Produced by virally-infected WBCs.
      - IFNβ – Produced by virally-infected Fibroblasts
      - IFNγ – Produced by Ag-Stimulated Effector T-Cells (Helper & Cytotoxic)
      - IFNω – Secreted by Embryonic Trophoblasts
    - § **Early, non-specific Anti-Viral Proteins (Particularly IFN-γ)**
      - Secreted by Virally Infected Cells to protect nearby cells that haven't yet been infected.
    - § **Mechanism of Action → IFN results in Synthesis of Gene Products:**
      - **Ribonuclease:**
        - o Cleaves Viral mRNA → Inhibits Viral Protein Synthesis & Reproduction.
        - o Allows time for Adaptive Immunity to destroy infected cells.
      - **Nitric Oxide Synthase:**
        - o Prevents viral growth in Macrophages
      - **Protein Kinase:**
        - o Prevents Elongation of Viral dsRNA

      Mx Protein:
        - o Can inhibit the Transcription & Translation of some viral mRNA.
    - § **Also Activates Natural Killer-Cells**.

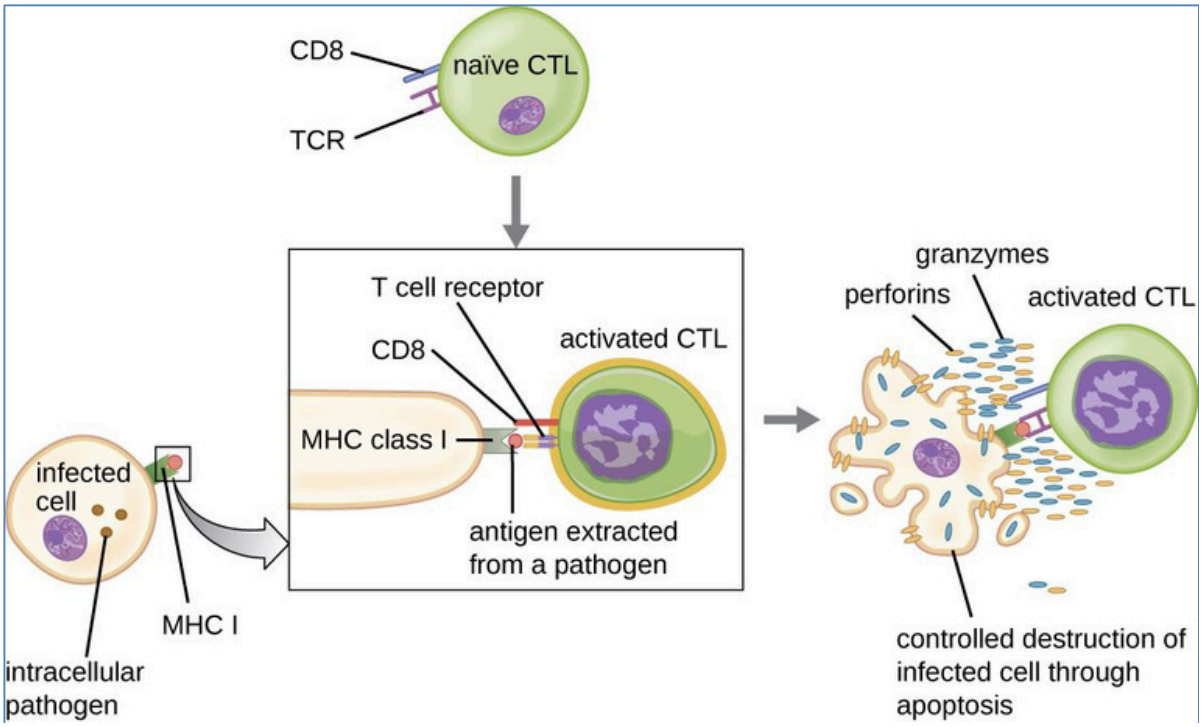


- **Natural Killer Cells:
  - (Activated by IFN-γ)
  - Lyse some Virally-Infected Cells.
  - Altered/Missing MHC-I → NK cell lyses cell.



- **Compliment Activation (Alternate Pathway) & Phagocytosis of Extracellular Viruses**:
  - C3b opsonisation → Phagocytosis
- **Lysozyme:**
  - (in Tears/Saliva/Mucus/Neutrophils)
  - Some viruses are susceptible.
- **Stomach Acid:**
  - Denatures some viruses.
- **Intestinal Enzymes:**
  - Degrade some viruses.

- **Adaptive Immunity:**
  - ****Helper CD4 T-Cells:**
    - § →Secretion of IFN-γ (→ Further activates NK Cells)
    - § → Activates Macrophages → Kill intracellular contents
    - § → Activates CD8-T-Cells → Proliferate
  - ****Cytotoxic CD8 T-Cells:**
    - § Recognition of **Viral Peptide:MHC-I** → Cytotoxic Granules line up @ site of cell contact
    - § • → Apoptosis of Virally Infected Cells
      (also →Secretion of IFN-γ) (→ Further activates NK Cells)



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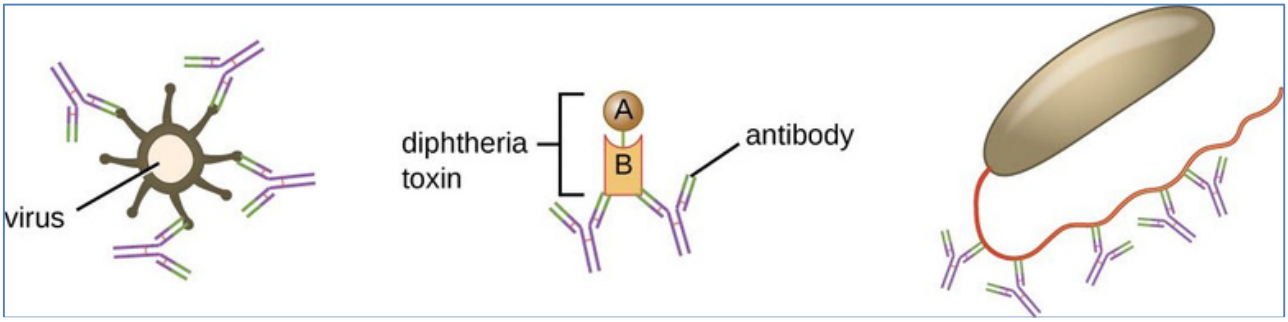
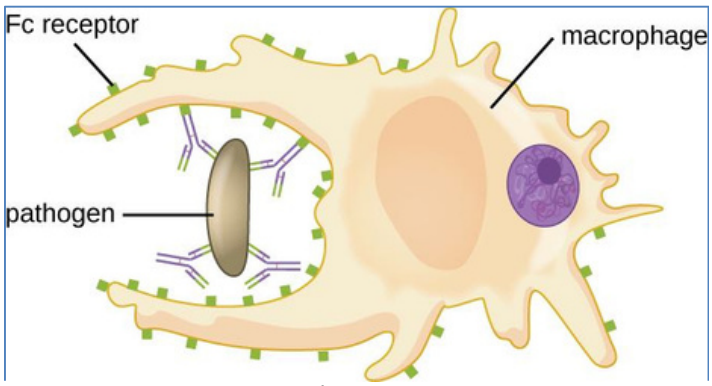
  - ****Antibodies:**
    - § **Antibodies** → **Neutralise** Extracellular Viruses
    - § • (By Blocking Viral Absorption & causing Agglutination)
    - § **Antibodies** → **Opsonisation** of Virus for **Phagocytosis** (Macrophages)
    - § **Antibodies** → **Opsonisation** of Virus for ***Antibody-Dependent Cell-Mediated Cytotoxicity***.
    - § • **(ADCC –** Fc Receptors on Cytotoxic cells bind to Antibody → Lysis of Virus**)**
    - § **Antibodies + Complement** → **Opsonisation** of Virus for Phagocytosis (Macrophages)
    - § **Antibodies + Complement** → **Virolysis** (NK Cells/Tc-Cells)
      Antibodies + Viral Ags on Cells → Initiate Compliment →CD8-mediated Lysis of infected cell.
      Antibodies + Viral Ags on Cells → Cell-Mediated Cytotoxicity → Lysis of infected cell.

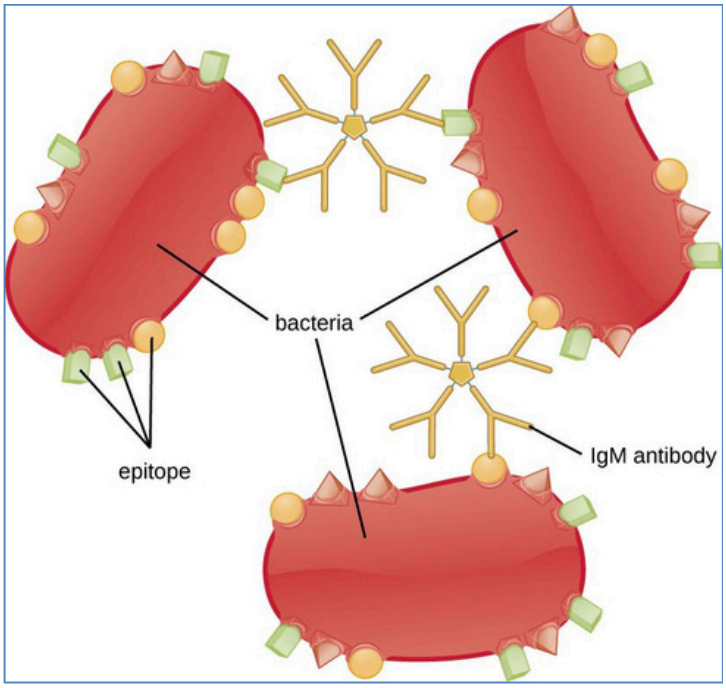
Neutralisation



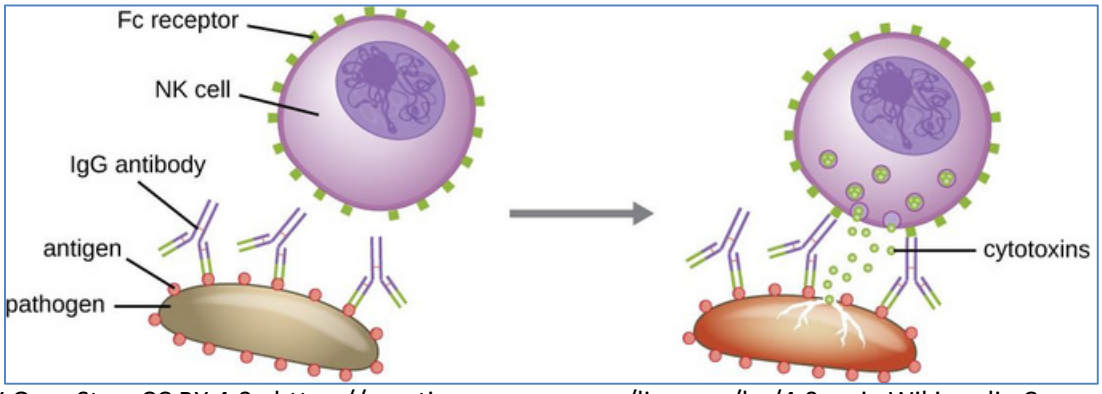
Opsonisation



Agglutination



Antibody-dependent cell-mediated cytotoxicity (ADCC)



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- **Activated Macrophages:**
  - (Via CD4 T-Helper Cells)
  - → Phagocytosis & destruction of Extracellular Viruses

Contribution of the Immune-Response to the Disease:

- **Destruction of Important Cells expressing Viral Antigens:**
  - Eg: Neuron Destruction → Brain Damage
  - Eg: Schwan cells Destruction → Inadequate Insulation in CNS
  - Eg: CD4-T-Helpers are destroyed in HIV Infection.
- **Immune Complexes (Ag:Ab) may deposit in Vessels/Ducts:**
  - → Glomerular Damage (Glomerulonephritis)
  - → Vascular Damage
- ***IE: Sometimes the Immune Response can be more detrimental than the disease***.

BACTERIA:

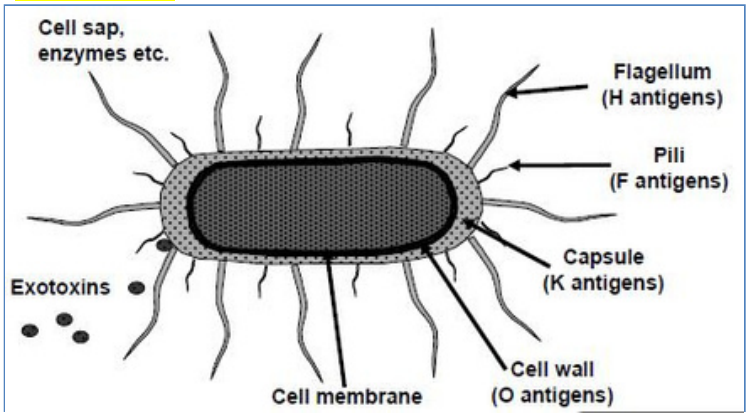
Properties of Bacteria:

- **Terminology:**
  - o **Normal Flora =** Bacteria consistently associated with an animal. (No disease)
  - o **Opportunistic Infections =** Bacteria which cause disease in a compromised host.
- **Tissue Invasion:**
  - o Some bacteria release enzymes to penetrate tissues:
    - § Eg: Hyaluronidase
    - § Eg: Collagenase
    - § Eg: Elastase
  - o Some secrete Coagulases → Induce Clotting (an environment in which they can grow).
  - o Some even invade *Cells* → Grow in the Cytoplasm/Nucleus.

Bacterial Antigens (Virulence Factors):

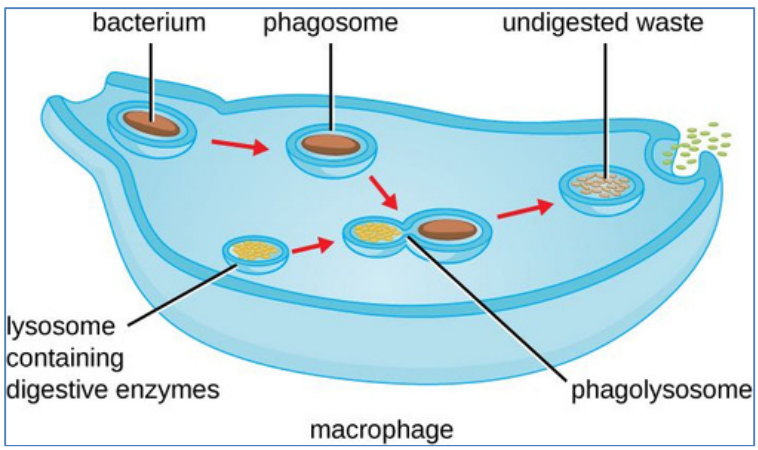
- **Endotoxins – (In the Walls of Gram Negative Bacteria) → Septic Shock:**
- **(Note: Recognised by Toll-Like Receptors on Macrophages → Cytokines)**
  - o ***Lipopolysaccharide (LPS)
  - o Surface Array Proteins (Eg: Enzymes)
  - o Flagellum
  - o o Adhesion Pili
  - o Cell Wall Antigens o Capsule Antigens
  - Cell Membrane

- **Exotoxins – (Toxic Molecules *Released* by the Bacteria) → Toxic Shock:**
  - o Eg: Tetani Toxin
  - o Eg: Staph → Superantigen.



Immunity Against Bacteria:

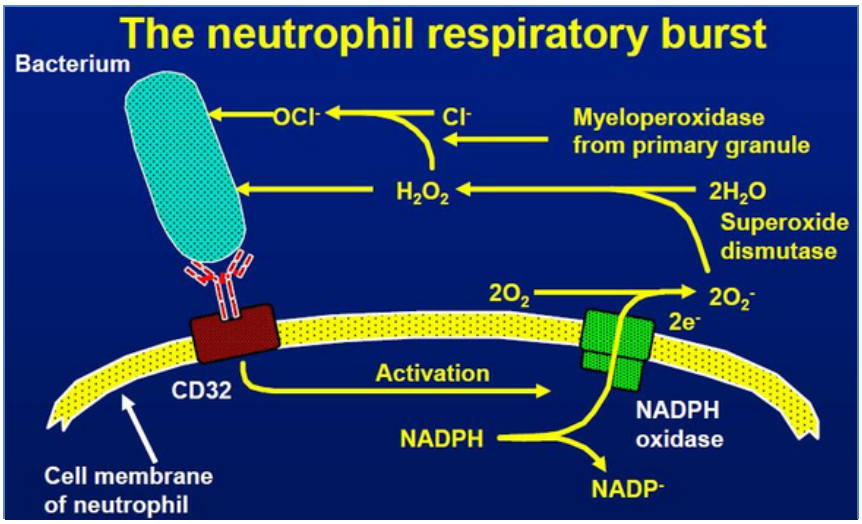
- **Innate Immunity:**
  - o ****Phagocytosis:**
    - § By Macrophages/Dendritic Cells/Neutrophils
    - § May be Independent, Antibody or Complement Mediated.



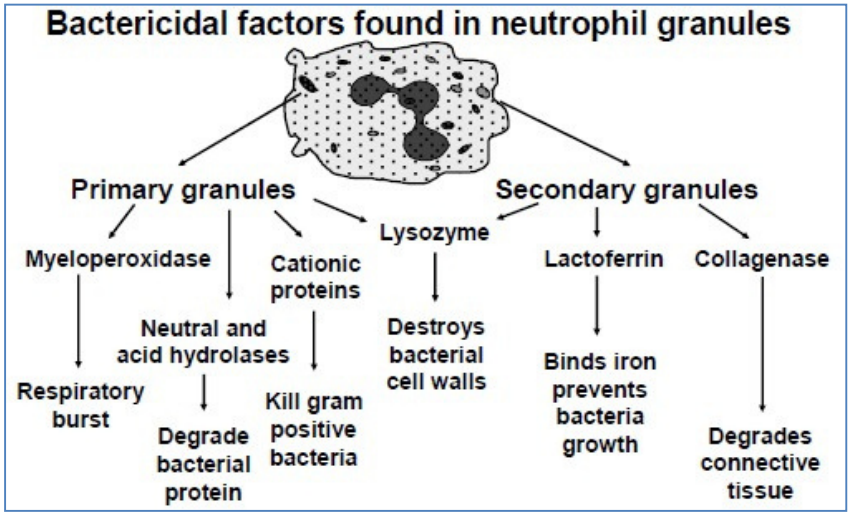
- ***Lysozyme:**
  - An Antibacterial enzyme dissolved in bodily secretions. (Tears/Saliva/Mucus/Neutrophils)
  - → Splits the Cell Wall Proteoglycans of Bacteria → Lysis
- ****Complement Activation – Via Alternative Pathway:**
  - **→Phagocytosis:**
  -
    - C3b opsonisation → Phagocytosis of Bacteria.

    →Lysis:
    - Membrane attack complex formation → Lysis of Bacteria.
- ****Neutrophils:**
  - **→ Phagocytosis:**
  -
    - Neutrophils ingest & kill many Microbes.

    → "Respiratory Burst":
    - Binding of Fc-portion of Antibodies on opsonised Bacteria stimulate production of Highly Oxidative Molecules which kills the bacteria.



  - **→ Bactericidal Granules:**

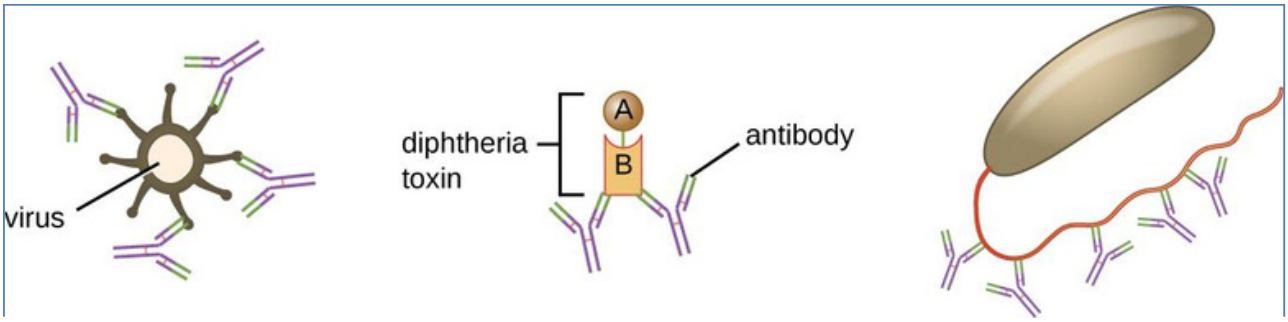


- **Local Inflammation – (Due to Cytokine Release after Macrophage Phagocytosis):**
  - →Local Inflammation
  - →Fever
  - →Acute Phase Proteins
- **Acute Phase Proteins:**
  - **(C-Reactive Protein [CRP], Mannose-Binding Lectin [MBL])**
  - **Both are:**
    - **Opsonising Agent for microbes** → Phagocytosis (Similar action to Antibodies – except have broad specificity for PAMPs)
    - **Complement Activators** → Activate the ***Classical (CRP)/Lectin (MBL) Pathways of the Complement Cascade***.

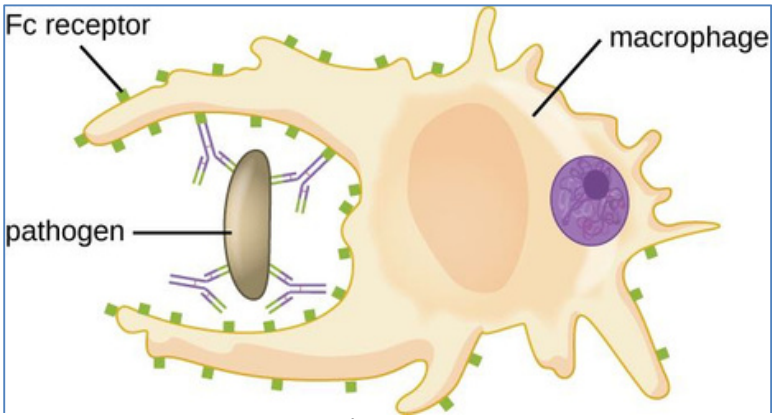
- **Adaptive Immunity:**
  - ****Antibodies – (Produced by B-Cells):**
    - § **→ Exotoxin Neutralisation:**
      - IgG is Entirely Responsible for this.
      - IgG essentially competes with the receptor for the toxin → Prevents binding to cellular target.
    - § **→ Endotoxin Opsonisation:**
    - § • Fc-Receptor-Mediated Phagocytosis

      → Bacteriolysis.

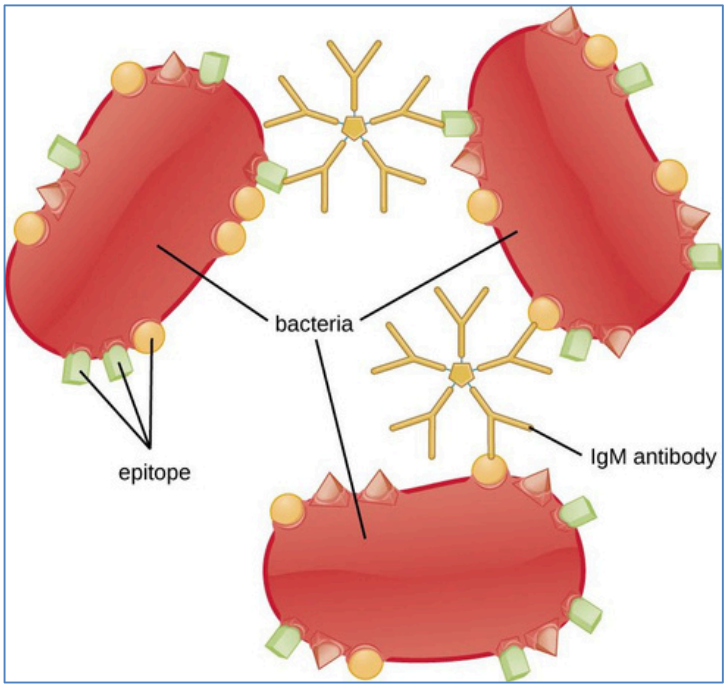
Neutralisation



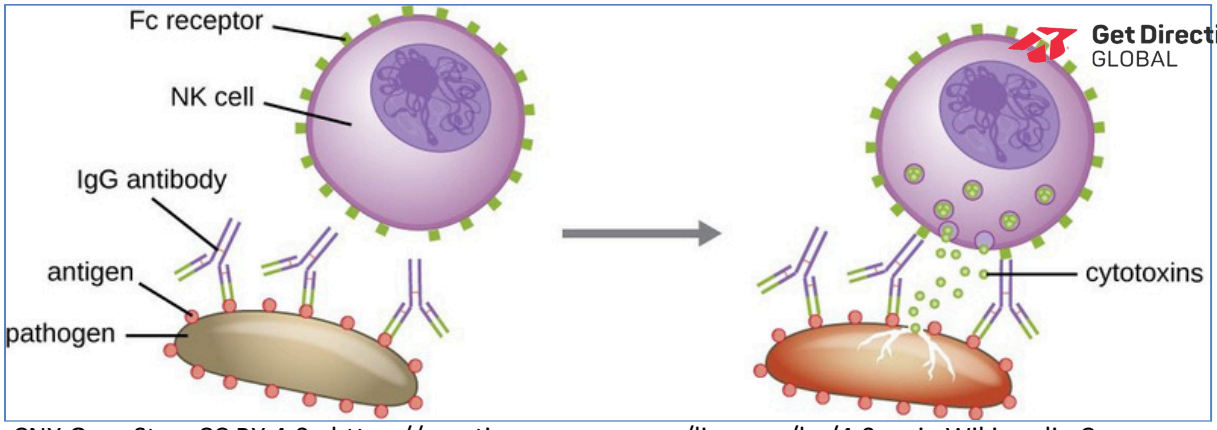
Opsonisation



Agglutination



Antibody-dependent cell-mediated cytotoxicity (ADCC)



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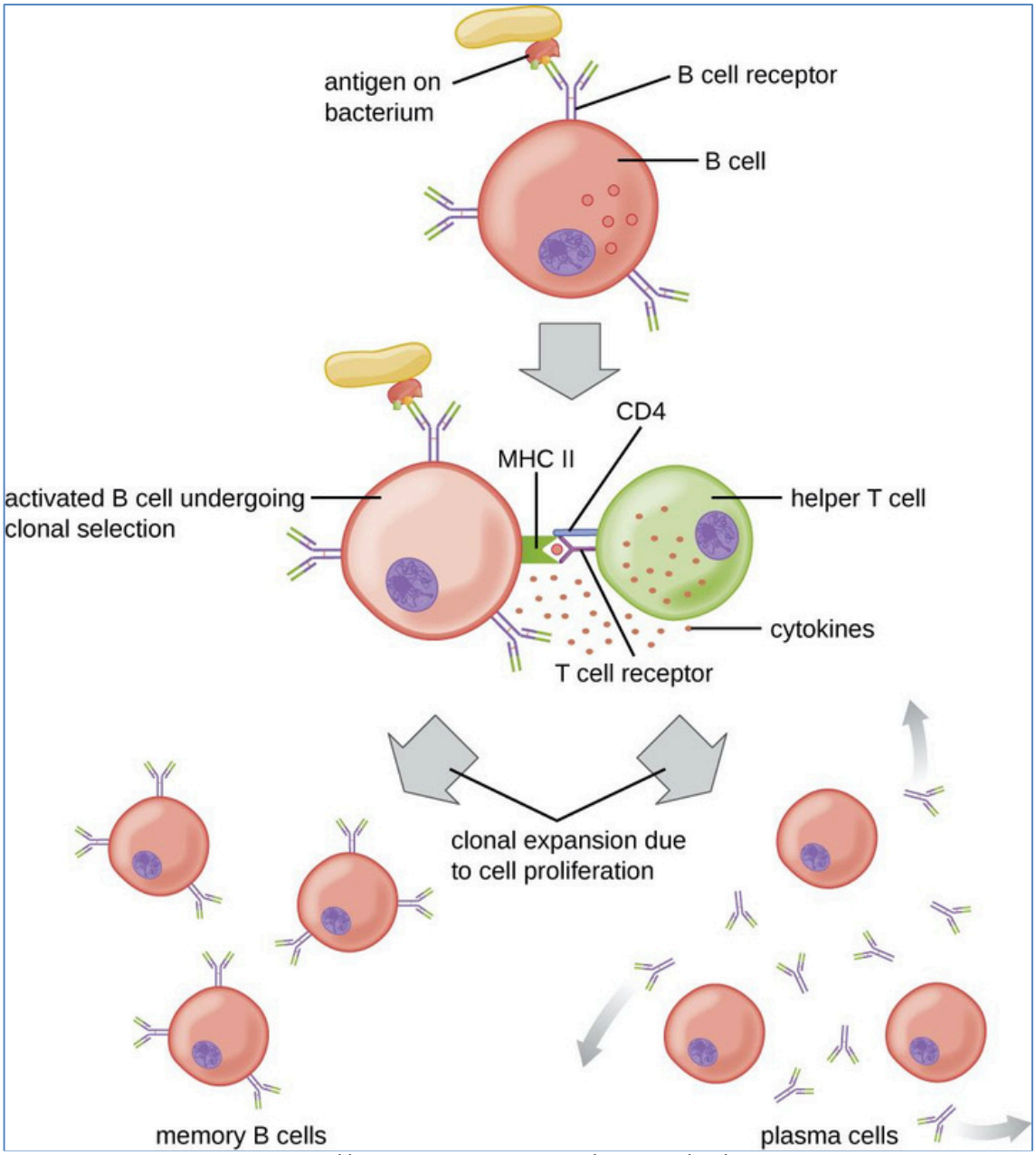
- **CD4-T-Helper Cells:**
  - **→ Activate Macrophages:**
    - → Destruction of Phagocytosed Bacteria
  - **→ Activate B-Cells:**
    - → Secretion of Antibodies



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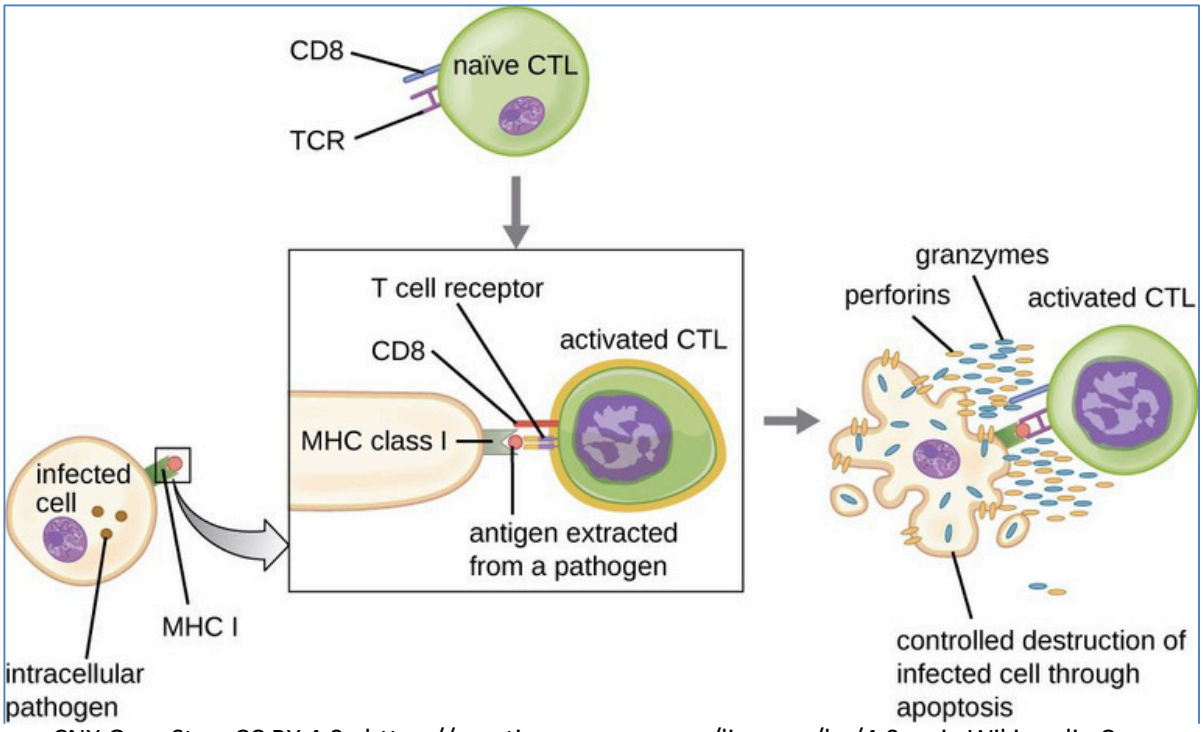
- **CD8-T-Cytotoxic Cells → Kill Infected Cells:**
  - Infected Cells displaying bacterial peptide on MHC-I are lysed by Perforins released by Cytotoxic CD8-T-Cells.



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M echanism s of Im m une Evasion:

- **Antigenic Variation** (Eg: N-Gonorrhoeae, E-Coli, S-Typhimurium)
- **Inhibition of complement activation** (Many bacteria)
- **Resistance to phagocytosis** (Pneumococcus)
- **Scavenging of reactive O2 intermediates** (Catalase-positive staphylococci, M-Leprae)
- **Inhibition of phagolysosome formation** (M-Tuberculosis, L-Pneumophelia)
- **Disruption of phagosome membrane → Escape into cytoplasm** (L-Monocytogenes)

PARASITES:

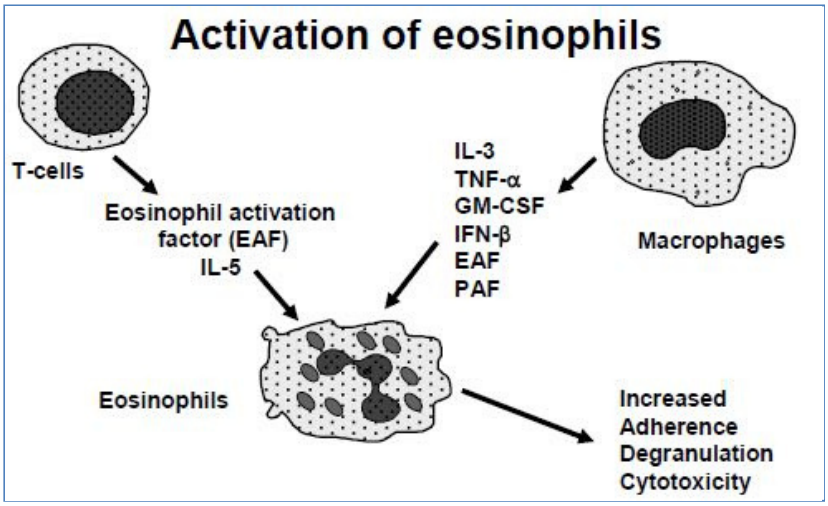
Properties of Parasites:

- **Parasites in General:**
  - o Lives at the expense of their host → Acquires Nutrients/Other Benefits without Reciprocal Benefits.
  - o Are Successful if:
    - § Produces minimal disturbance
    - § Not regarded by host as foreign
  - o Parasite infections tend to be Long-Term (As opposed to Bacteria/Viruses)
  - o Many make use of the Host's growth-factors to promote their *own* growth
  - o **(Incl: Protozoa, Metazoa [Helminths/Worms] & Arthropods)**

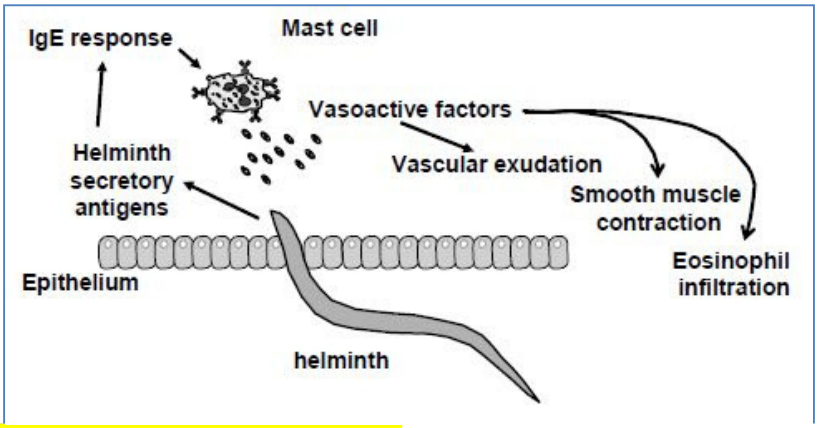
Im m unity A gainst Parasites:

- **Innate Immunity:**
  - o **Lysozyme:**
    - § (in Tears/Saliva/Mucus/Neutrophils)
    - § Some parasites are susceptible.
  - o **Eosinophils (Eosinophil Granulocytes):** Combat multicellular Parasites. Degranulate → Release Reactive Oxygen Species → to kill parasites.
    - §
    - §
  - o **Complement Activation:**
    - § By Alternate Pathway – Complement Activation by Binding to Pathogen Surface
    - § By MB-Lectin Pathway – Complement Activation by Binding to Lectin on Pathogen Surface.
    - § (Note: Classical Pathway is Adaptive – Complement Activation by Ab's on Pathogen Surface)
  - o **Phagocytes in Spleen:**
    - § Infected RBCs express specific Parasite Antigens which are opsonised by antibody/complement → Recognised & Removed by Phagocytes in the Spleen.
- **Adaptive Immunity:**
  - o **Antibodies (B-Cells):**
    - § **Typically for Extracellular Infections (in blood/Tissues)**
    - § **IgE** is the Major Isotype (Important in eliminating many helminth infections)
      - → (Hence, many infections are associated with **Type-1 Hypersensitivity** reactions)
        - o →Oedema, Asthma, Urticaria.
    - § **- Can destroy Tachyzoites (young parasites) in blood**.
    - § - Can neutralise *Proteases* used by parasites to enter tissues.
    - § - Can block 'Anal Pores' of parasites.
    - § - Can block enzyme pathways of some helminths (Can arrest egg production)
    - § (Note: However, Many parasites are unaffected by antibodies)
  - o **Complement Activation (By Classical Pathway):**
    - § Complement Activation by Ab's on Pathogen Surface
    - § - Can destroy Tachyzoites (young parasites) in blood.
  - o **Cell-Mediated:**
    - § **Typically for Intracellular Infections**.
    - § **Th1-Cells Activate Macrophages:**
      - Macrophages become more Phagocytic and Destroy Intracellular Parasites.
      - (Note: Typically, only Protozoan parasites are small enough to live intracellularly)
    - § **Th2-Cells Help B-Cells produce Antibodies:**
      - (Th2 is the predominant response)
    - § **Tc-Cells Destroy Infected Cells:**
      - May also directly destroy larvae.

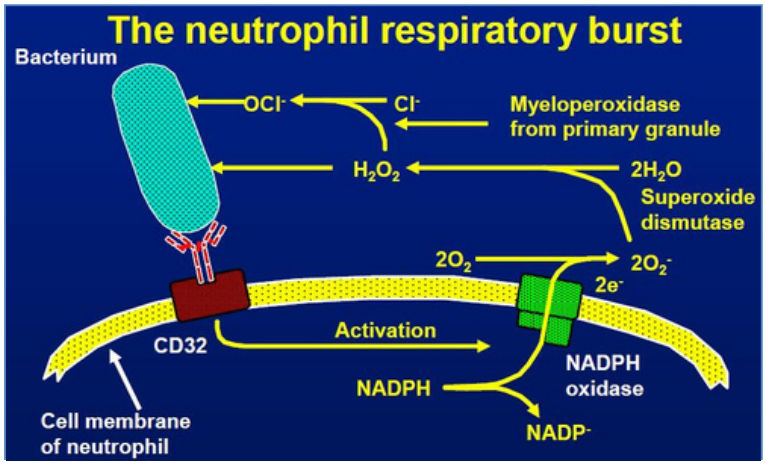
- **Eosinophils:**
  - **Note: They are the MAIN Effector Cell against Helminth Infections.**
  - **Activated by:**
    - Th-Cells (IL-5) & Macrophages (TNF-α, IFN-β, IL-3)
    - → Increased Adherence & Degranulation Cytotoxicity.



  - **Eosinophils have Fc receptors (Allow binding to Parasites covered with IgE-Antibodies)**
    - Binding of Antigen to Eosinophil-Bound-IgE → Degranulation.
    - **Similar to Mast Cells:**



  - **Release Granules onto the worm:**
    - ***Major Basic Protein** (Damages Cuticle of Helminths)
    - Eosinophil-Cationic Protein (A Ribonuclease – Toxic to Helminths)
    - Lysophospholipase
    - Phospholipase D
  - **Respiratory Burst:**
    - Superoxide
    - Chloride Ions
    - Hydrogen Peroxide
    - **Similar to Neutrophils:**



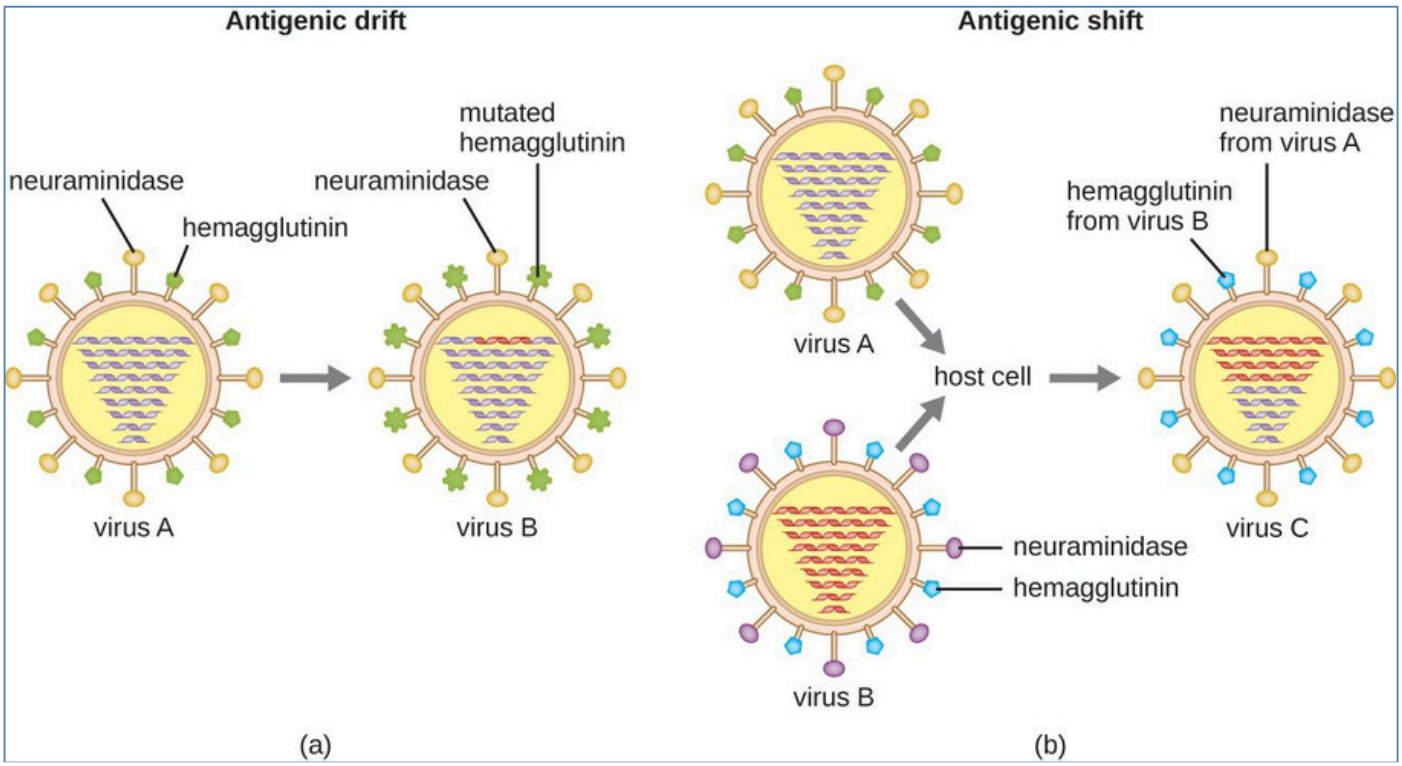
Immune-Evasion by Various Pathogens:

- **Antigenic Variation:**
  - **(Ie: Pathogens can evade detection by altering their antigens – Especially *Extracellular* Pathogens)**
  - § (Viruses, Bacteria & Protozoa)

1- Antigenic "Serotypes":

- § **Many pathogens exist in a wide variety of Antigenic Types**.
  - (Eg: Strep. **Pneumoniae** has 84 known types – each with different surface antigens)
  - (Eg: Some **Protozoa** have several *Variable Antigens,* encoded by different genes, and can *Switch* between different genes once the immune system is sensitised)
- § **Therefore**, infection with *One Serotype* leads to *'Type-Specific Immunity*', which protects against reinfection of *That Same Serotype*, but NOT against a Different Serotype.

- **2- Antigenic "Drift":** (RNA Viruses only):
  - § **Some Pathogens can *Mutate* Genes encoding for Surface Antigens → Change in Epitopes of Surface Antigens → Leads to Different "*Strains*" of the same pathogen**.
    - (Eg: Influenza Virus – There is a new strain of Influenza Virus every 2-3 years.)
  - § **Therefore**, Antibodies & T-Cells produced in earlier infections are *LESS* protective.
- **3- Antigenic "Shift":** (RNA Viruses only):
  - § **Some Pathogens can *Exchange* Genes between their Human & Animal counterparts → Resulting in a virulent "*Hybrid-Virus*" or "*Quasispecie*" that can infect Humans**.
    - (Eg: Human Influenza Virus + Swine Influenza → Human-Swine-Flu → Pandemics)
  - § **Therefore**, Antibodies & T-Cells produced in earlier infections are *NOT* protective.
    - → Leads to Global Pandemics of Severe Disease & High Mortality.



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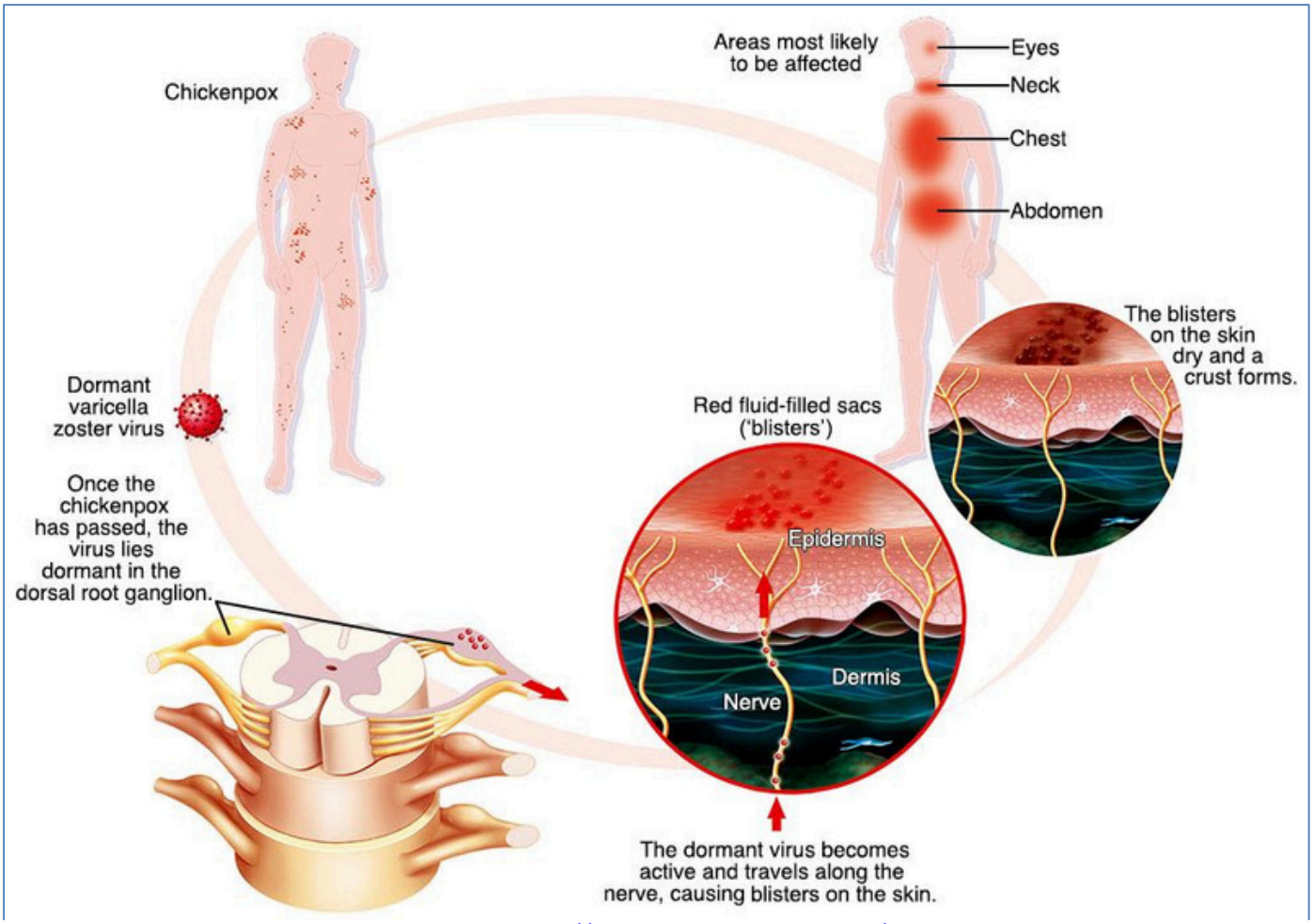
- **Latency:**
  - o **(Ie: Some Viruses persist *In Vivo* by Ceasing to Replicate until Immunity Wanes).**
  - o **Normally: Non-Latent Viruses**:
    - § To replicate, viruses need to direct the synthesis of viral proteins, which can be displayed on the MHC-I molecules of the Infected Cell → CD8-T-Cell Immune Response.
  - o **However, Latent Viruses – Eg: Herpes Simplex Virus:**
    - § Some viruses enter a state of ***Latency***, where the Virus lies dormant.
    - § In the latent state, there is *NO* viral Replication→ *NO* Disease & *NO* Immune Response.
    - § Often, such viruses persist in their *Latent State* inside *Sensory Neurons* – Which express few
    - § MHC-I molecules → Low CD8-T-Cell Recognition.
      Reactivation ("*Recrudescence*") can be triggered by Immunosuppression/Stress/Sunlight/ Hormonal Changes/etc.



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- **Resistance to Immune Effector Mechanisms:**
- **(Ie: Some pathogens induce a normal Immune Response, but have Mechanisms for Resisting them)**
  - (Viruses, Bacteria & Parasites)

  - **Eg: Preventing Fusion of Lysosome with Phagosome:**
    - **Eg: Bacteria: M-Tuberculosis** is phagocytosed, but *Blocks* fusion of Lysosome with Phagosome → Protects itself from Lysosomal Contents.
      Eg: Protozoa: Toxoplasma Gondii – Tachyzoites are phagocytosed, but *Blocks* fusion of Lysosome with Phagosome → Protects itself from Lysosomal Contents.

  - **Eg: Neutralising the Respiratory Burst:**
    - **Eg: Bacteria: Pseudomallei** Produces ***Superoxide Dismutase*** (to neutralise Respiratory Burst Free-Radicals.) – Hence avoid Bactericidal Effects.
      Eg: Helminths may also produce Antioxidants (to protect against the respiratory burst)

  - **Eg: Escaping from Phagosome into Cytoplasm of Cell:**
    - **Eg: Bacteria: Listeria** escapes from the Phagosome → Into the Cytoplasm of the Macrophage.
      - → Multiply inside the Cytoplasm of the Macrophage.
      - → They can also spread to Adjacent Cells *Without* emerging into the Extracellular Environment.
    - (Ie: Avoids attack by Antibodies, but still vulnerable to CD8-T-Cell attack)

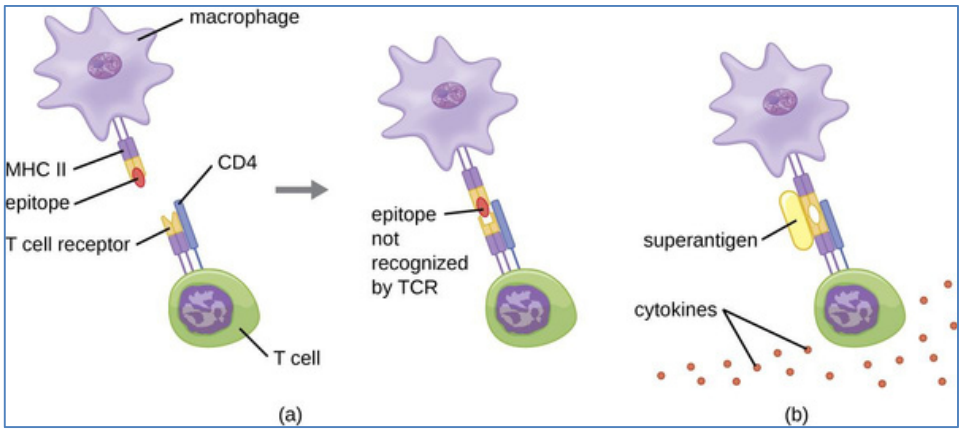
  - **Eg: Self-Isolation by Creating its *Own* Vesicle:**
    - **Eg: Parasite: Toxoplasma Gondii** Generates its *OWN* Vesicle once inside the cell, and doesn't fuse with any cellular vesicle.
      → Isolates the Parasite from the rest of the cell.
      → Also means less peptides are available for loading onto MHC-I molecules.

  - **Eg: Molecular Mimicry:**
    - **Eg: Expression of Host-Proteins:**
      - **Eg: Bacteria: Syphilis** coats itself with *Host Proteins* while it is Extracellular.
        - **→ Avoids Recognition by Effector Immune Mechanisms**
        - It also likes to invade CNS tissue (which is less accessible to antibodies).
      - **Eg: Some Schistosomes** cover themselves with *Host Proteins* (Eg: Blood-Group Antigens & MHC products)
        - **→ Avoids Recognition by Effector Immune Mechanisms**
    - **Eg: Expression of the Complement-Inhibitor Protein, "*Factor-H*":**
      - **Eg: Bacteria: Lyme Disease** avoids Complement-Lysis by coating itself with the *Complement-Inhibitory Protein = "Factor H"*, normally made by the host.

  - **Eg: Protease Production to Neutralise Anti-Parasite Immune Components:**
    - **Eg: Shistosomula (Helminth)** Produces Proteases → Cleave Antibodies
      - They also Inhibit Macrophage Function.

    Host Proteases may be Inactivated by Protease Inhibitors.

- **Immunosuppression or Inappropriate Immune Responses:**
  - **Superantigens:**
    - **Superantigens (Bacterial/Viral)** – facilitate *Non-Specific* binding between TCRs & MHCs → Mass Non-Specific T-Cell Activation → Huge Release of Cytokines → "Cytokine Storm" or **"Toxic Shock Syndrome"**.
    - **Note:** These stimulated T-Cells proliferate and then rapidly undergo *Apoptosis*:
      - → Generalised Immunosuppression
      - → Deletion of Certain Families of T-Cells.



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  - **Capturing Host Genes by Viruses:**
    - **Eg: For Cytokines (Virokines)/Cytokine Receptors:**
      - **Eg:** Some viruses direct production of Viral Cytokines (Virokines) which act as antagonists @ Cytokine Receptors → Inhibits Inflammation.
      - **Eg:** Large Viruses (Eg: Poxviruses) also direct production of IL-1-Receptor Analogues that M op U p & Inactivate IL-1 → Inhibits Inflam m ation.
    - **Eg: For Complement-Regulatory Molecules:**
      - **Eg:** Herpes Simplex can direct production of Complement Inhibitory Proteins →which Reduce the Effects of Complement.
    - **Eg: Inhibition of MHC-I Synthesis/Assembly:**
      - **Eg:** Herpes Simplex Virus direct expression of a protein → Inhibits synthesis of MHC-I
        - Or → Inhibits MHC-I Assembly.
        - Or → Inhibits the 'TAP' → Prevents Peptide Transport into the ER → Prevents Peptide-Loading onto MHC-I.
      - → Infected cells Can't Present Viral Peptides to Tc-Cells.
    - **Eg: Production of Decoy Proteins**
      - **Eg:** Human Cytomegalovirus directs expression of 'UL18', an MHC-I Analogue → Binds to Inhibitor Receptor on NK-Cells → Inhibits NK-Cells.
      - **Eg:** Epstein-Barr Directs expression of IL-10 → Inhibits Th1-Lymphocytes → Reduces IFNγ Production.

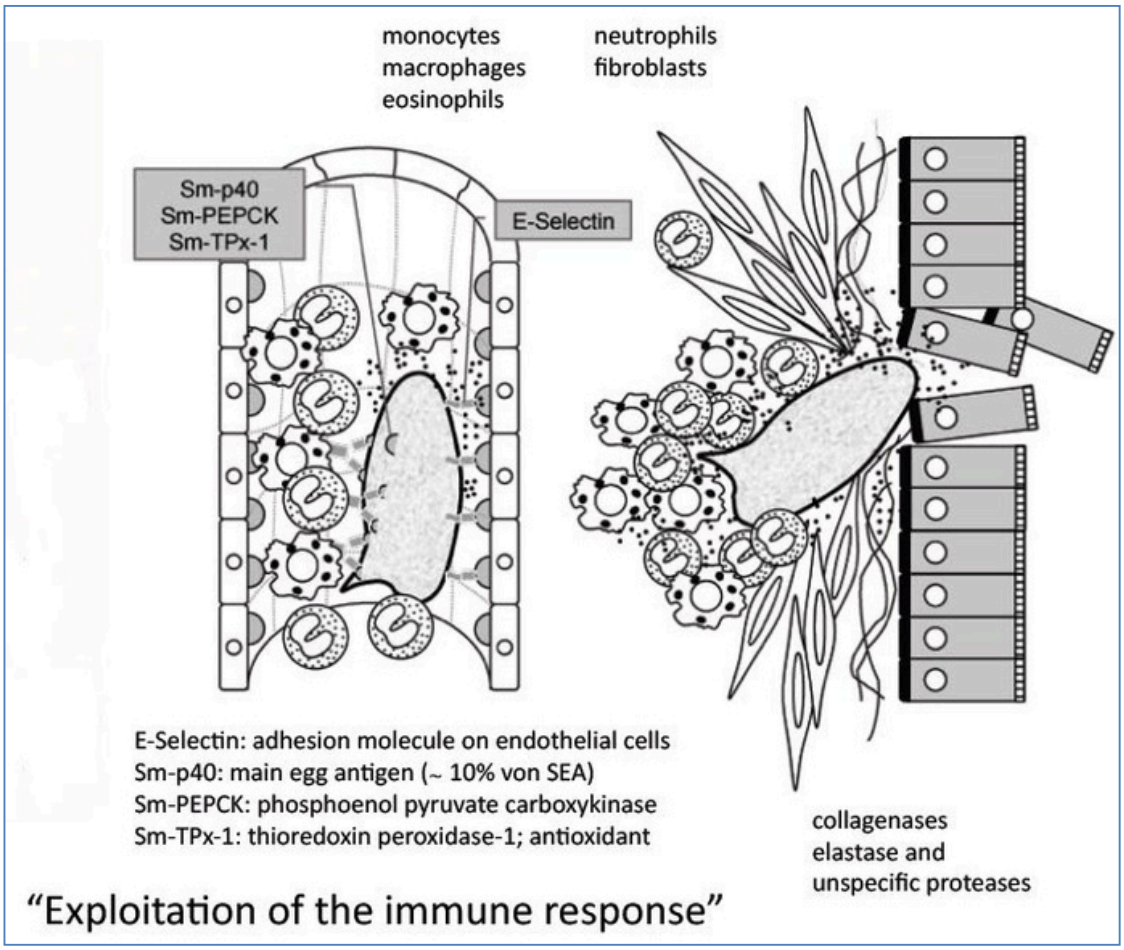
  - **Eg: Anthrax Toxin – Suppresses the Immune Response:**
    - **Bacteria: Anthracis –** suppresses the immune system via a Toxin: "Anthrax Lethal Toxin".
      - Anthrax Lethal Toxin is a *Metalloproteinase* → Alters MAP-Kinase cascades → Apoptosis of Infected Macrophages & Abnormal Dendritic Cell Activity→ Immunosuppression.

  - **Eg: Helminths – Secrete Soluble Immunosuppressant Factors:**
    - **→Inhibit Lymphocyte Function**.
    - **→Inhibit Mast-Cell Degranulation**.

  - **Eg: Helminths – Skew the T-Helper Response to Favour Th1-Cells:**
    - By favouring the Th1-response, you don't get class-switching to IgE, the primary AntiParasitic Antibody.
      Note: Some can even *Upregulate* IL-10, → T-Regulatory-Response → ↓Immune Response.

- **Sheltering in Immune-Privileged Sites:**
  - **(Ie: Sites where antigens CANNOT be targeted by Immune Activity)**
    - § Eg: Intracellular (Ie: Eg: Inside macrophages)
    - § Eg: Brain
    - § Eg: Eye
    - § Eg: Testis
    - § Eg: Uterus (Foetus)
    - § Eg: Vagina
    - § Eg: Urethra
    - § Eg: RBCs:
      - *Plasmodium Falciparum* (Malaria) – lives inside RBCs which don't express MHC-I:
        - o → Can't be recognised by CD8-T-Cells.
        - o → Are Shielded from Antibodies.
      - However, Infected RBCs *Can* be recognised/destroyed in the spleen:
        - o To avoid this, Malaria Parasites cause the RBCs to become *Sticky* →
        - o RBCs adhere to endothelium in peripheral organs.
        - o (Note: Can lead to peripheral vasculopathies & ischaemic organ failure)
    - § Eg: GI-Lumen

- **Exploiting The Immune System to Aid in Life-Cycle:**
  - **Eg: Some Helminths Exploit the Increased Expression of Cell-Adhesion-Molecules in Inflammation:**
    - § **Eg: Helminths which lay eggs need to get the eggs out of the Blood Vessels**.
      - Therefore, by causing Inflammation, Endothelial Cells Increase CAM Expression.
      - → Eggs use these Adhesion Molecules to adhere to the Endothelium.
      - → They then secrete Collagenases/Elastases/Proteases → to Exit the Blood Vessel.



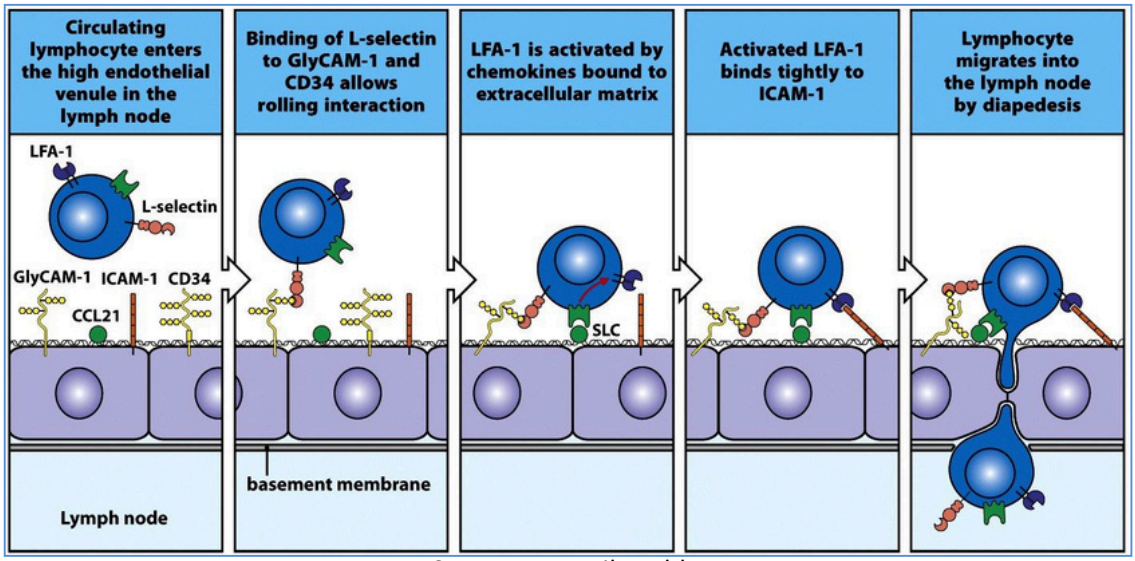
Cell Adhesion Molecules (CAM's) & Leukocyte Migration:

CAMs = Proteins displayed on Immune Cells and Vascular Endothelium, that aid in:

- **1) Routine Lymphocyte Circulation**, and
- **2) Migration & 'Homing' of WBCs** to Extravascular sites.

CAMS – The Basics: With the help of various cytokines, interactions between CAMs on Immune Cells & the Endothelium cause ***Margination*** (Adhesion) of Immune Cells to the Endothelium Wall. Following margination, ***Diapedesis*** occurs (Migration of immune cells through the endothelium wall). There are multiple types of CAMs, including Selectins, Integrins, Addressins, ICAM, GlyCAM & LFA-1. See below for more detail...

- **1) Routine Lymphocyte Circulation (Blood → Lymphatics):** Lymphocytes are constantly circulating between the Blood Vessels, the Lymphatic System & Lymphoid Tissues to ensure that they are readily available to attend to infected/damaged sites quickly. **How?**:
  - o Naive T-Cells preferentially leave the blood & enter Lymph Nodes across High Endothelial Venules (HEVs – specialised post-capillary vessels found in T-Cell areas of all secondary lymphoid organs, except the spleen. They are the Naive T-Cell's gateway into the lymphatic system – Particularly to Lymph Nodes)
  - o The specialised endothelium lining these HEVs expresses a number of molecules involved in lymphocyte homing to the lymph node:
    - § **GlyCAM-1**
    - § **ICAM-1**
    - § **Chemokines** (Membrane Bound)
  - o The initial binding of the Naive T-Cell to the vascular endothelium (HEV) is mediated by **L-Selectin** binding to **GlyCAM-1**.
  - o Next, the binding of **Chemokines** on the vascular Extracellular Matrix to the Naive T-Cell triggers TIGHT binding of **LFA-1** to **ICAM-1**, arresting the lymphocyte on the endothelium.
  - o The Naive T-Cell is then able to migrate across the endothelium, and into the T-Cell area of the Lymph Node. There it can inspect Dendritic Cells in the lymph node for the presence of its specific Antigen.
    - § If it doesn't recognise any Antigens, the T-Cell is not activated & passes out of the lymph
    - § node to return to the circulation.
      The Naive T-Cells that do meet their specific antigen, are then activated via Antigen Presentation to their Antigen Receptors (TCRs), and begin to proliferate & mature into Effector CD4 & CD8 T-Cells within the Lymph Node.
    - § The activated CD4-T-Cells then activate antigen-specific B-Cells which migrate to nearby
    - § follicles & begin secreting Antibodies into the lymph → Blood.
      The activated CD8-T-Cells leave the lymph node & return to the Blood ready to fight off invaders. They exit the lymphatic system through the Efferent Lymphatics →The Thoracic Duct → the Superior Vena Cava.
  - o **Note:** Most of the Lymphocytes in Peripheral Blood are T-Cells, despite being only 2% of the total lymphocyte population.



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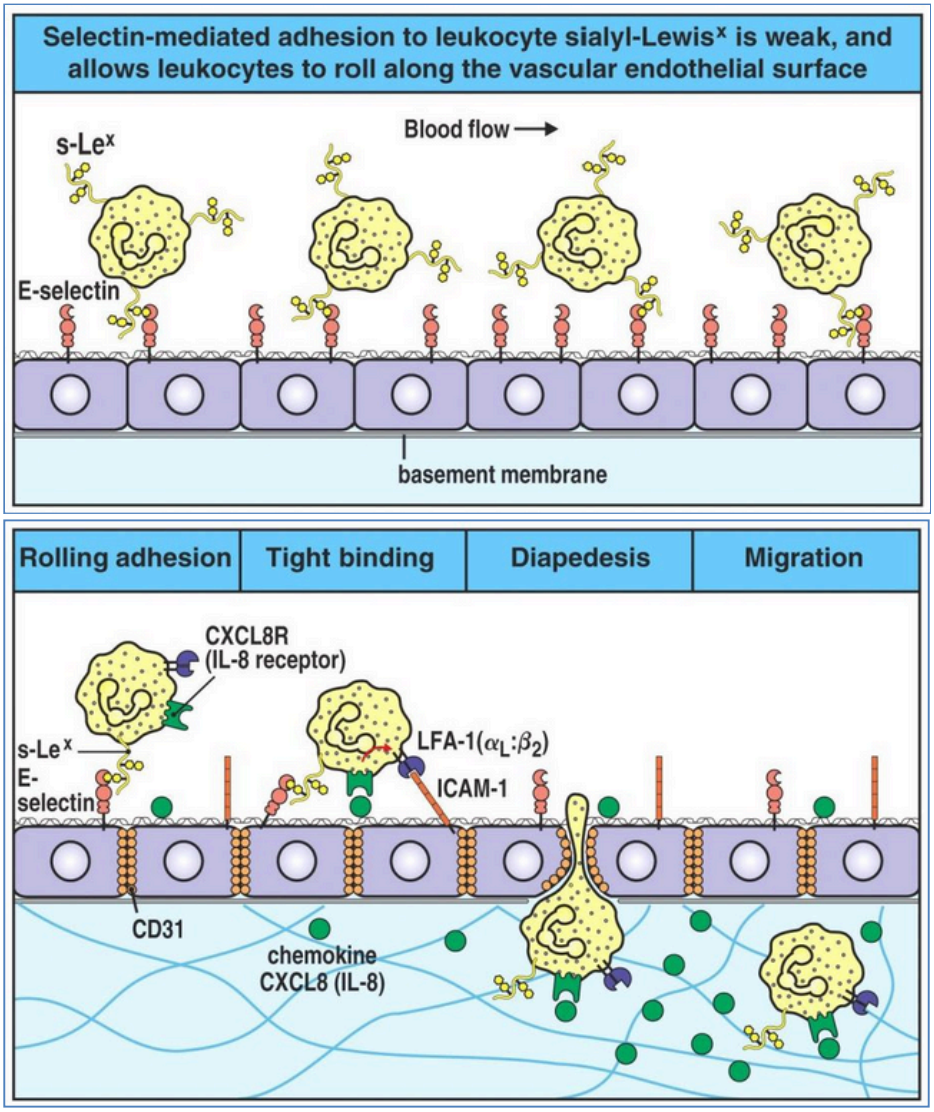
- **2) Migration & Homing of WBCs (Blood → Peripheral Tissue): Effector+Memory T-Cells** (Ie: Activated T-Cells), as well as **Monocytes** and **Granulocytes**, are recruited from the blood and enter Peripheral Tissues through the vascular Endothelium of Venules at sites of Infection/Injury.
  - o **Leukocytosis** – Injured cells release **'Leukocytosis-Inducing Factors'** which promote rapid release of WBC's from red bone-marrow → Leukocytosis (High WBC count).
  - o **Margination** – Activated vascular endothelial cells express a number of Adhesion Molecules involved in arresting WBCs at the site of infection:
    - § **E-Selectin**
    - § **ICAM-1**
    - § **Chemokines** (Membrane Bound) (In this case = **IL-8**)
  - o Leukocytes (WBCs) initially adhere by binding to **E-Selectin** on the endothelium, which recognises the **Sialylated Lewis X Carbohydrate (S-LeX)**, & other glycoprotein ligands on the leukocytes.
  - o Next, as the leukocyte rolls over, **LFA-1** weakly binds to **ICAM-1**.
  - o Subsequently, the binding of **Chemokine IL-8** on the vascular Extracellular Matrix to the Leukocyte triggers TIGHT binding of **LFA-1** to **ICAM-1**, arresting it on the endothelium.
  - o **Diapedesis –** The tightly-bound leukocyte now migrates across the endothelium, squeezing between adjacent endothelial cells.
  - o **Chemotaxis** – The Leukocyte then follows the Chemokine Concentration Gradient to the site of injury/infection. (Specifically, IL-8 – a Chemoattractant & Angiogenic Factor).
    - o **Note:** Monocytes that migrate into inflamed tissue mature into macrophages



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Note: Leukocyte Adhesion Deficiency: This disorder stems from a defect in the B2 chain of the LFA-1 Molecule required for tight binding of the Leukocyte to the ICAM-1 receptor on the Endothelium. These patients are prone to recurrent infection & impaired wound healing due to diminished capacity to recruit inflam m atory cells in response to infection or injury.

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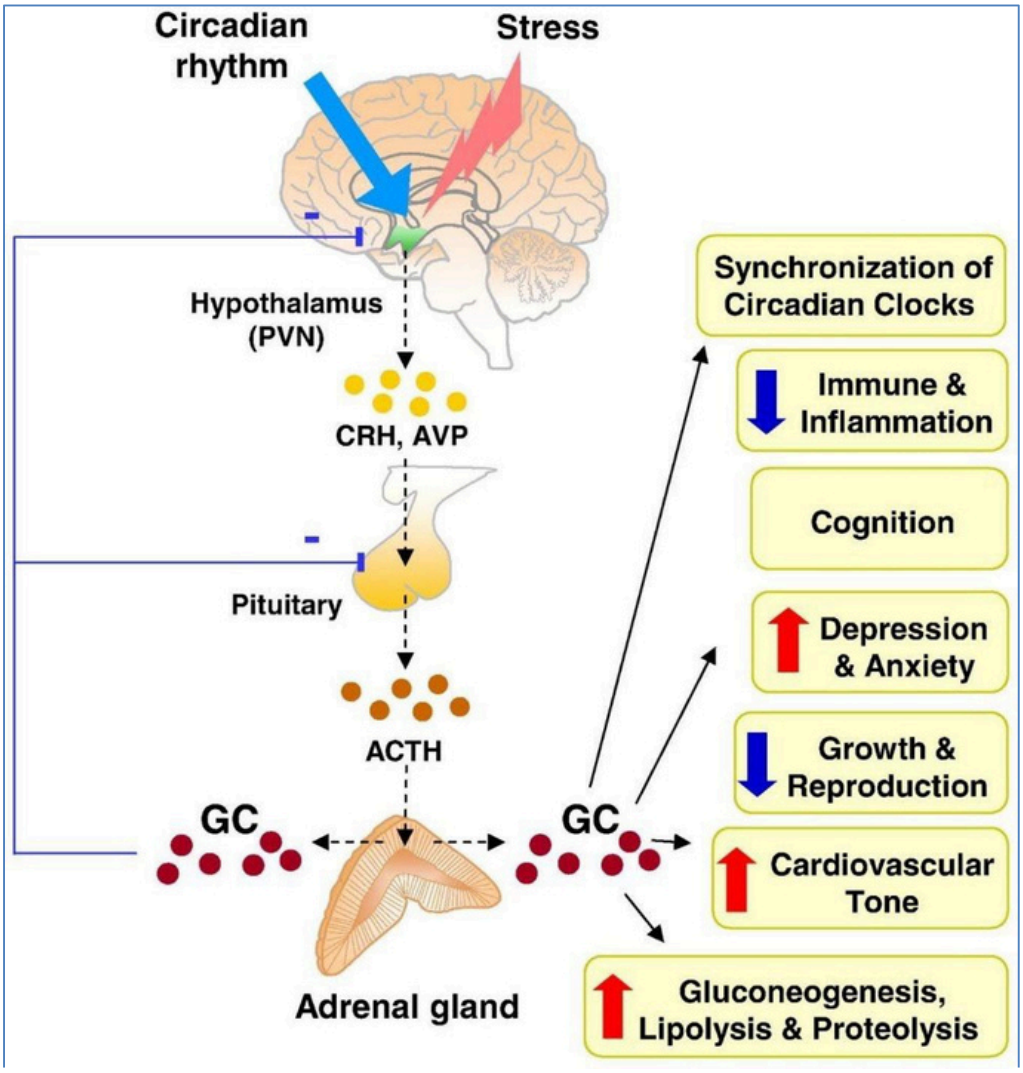
The Brain-Endocrine-Immune System Interactions:

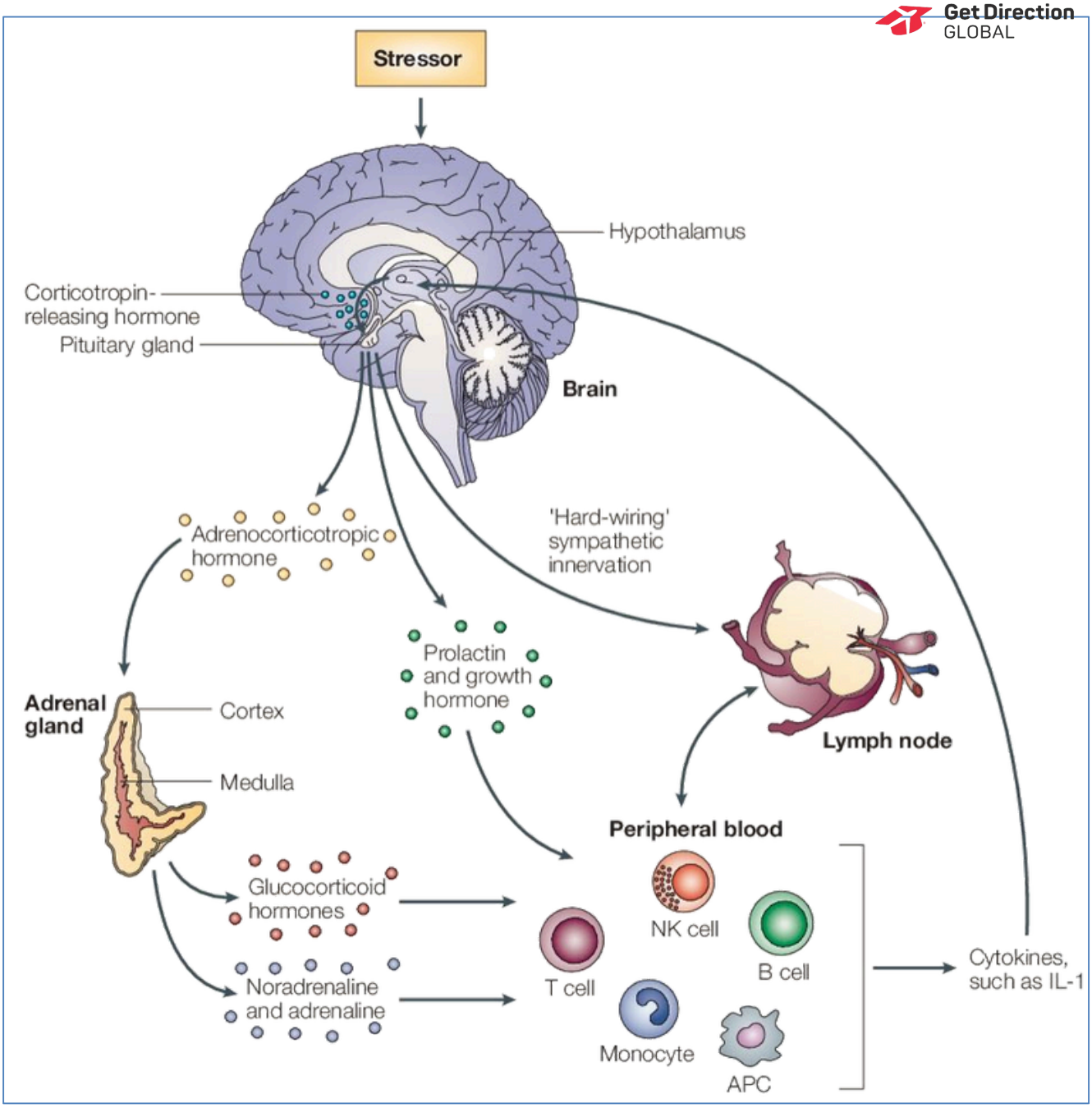
- **Immune Cells are Regulated by:**
  - o Neurotransmitters
  - o Hormones
  - o Neuropeptides

- **Immune Cells Communicate with Nervous Tissue through Cytokines:**
  - o – Either Local or Systemic Cytokines
  - o – Cytokines (IL1, IL6) Stimulate Peripheral Nerves → Stimulate Vagus Nerve → Stimulates Cytokine Release in CNS → Cytokines in CNS Activate Hypothalamus → Sickness Behaviour.

- **Physical/Emotional Stress & Psychiatric Illness can compromise the Immune System:**
  - o ***Acute Stress ENHANCES*** the Immune System, but ***Chronic Stress SUPPRESSES*** the Immune System:
    - § 1- During Acute Stress – There is a shift towards ↑Innate Immune Responses.
    - § 2- If Chronic Stress – There is a Decrease in almost all functional Immune Responses
    - § (**Hence: Increase in Stressor Duration → Shifts from Adaptive to Detrimental**.)
  - o **Some Hormones are *Immunostimulatory*:**
    - § Prolactin & Growth Hormone
  - o ***Stress Hormones* (Adrenocortical & Glucocorticoid) are *Immunosuppressive* & *Anti-Inflammatory*:**
    - § Stress → CRH Release from Hypothalamus
      - CRH → ACTH Release from Pituitary
        - o ACTH → **Noradrenaline & Cortisol** Release from Adrenal Gland.



Circadian rhythm of adrenal glucocorticoid Figure on ResearchGate; https://www.researchgate.net/figure/Neuroendocrine-regulation-of-adrenal-GC-and-its-physiological-roles-GC-is-primarily_fig3_49835615



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AUTOIMMUNITY

AUTOIMMUNITY

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Concepts Behind Autoimmune Diseases:

- **General Info:**
  - o **Autoimmune Diseases = "Specific, Adaptive Immune Responses *Against Self Antigens*":**
    - § Autoimmune responses *resemble* normal immune responses to pathogens → Give Rise to:
      - Specific Autoreactive Effector Cells
      - Specific Autoreactive Antibodies (Autoantibodies).
  - o 2/3 are Female
  - o **There are many Autoimmune Disease Manifestations:**
    - § **Some are 'Organ-Specific'** – (Because some Ags are specific to certain organs):
      - Eg: Type 1 Diabetes Mellitus
      - Eg: Multiple Sclerosis
      - Eg: Myasthenia Gravis
    - § **Some are 'Organ Non-Specific'** – (Because many Ags are expressed on multiple organs):
      - Eg: Rheumatoid Arthritis
      - Eg: Systemic Lupus Erythematosus
  - o **Type II, III & IV Hypersensitivity Reactions may be involved**.
  - o **Note:** The Presence of *Autoantibodies* is *Not Always* Harmful – (Because there is an extra '*level*' of control – Exerted by T-Cells; Ie: ↓T-Cell Help → ↓Antibody Levels)

- **Autoreactive T & B-Cells:**
  - o ***Both* T & B-Cells are Involved in the Autoimmune Process:**
    - § **Autoreactive T-Cells:**
      - → Cell-Mediated Destruction of Tissues expressing Self-Antigen.
    - § **Autoreactive B-Cells:**
      - → Humoral Immunity (Abs) against Self-Antigen.
  - o **But *How*???**
    - § Gene rearrangement during lymphocyte development in the Primary Lymphoid Organs is
    - § ***Random***, and thus inevitably results in *some lymphocytes* with affinity for Self-Antigens.
    - § These Autoreactive Lymphocytes are normally Removed/Inactivated by a variety of m echanism s → Self-Tolerance.

      ***However*, Autoimmunity is a *Failure* of these mechanisms of Self-Tolerance**.

Revision of Tolerance Mechanisms – How they Normally Prevent Autoimmunity:

- ***Central* ('Thymic') *Tolerance*:**
  - **Elimination of Self-Reactive Lymphocytes in the Thymus:**
    - Many (But not all) of the body's Self-Antigens are expressed in the Thymus/Bone Marrow by a subset of Dendritic-Like Cells → Delete Strongly-Autoreactive Lymphocytes.
  - **- However, Some Self-Reactive Lymphocytes *Escape* Elimination**.
    - These Lymphocytes leave the Thymus & can be Activated to cause Autoimmune Disease.

- ***Peripheral Tolerance*:**
  - **Anergy (& Lack of Co-Stimulation):**
    - **Relies on the Innate Immune System to Signal Infection → Permits the Adaptive Immune**
    - **System to be Activated:**
    - In the *Absence* of infection, these signals are not generated.
      In such circumstances, Interactions between a Naive Lymphocyte with Self-Antigen, *without* Co-stimulation, leads to a *Negative, Inactivating* Signal → Anergy.
  - **Regulatory Tolerance:**
    - **(Ie: Suppression induced by Regulatory-T-Cells.)**
    - TReg-Cells develop in the Thymus in response to *Weak Stimulation* by *Self-Antigens*.
    - → If they encounter Self-Antigens in the Periphery, they Secrete Inhibitory Cytokines.
  - **Ignorance:**
    - **(Ie: Self-Antigens are "invisible" to the immune system)**
    - Some lymphocytes with Relatively Low Affinity for Self-Antigens make *No Response* to them and are considered *'Ignorant of Self'*.
    - **- However, these *Ignorant* but *Latently Self-Reactive* cells can be recruited if the stimulus, (Eg: Infection), is strong enough**.
      - Eg: Naive Self-Reactive *Ignorant* T-Cells become activated by a Dendritic Cell presenting Self-Antigen + High Levels of Co-Stimulatory signals.
  - **Separation of Autoreactive T-Cells and Self-Antigens:**
    - Antigens may be located in *'Immunologically Privileged'* Sites.
    - (Eg: Brain & Anterior chamber of the Eye.)

PATHOGENIC MECHANISMS OF AUTOIMMUNE DISEASES:

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Contributing Factors:

- **Genetic Factors:**
  - o Some individuals are Genetically Predisposed to Autoimmunity.
  - o Autoimmune diseases are more common in females than males.
  - o Some Autoimmune diseases (Eg: Type 1 Diabetes) run in families.
  - o Scientists have isolated several Single-Gene traits associated with Autoimmunity.
- **Environmental Factors:**
  - o Eg: SLE will only occur in *Both* Identical Twins around 25% of the time. Therefore, Environmental Variables must be at play.

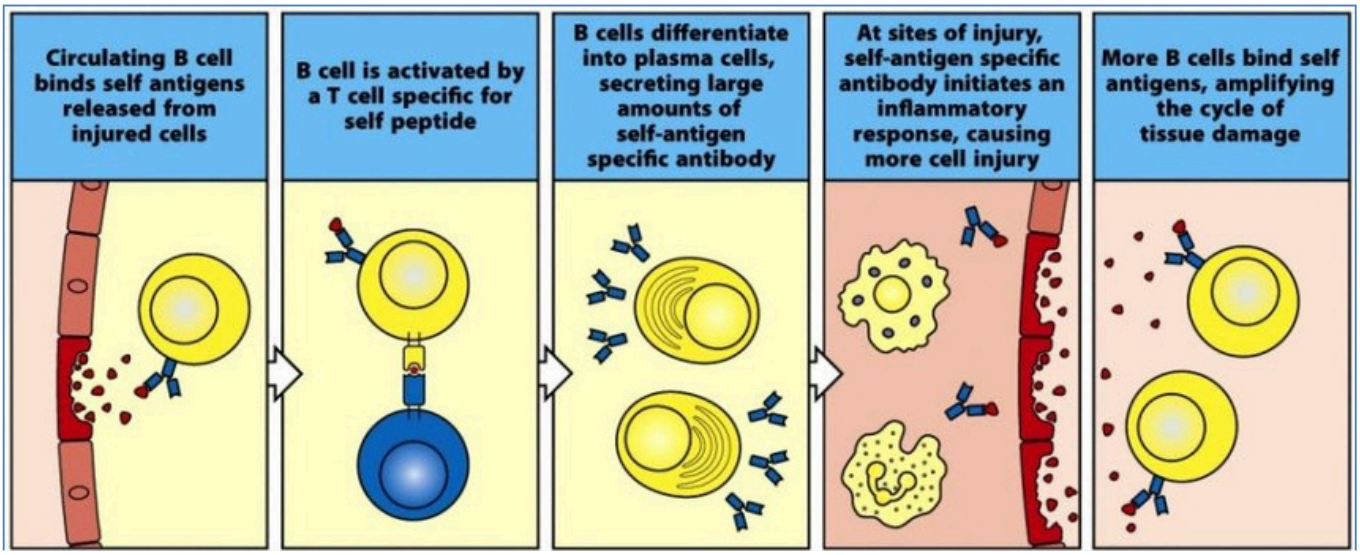
Exposure of Hidden Epitopes →Chronic Inflammation →Perpetuates Autoimmunity:

- **(Note: Some antigens are not normally exposed – However, following Trauma/Disease, these antigens**
- **may be exposed → Formation of Auto-Antibodies → Chronic Inflammation.)**
- **1-** Cell damage releases self-antigens →Specific Circulating B-Cells may bind to these Self-Antigens.
- **2-** APCs may ingest & present these Self-Antigens to specific CD4-T-Cells → Active Effector Th-Cells.
- o Active Effector Th-Cells → Activate Specific B-Cells.
- **3-** Specific B-Cells differentiate into Plasma-Cells → Secrete Self-Ag-Specific Antibody.

4- Antibodies attack the sites of injury → Causing an Inflammatory Response → Further Cell Injury.

5- Further Cell Injury → ↑Release of Self Antigens → More B-Cells binding to Self-Antigens.

- o → Potentiates Tissue Damage.



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"Epitope Spreading" *Amplifies* Autoimmunity:

- Epitope Spreading occurs when an Autoreactive B-Cell endocytoses & processes a specific antigen, and then
- Presents the Antigen-Derived Peptides to T-Cells.
- However, Processing of Antigens reveals previously hidden Epitopes → Therefore, a variety of T-Cells will be activated by that B-Cell.
- These Autoreactive T-Cells then provide help to multiple subsets of B-Cells → Production of a Greater Variety of Autoantibodies.
  (Eg: In SLE (Lupus), Autoreactive T-Cells specific to Histones, provide help not only to the original Histone-Specific B-Cells, but also DNA-Specific B-Cells → Production of both Anti-Histone & Anti-DNA antibodies)

MHC & Autoimmune Disease:

- **Note: There is a Tendency for Autoimmune Diseases to "Run in Families" – HLA Genes (MHC) are Involved:**
  - o **Different HLA Types are Associated with different Autoimmune Diseases:**
    - § For Most Autoimmune Diseases, MHC-II is mostly implicated. (Some are MHC-I)
  - o **Many Autoimmune Diseases are Linked to Certain MHC Alleles:**
    - § Eg: Siblings with an Autoimmune Disease are likely to *also* share the Same MHC Haplotypes.

Infectious Agents Can Induce Autoimmune Diseases:

- **How? – By Providing an Environment that Promotes Lymphocyte Activation:**
  - o → ↑Inflammatory Mediators from APCs & Lymphocytes.
  - o → ↑Expression of Co-Stimulatory Molecules on APCs.
  - o → Tissue Destruction → ↑Availability of the Self-Antigen.
- → APCs presenting Self-Antigen can activate Autoreactive T-Cells (Incl: Ignorant T-Cells).
  - o → Autoimmune Disease.

Cross-Reactivity with Micro-Organisms – (Molecular Mimicry):

- Some Pathogens express Antigens that resemble Host Molecules – (Molecular Mimicry).
- → Stimulate Adaptive Immune Response:
  - o → B-Cells secrete Antibodies that may cross-react with self-protein.
  - o → T-Cell attack on self-tissues.
- → Autoimmune Disease.
- (Eg: Rheumatic Fever – Similarity of Epitopes on Strep. Antigens (Eg: M-Protein) and Host Cardiac Tissue →
- Causes Antibody-Mediated damage to a variety of tissues (Incl: Heart Valves/Myocardium))
- (Eg: Antibodies to Epstein-Barr Virus may react with Myelin → Multiple Sclerosis)

Background Info on Group-A-Strep (GAS):

- o **As a Normal Flora:**
  - § ***Strep. Pyogenes* is one of the most frequent pathogens of humans**.
    - ≈5-15% of people harbour the bacteria (Respiratory Tract) – Asymptomatic.
    - There are ≈120 Strains – Some more rheumatogenic than others.
  - § **Can Infect when Immunocompromised** → Pharyngitis/Cellulitis/Fasciitis/Toxic Shock.
  - § **However, *'Rheumatic Strains'* Can *Also* Cause Autoimmune Diseases** →Post-Strep Glomerulo-Nephritis/ Acute Rheumatic Fever (→ Rheumatic Heart Disease)
- o **'Rheumatogenic' GAS:**
  - § ***'Rheumatic Strains'* Can Cause Autoimmune Diseases:**
    - Eg: Rheumatic Fever (→ Rheumatic Heart Disease)
    - Eg: Post-Streptococcal Glomerular Nephritis
    - Eg: Reactive Arthritis (Note:NOT Rheumatoid Arthritis)
  - § **Note: The degree of "Rheumatogenicity" depends on the concentration of M Proteins**.
- o **Immunogenic Virulence Factors:**
  - § **GAS produces a wide array of Virulence Factors:**
    - **M-Protein (Antiphagocytic, & Anti-Complement)
    - *Exotoxins (*Superantigens →Toxic Shock, *Pyrogens & Mitogens)
    - *Invasins (Streptolysin) (Lysis of RBCs/WBCs & Release of Lysosomal Enzymes)
    - *DNAse (Depolymerises free DNA)
  - § **The Importance of 'M-Protein' in RHD:**
    - The M-Protein Antigen is remarkably similar to Cardiac Myosin (in Heart Muscle)
    - → Stimulates an Adaptive Immune Response → Anti-M-Protein Antibodies.
      - o Anti-M-Protein Antibodies *Cross-React* with Cardiac Myosin →
        - § → Valvular Thickening
        - § →Thickening/Fusion of Chordae Tendonae
        - § → Diffuse fibrosis
        - § →Focal Fibrinoid Necrosis

Organ-Specific Autoimmune Diseases To Be Aware Of:

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Select Autoimmune Diseases

Disease	Cause	Signs and Symptoms
Addison disease	Destruction of adrenal gland cells by cytotoxic T cells	Weakness, nausea, hypotension, fatigue; adrenal crisis with severe pain in abdomen, lower back, and legs; circulatory system collapse, kidney failure
Celiac disease	Antibodies to gluten become autoantibodies that target cells of the small intestine	Severe diarrhea, abdominal pain, anemia, malnutrition
Diabetes mellitus (type I)	Cytotoxic T-cell destruction of the insulin-producing β cells of the pancreas	Hyperglycemia, extreme increase in thirst and urination, weight loss, extreme fatigue
Graves disease	Autoantibodies target thyroid-stimulating hormone receptors, resulting in overstimulation of the thyroid	Hyperthyroidism with rapid and irregular heartbeat, heat intolerance, weight loss, goiter, exophthalmia
Hashimoto thyroiditis	Thyroid gland is attacked by cytotoxic T cells, lymphocytes, macrophages, and autoantibodies	Thyroiditis with goiter, cold intolerance, muscle weakness, painful and stiff joints, depression, memory loss
Multiple sclerosis (MS)	Cytotoxic T-cell destruction of the myelin sheath surrounding nerve axons in the central nervous system	Visual disturbances, muscle weakness, impaired coordination and balance, numbness, prickling or “pins and needles” sensations, impaired cognitive function and memory
Myasthenia gravis	Autoantibodies directed against acetylcholine receptors within the neuromuscular junction	Extreme muscle weakness eventually leading to fatal respiratory arrest
Psoriasis	Cytokine activation of keratinocytes causes rapid and excessive epidermal cell turnover	Itchy or sore patches of thick, red skin with silvery scales; commonly affects elbows, knees, scalp, back, face, palms, feet
Rheumatoid arthritis	Autoantibodies, immune complexes, complement activation, phagocytes, and T cells damage membranes and bone in joints	Joint inflammation, pain and disfigurement, chronic systemic inflammation
Systemic lupus erythematosus (SLE)	Autoantibodies directed against nuclear and cytoplasmic molecules form immune complexes that deposit in tissues. Phagocytic cells and complement activation cause tissue damage and inflammation	Fatigue, fever, joint pain and swelling, hair loss, anemia, clotting, a sunlight-sensitive "butterfly" rash, skin lesions, photosensitivity, decreased kidney function, memory loss, confusion, depression

Type 1 Diabetes Mellitus:

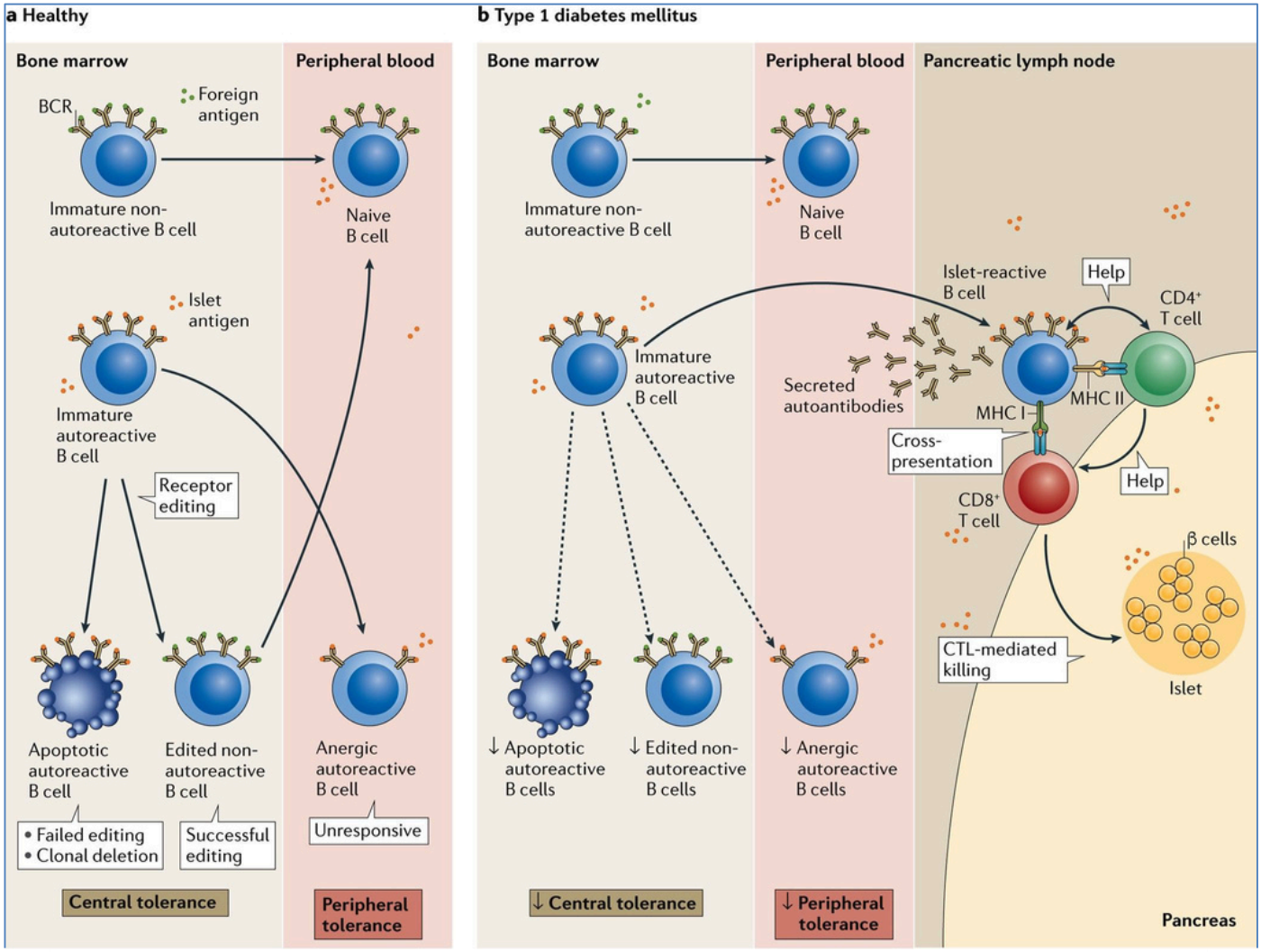
- **What is it?**
- o Deficiency of Insulin leading to Abnormalities in Glucose Utilisation by Insulin-Dependent Tissues.

Aetiology:

o Deficiency in Insulin due to CD8-Mediated Autoimmune Destruction of β-Cells in the Islets of Langerhans in the Pancreas.

- **Genetics:**

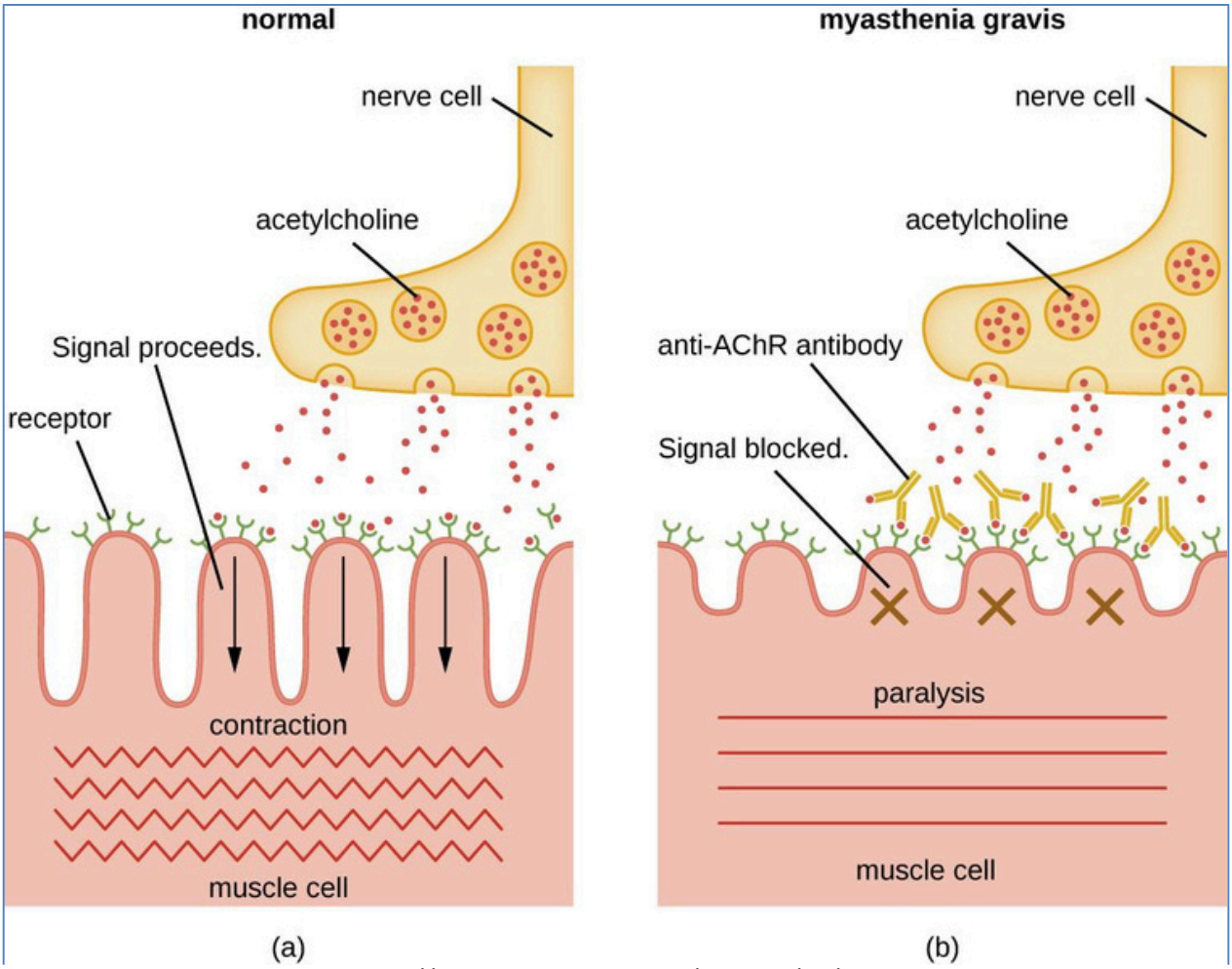
o Note:Type1 Diabetes is strongly linked to Mutations in the HLA-DQ Genotype.



Sm ith, M ., Sim m ons, K. & Cam bier, J. B cells in type 1 diabetes m ellitus and diabetic kidney disease. *N at Rev Nephrol* **13,** 712–720 (2017). https://doi.org/10.1038/nrneph.2017.138

Myasthenia Gravis:

- **What is it?**
  - o MG is an Antibody-Mediated Autoimmune Disease which attacks the ACh-Receptors @ the NMJ, leading to Failure of Neuromuscular Transmission.
  - o **How? By 3 Mechanisms:**
    - A) Complement Binding & Activation @ the NMJ
    - B) 'Antigenic Modulation'
    - C) Functional AChR-Block by Antibodies (Relatively Rare)
- **Treatment:**
  - o **Acetyl-Cholinesterase Inhibitors:**
    - § Drugs that Inhibit the Cholinesterase Enzyme from degrading ACh in the Synapse.
      - → Prolonged Action of ACh in the Synapse
      - → ↑[ACh] in the Synapse



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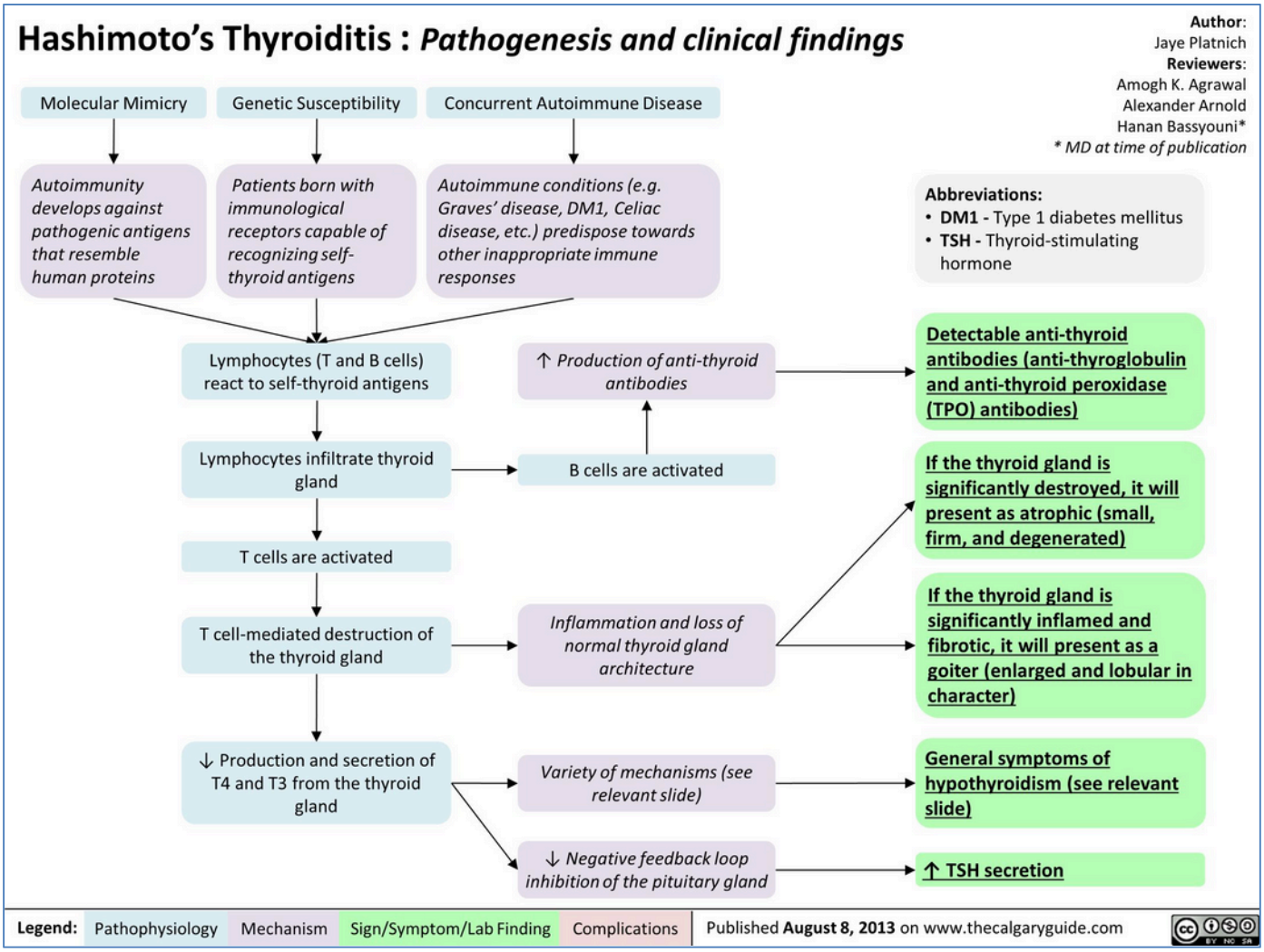
M ultiple Sclerosis:

- **What is it?**
  - o Autoimmune Destruction of the Myelin Sheaths of Axons in the CNS.
    - § (Ie: Strips the brain's 'wires' of 'insulation')
  - o Note:'*Myelin Basic Protein*' (MBP) Seems to be the targeted antigen.

Hashimoto's Thyroiditis:

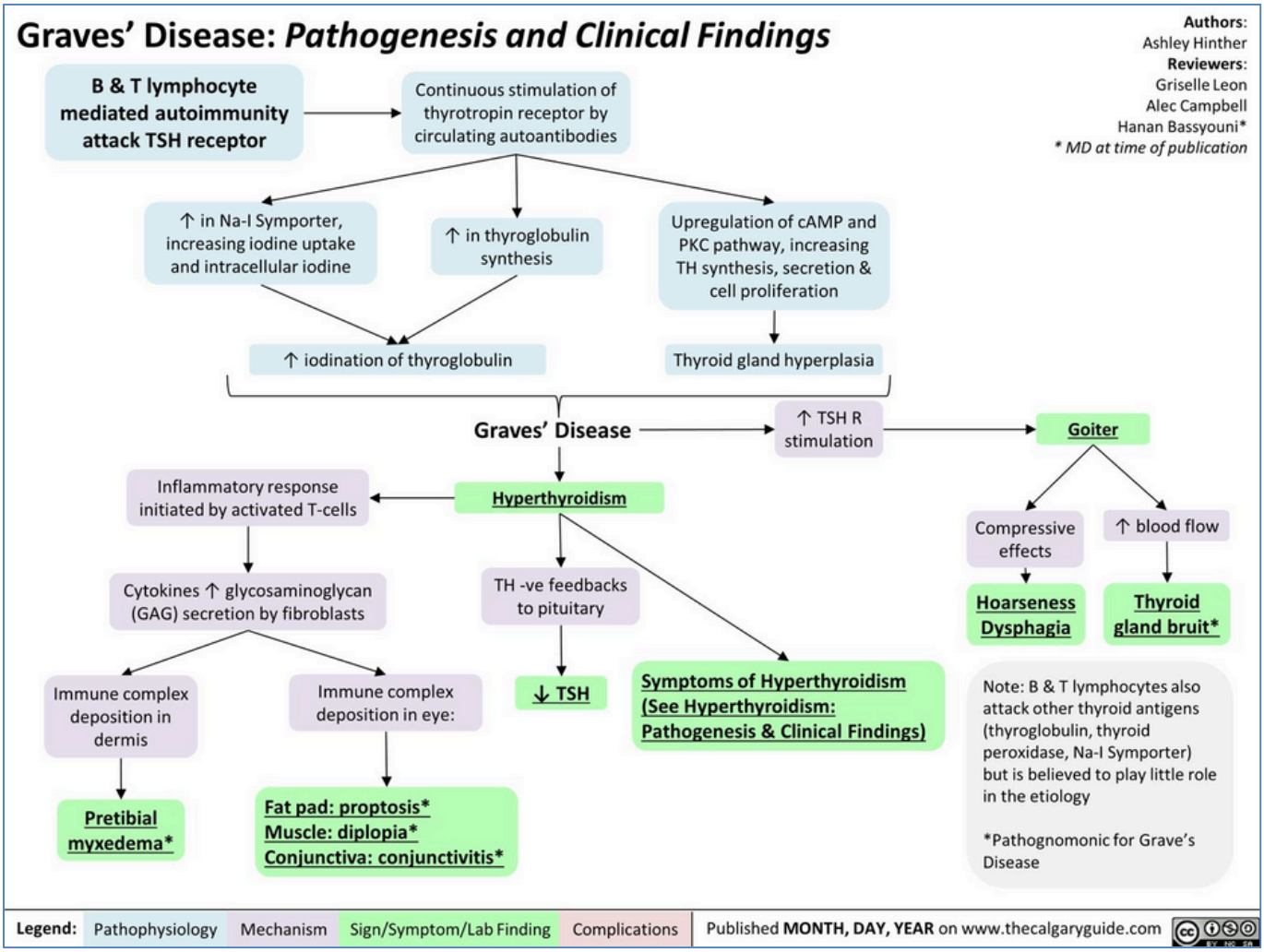
- **What is it?**
  - o Autoimmune Destruction of the Thyroid Gland:
    - § Antibodies against Thyroid Peroxidase &/or Thyroglobulin → Destruction of Thyroid Follicles.
  - o Strongly linked to the HLA-DR5 Gene.
- **Symptoms:**
  - o Often Presents as Hypothyroidism
  - o Weight Gain
  - o Depression
  - o Sensitivity to Heat/Cold
  - o Fatigue Others.
  - o



https://calgaryguide.ucalgary.ca/hashimotos-thyroiditis-pathogenesis-and-clinical-findings-2/

Graves' Disease:

- **What is it?**
  - An Autoimmune disease where the Thyroid is Enlarged & Overactive → Excessive Thyroid Hormones.
  - Due to Autoantibodies against the TSH-Receptor → Activate TSH-Receptor → Stimulate Thyroid
  - Hormone Synthesis/Secretion.
    →Hyperthyroidism.



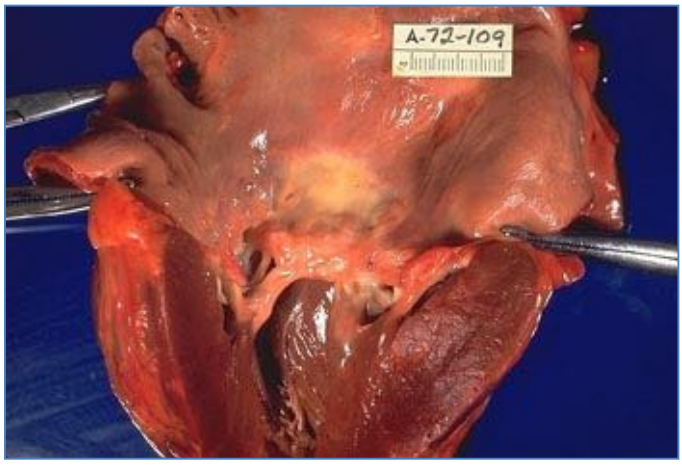
https://calgaryguide.ucalgary.ca/graves-disease-pathogenesis-and-clinical-findings/

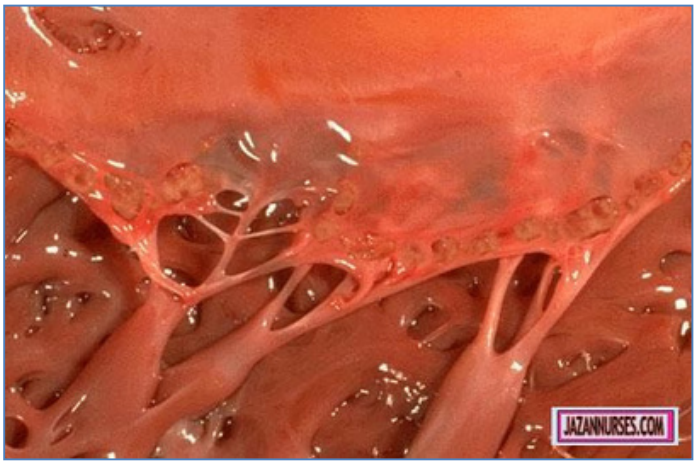
Rheumatic Fever & Rheumatic Heart Disease:

- **What is it?**
  - o **= A Complication of GAS infection characterised by Inflammatory changes in the Heart:**
    - § →Activation of T-Cells
    - § →Activation of B-Cells → Antibodies against M-Protein (& Cardiac Myosin).
      - → **Damage to Heart Valves &/or Muscle**.

- ***Question - What is the difference between Rheumatic Fever (RF) & Rheumatic Heart Disease (RHD)?***
  - o **(Note: Neither RF or RHD is an Infection, and *Both* can affect the Heart.)**
    - § **(The Distinction is whether it is *Reversible* (RF) or *Irreversible* (RHD).)**
  - o **Rheumatic Fever:**
    - § An acute, *Post*-GAS-Infection Inflammatory Disease.
    - § Occurs a few weeks *After* a GAS Infection.
    - § If not treated aggressively →Acute Rheumatic Carditis → Valvular Deformities.
  - o **Rheumatic Heart Disease:**
    - § The Chronic Stage which causes Irreversible Myocardial Damage & Heart Valve Damage.
- **Aetiology – (Role of Group-A-Strep (GAS) in Rheumatic Heart Disease):**
  - o (Note: For Background Information on GAS, see section on '*Cross-Reactivity with Micro-Organisms*')
  - o **The Main Point:**
    - § Rheumatic Heart Disease is a *Consequence* of the lasting, *Cross-Reactive, Adaptive Immune Response* to a Previous GAS Infection.

  - o ***Immunogenic* Virulence Factors:**
    - § **GAS produces a wide array of Virulence Factors:**
      - ****M-Protein** (Antiphagocytic, & Anti-Complement)
      - *Exotoxins (*Superantigens →Toxic Shock, *Pyrogens & Mitogens)
      - *Invasins (Streptolysin) (Lysis of RBCs/WBCs & Release of Lysosomal Enzymes)
      - *DNAse (Depolymerises free DNA)
    - § **The Importance of 'M-Protein' in RHD:**
      - The M-Protein Antigen is remarkably similar to Cardiac Myosin (in Heart Muscle)
      - → Stimulates an Adaptive Immune Response → Anti-M-Protein Antibodies.
        - o Anti-M-Protein Antibodies *Cross-React* with Cardiac Myosin →
          - § → Valvular Thickening
          - § →Thickening/Fusion of Chordae Tendonae
          - § → Diffuse fibrosis
          - § →Focal Fibrinoid Necrosis





Source: Unattributable

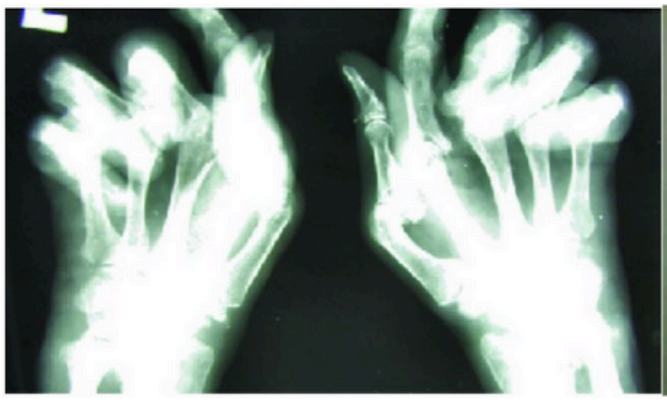
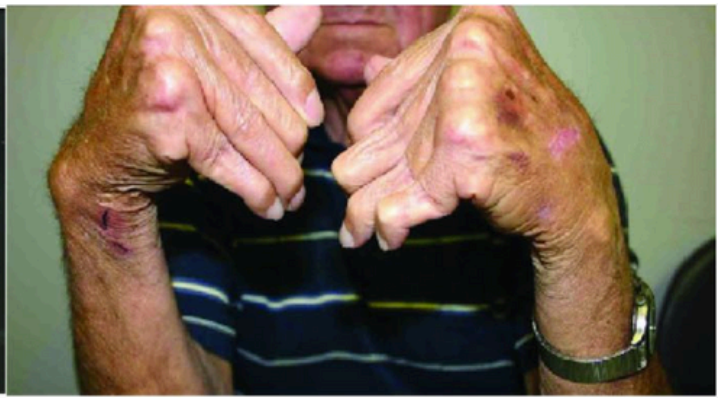
- **Clinical Features & Diagnosis – "The Revised Jones Criteria":**
  - **= Evidence of Prior Strep Infection + 1x Major *OR* a Few Minor Manifestations.**
  - **Major Manifestations:**
    - Carditis – (Inflammation of the Heart)
    - Erythema (Erythematous Rash) – (pink rings on the trunk, arms &/or legs) – due to immune
    - complexes depositing in the Vessels.
    - Polyarthritis
    - Chorea – (spasmodic movements of the body and limbs)
      Subcutaneous Nodules
  - **Minor Manifestations:**
    - Fever
    - Prolonged PR-Interval (Cardiac Fibrosis → Disruption in the Heart's Conduction Pathway)
  - **Lab Tests:**
    - Presence of Anti-Strep Antibodies – (Definitive)
    - Elevated ESR (Erythrocyte Sedimentation Rate) – (Non-Specific Inflammatory Marker)
    - Elevated CRP (C-Reactive Protein) – (Non-Specific Inflammatory Marker)
    - Anti-DNA Antibodies.

- **Treatment:**
  - **Eradication Treatment:**
    - Antibiotic Treatment to treat the Initial Strep Infection & prevent the *Development* of RF.
    - If commenced within 9 days of onset → Prevents progression to Acute Rheumatic Fever.
  - **Secondary Prophylaxis:**
    - Long-Term Antibiotic Treatment to prevent Re-Infection → Prevents progression to RHD.

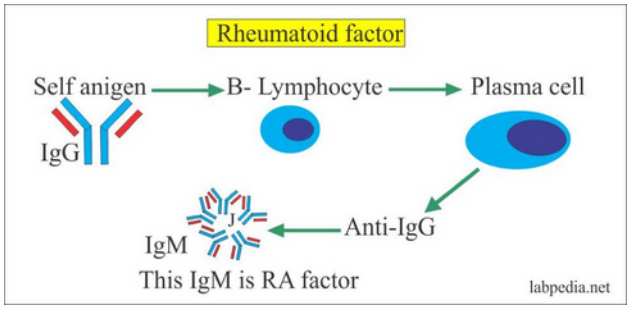
Rheumatoid Arthritis:

- **What is it?**
  - **Autoimmune Destruction of the Joint Cartilage & Inflammation of the Synovium**.
  - § → Infiltration of Granulocytes, CD4-Th-Cells, Macrophages & Plasma cells into the synovium.
  - Peak onset ≈ 55yrs.
  - F:M (3:1)

    Note: *Rheumatoid Factors* are present in 70% of all Rheumatoid Arthritis Pts. – (A Diagnostic Test)
- **Articular Features:**
  - Inflammation in joints
  - Joint pain & Swelling
  - Bony Malformation (Deformities)
  - Functional disability
- **Extra-Articular Features:**
  - Dermatologic - Rheumatoid Nodules (Eg: Elbows), & Vasculitis
  - Ophthalmologic - Dry eyes, Scleritis
  - Pulmonary -Fibrosis, lung nodules, pleuritis, effusion
  - Cardiac -pericarditis, pericardial effusion, valvular defects, conduction defects
  - GI -PUD (from NSAIDS), dry mouth
  - Renal -Amyloidosis --> proteinuria
  - Hepatic -Nodules (Nodular regenerative hyperplasia), portal fibrosis
  - Neurologic -Cervical spine instability, peripheral nerve entrapment
  - Haematologic - Lymphadenopathy, splenomegaly and leukopenia, amyloidosis, anaemia.
- **Clinical Features & Diagnosis:**
  - **Early Stages:**
    - § Morning Stiffness
    - § 3/more joints.
    - § *Smaller Joints* of Hands/Feet.
    - § Bilateral Symmetric Distribution.
    - § *Positive* Rheumatic Factor.
    - § Rheumatoid Nodules
    - § Intrinsic Muscle Wasting
    - § ↑*ESR/CRP*
  - **Established Disease:**
    - § Typical *Ulnar-Deviation* of fingers.
    - § Erosions (seen in x-rays)
  - **Serological Tests:**
    - § ***Anti-Citrullinated Protein Antibody (ACCP)**.
      - Visible up to 10yrs before onset of disease.
      - Can discriminate between RA & Arthritic-SLE.
    - § Test for Rheumatoid Factors.
    - § Erythrocyte Sedimentation Rate (ESR) – Non Specific
    - § C-Reactive Protein (CRP) – Non Specific

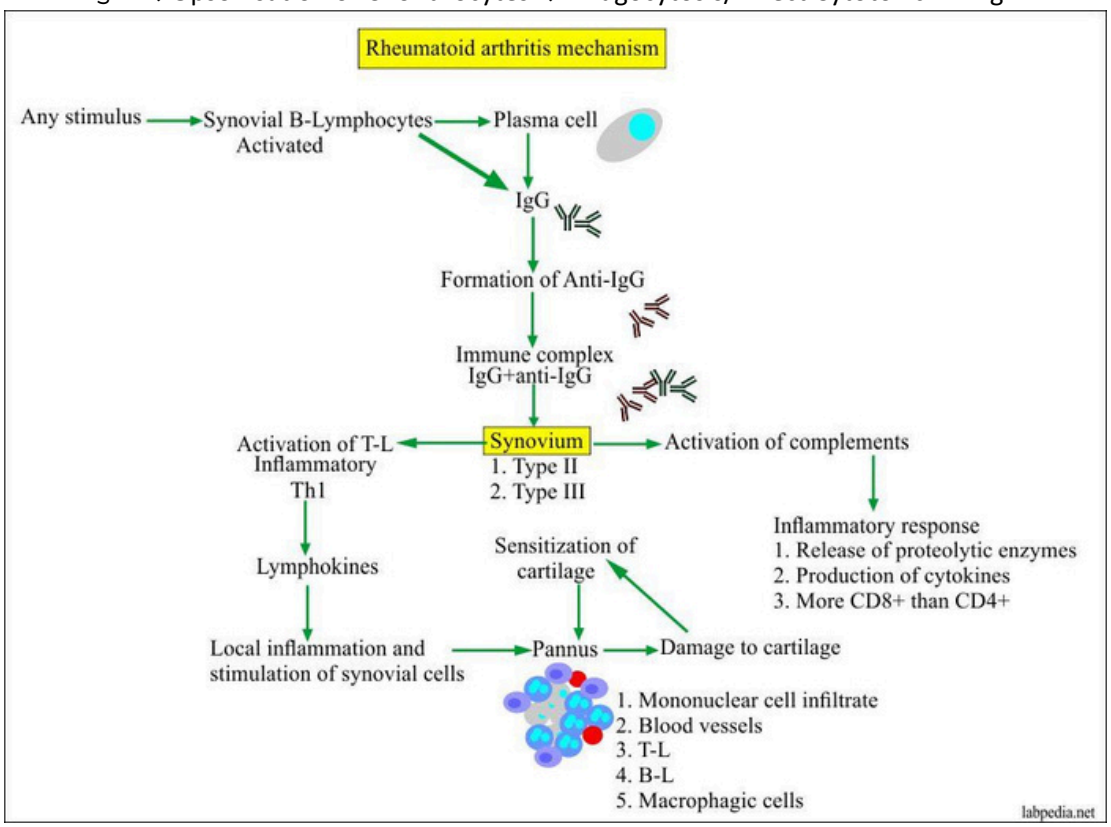



- **Aetiology:**
  - o ****Autoantibodies called Rheumatoid Factors are generated (Aetiology unknown) and Accumulate in Joint Tissue →**
    - § **→Inflammation Via Inflammatory Mediators (Bradykinins, Prostaglandins, Cytokines).**
      - **→Vascular Changes in Joint → Accumulation of Immune Cells.**
      - **→Phagocytosis of Immune Complexes**
      - **→Release of Enzymes → Attack Joint Tissues.**
      - **→Free Radical Production**
    - § **→→*JOINT DAMAGE*.**
  - o **Note: Both *Humoral Responses* & *Cell-Mediated* are thought to play a part:**
  - o (Therefore Type-III & -IV hypersensitivities involved)
    - § ***CD4-Th-Cells* → Activate Macrophages → Release Cytokines (TNFa, IL-1 & IL-6) → Inflammation:**
      - →Potentiate Production of Rheumatoid Factors (IgM Anti-IgG-Abs) by RF-B-Cells.
      - →Activate Osteoclasts → Bone Erosion
      - →→Joint Destruction.
    - § ***Plasma Cells* → secrete Rheumatoid Factors (IgM Anti-IgG-Antibodies) that bind to the Fc-Portion of IgG Antibodies →Forms Immune Complexes →Deposition in Joints & Periphery.**
      - (Note: Systemic Complications are due to peripheral deposition of Immune Complexes)



Source: Labpedia

  - o **Binding of RF:IgG Complexes to Articular Cartilage →**
    - § →Complement Activation → Lysis of Chondrocytes
    - § →Opsonisation of Chondrocytes → Phagocytosis/Direct Cytotoxic Killing.



Source: Labpedia

- **Treatment:**
  - (Note: Since Tissue Injury occurs due to an Inflammatory Response, Meds aim to Decrease/Stop this.)
  - **NSAIDs:**
    - (COX Inhibitors) → ↓Prostaglandin Synthesis → ↓Pain & ↓Inflammation.
  - **DMARDs:**
    - (Disease Modifying Anti-Rheumatic Drugs) – Mild Chemotherapy drugs, used due to their
    - *Immunosuppressive* 'Side-Effects'.
    - Eg: Methotrexate (an Antimetabolite)→ Inhibits folate-dependent DNA Synthesis → Inhibits
    - Lymphocyte Proliferation.
    - Eg: Sulfasalazine.
    - Eg: Hydroxychloroquine - ↓Acidity of lysosomes.

      Eg: Leflunomide (an Antimetabolite) → Inhibits Pyrimidine Synthesis.

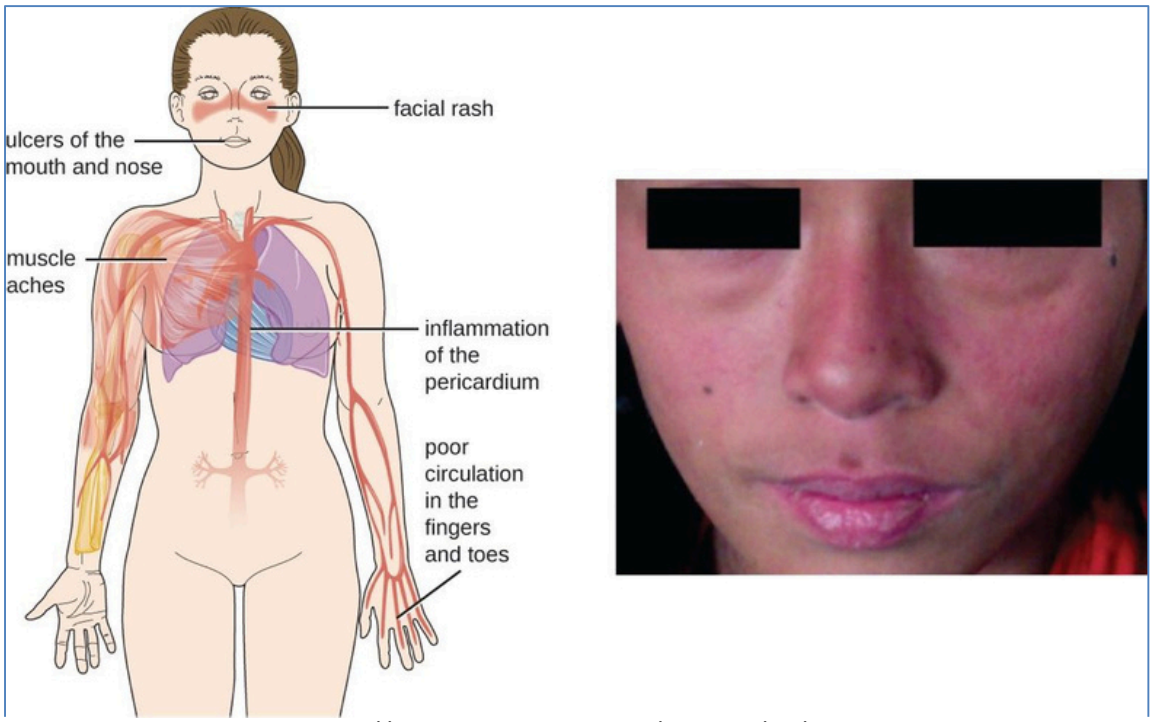
      Eg: Cyclosporin – Inhibits IL-2 Receptors → (↓Antigen-Induced Lymphocyte Proliferation)
  - **Corticosteroids – (Eg: Prednisone, Hydrocortisone, Prednisolone, Dexamethasone):**
    - A General Immunosuppressant → ↓Cytokine Secretion & ↓Immune Cell Activity.
  - **Biological Drugs:**
    - Direct inhibition of Pro-Inflammatory Cytokines:
      - TNFα Inhibitors
      - IL-1 Inhibitors
      - IL-6 Inhibitors
    - Inhibition of T-Cell Co-Stimulation.
  - **Monoclonal Antibodies**
    - Against Osteoclasts.
    - Against B-Cells
    - Against Pro-Inflammatory Cytokines.

System ic Lupus Erythem atosus (SLE):

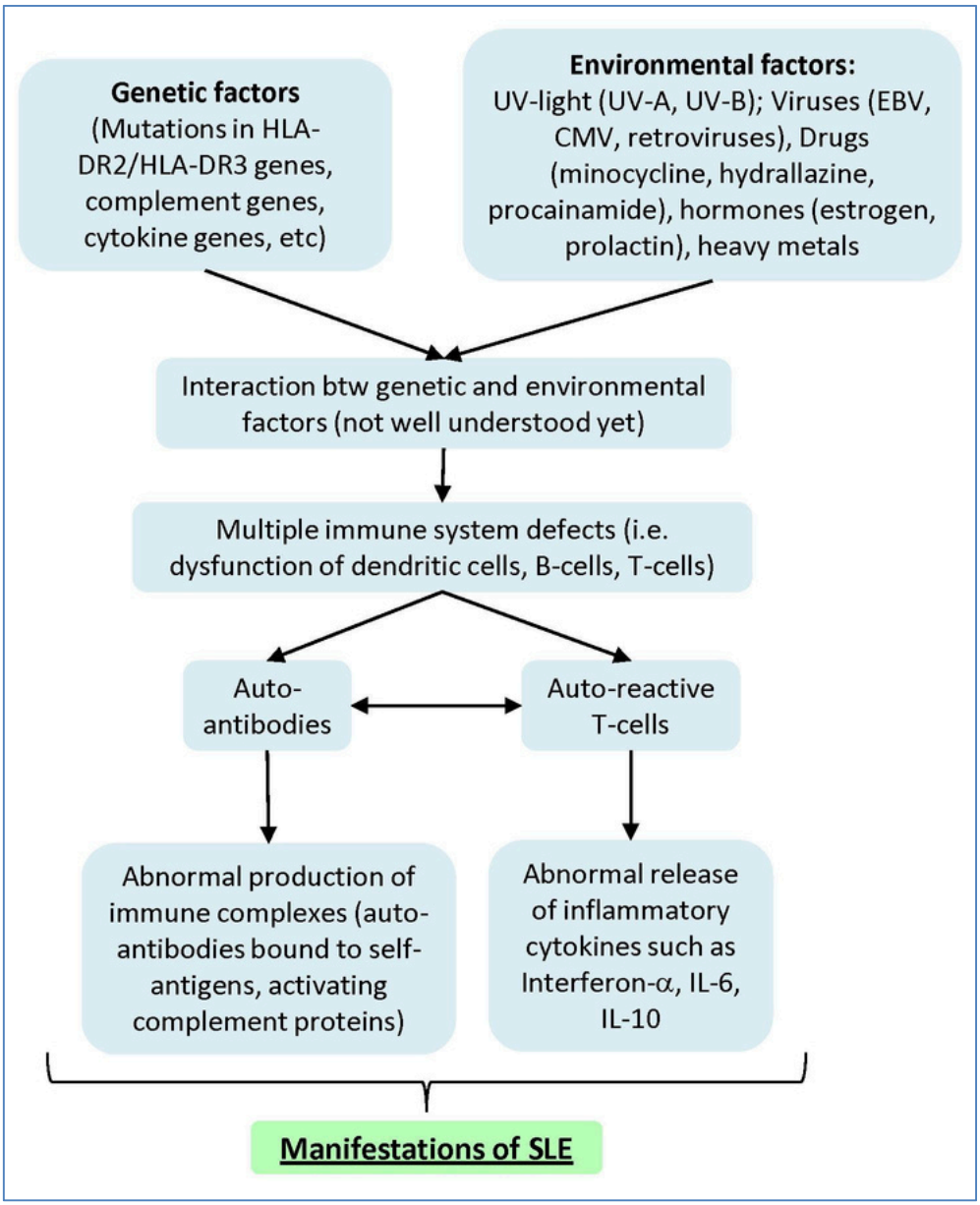
- **What is it?**
  - o **Chronic Multi-System Autoimmune Disease**.
  - o ***Characterised by Many Different Anti-Nuclear Antibodies:**
    - § * Anti-DNA
    - § Anti-Ribonucleoprotein
    - § Anti-Histone
    - § (Note: Autoantibodies may attack directly or form Immune-Complexes → Disease)
  - o **F:M (10:1)**

- **Manifestations:**
  - o o Skin Rash
  - o Glomerulonephritis o Arthritis
  - Haemolytic Anaemia o
  - Thrombocytopenia o
  - CNS Involvement

- **Diagnostic Criteria:**
  - o Malar Rash (Scaly, Red, Butterfly-Shaped rash on face)
  - o o Disc ike rash
  - o Renal Disorders – (Eg: Glomerulonephritis, Proteinuria, Cellular Casts) Photosensitive Rash
    - Oral Ulcers (Or in Nasal Cavity)
    - Arthritis (Non-erosive)
    - Serositis – (Eg: Pleuritis or Pericarditis)
  - o Neurological Disorders – (Eg: Seizures/Psychosis)
  - o Haematological Disorders – (Eg: Haemolytic Anaemia, Leukopenia, Thrombocytopenia)
  - o Antinuclear Antibody Test – Positive.
  - o **Serological Tests:**
    - § **Antinuclear Antibody (ANA) Test** – (95% of SLE Pts are ANA positive):
      - The hallmark of systemic autoimmunity
      - However, not specific to SLE. (ENA test required for definitive diagnosis)
    - § **Extractable Nuclear Antigens (ENA):**
      - Once presence of ANAs have been determined, ENAs are used to determine the specific Ag that the ANAs are binding to in the nucleus.



- **Pathogenesis:**
  - ***SLE is Caused by Presence of Different Anti-Nuclear Antibodies – So How are they formed?:**
    - **Epitope Spreading:**
      - (Autoreactive T-Cells specific to Histones, provide help not only to the original Histone-Specific B-Cells, but also DNA-Specific B-Cells → Production of both Anti-Histone & Anti-DNA antibodies)
    - **1-** A Damaged/Apoptotic cell releases Nuclear Material.
    - **2-** An Autoreactive Histone-Specific B-Cell binds, endocytoses, and present it to Autoreactive
    - CD4-Th-Cells – (Incl: Those specific to *other* Nuclear Antigens. – Eg: DNA-Specific)
    - **3-** The Histone-Specific T-Cells then help DNA-Specific B-Cells → Produce Anti-DNA Antibodies, which form complexes with Nucleosomes and Complement protein C3.
      4- These complexes then deposit in the kidneys → Cause Glomerulonephritis.
  - **Note: Some Genetic Predisposition**
  - Deficiency of Fas Ligand → Failure to remove Autoreactive T-Cells by Apoptosis.



Source: Calgaryguide; https://calgaryguide.ucalgary.ca/Pathogenesis-of-Lupus/