BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
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Programme: M.Sc., Biochemistry

Course Title : Immunology
Course Code : BC301CR

Unit-II
Complement pathways

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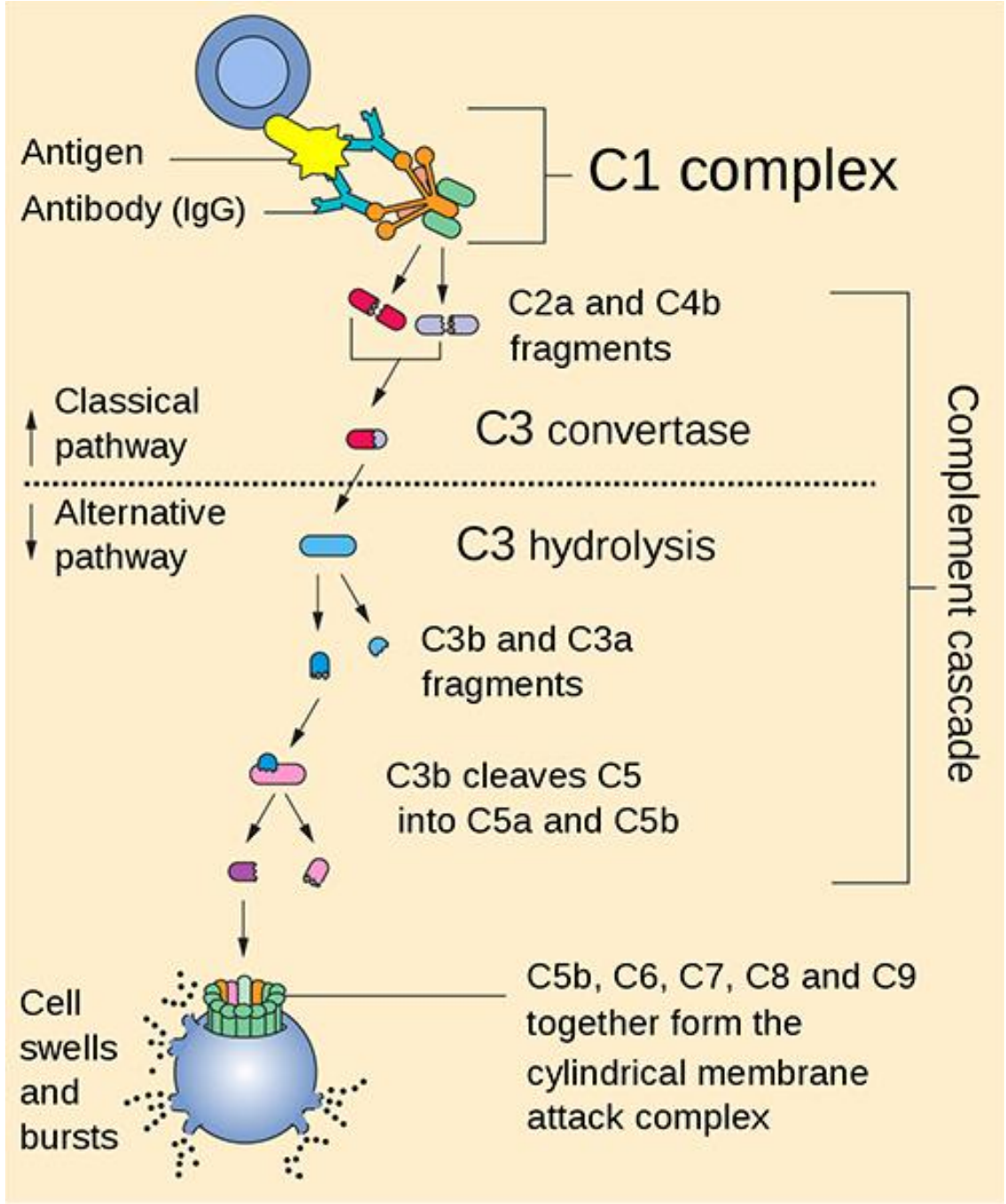
Complement System

- The proteins that make up your complement system are inactive or turned off until a trigger turns them on.
- Triggers could include an injury to your body or bacteria that enter your body.
- Proteins turn on in a line that's similar to dominos.
- One protein will turn on, which activates the next protein in line to turn on, just like how one domino falls onto another domino to create a chain reaction.
- This chain reaction is called a cascade.
- When each protein activates, it can perform its function to protect your body

Classical Pathway

- This pathway involves complement components **C1**, **C2** and **C4**.
- The pathway is triggered by **antibody-antigen complexes** binding to **C1**, which itself has three subcomponents **C1q**, **C1r** and **C1s**.
- The pathway forms a C3 convertase, **C4b2a**, which splits C3 into two fragments; the large fragment, **C3b**, can covalently attach to the surface of microbial pathogens and **opsonise** them; the small fragment, **C3a**, activates **mast cells**, causing the release of vasoactive mediators such as histamine.

Classical Pathway

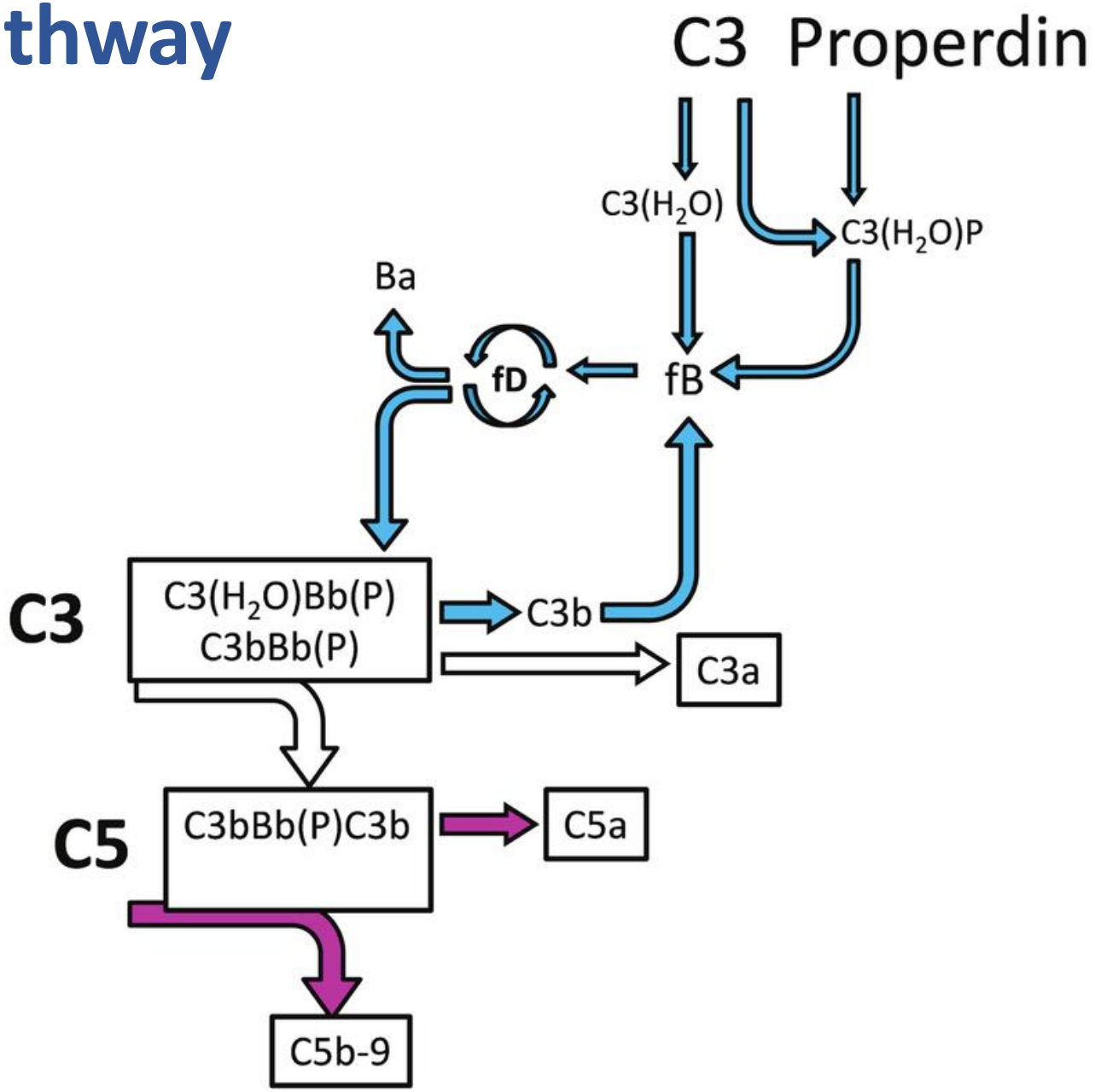


Source: Wiki

Alternative Pathway

- his pathway involves various factors, **B, D, H** & **I**, which interact with each other, and with C3b, to form a C3 convertase, **C3bBb**, that can activate more C3, hence the pathway is sometimes called ‘the amplification loop’
- Activation of the loop is promoted in the presence of bacterial and fungal cell walls, but is inhibited by molecules on the surface of normal mammalian cells.

Alternative Pathway



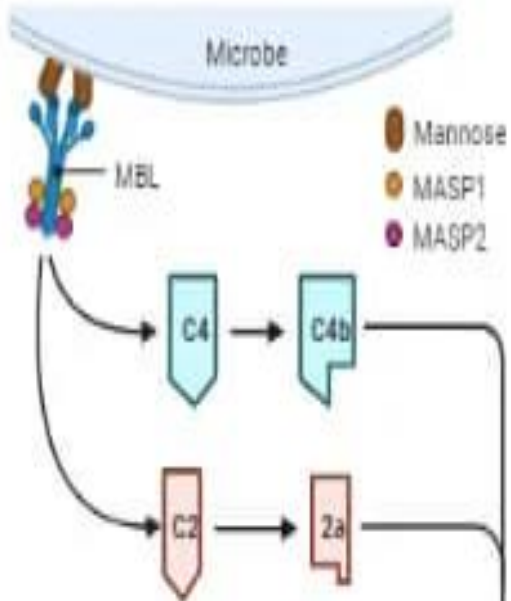
Source: Juha Kotimaa, 2017

LECTIN PATHWAY:

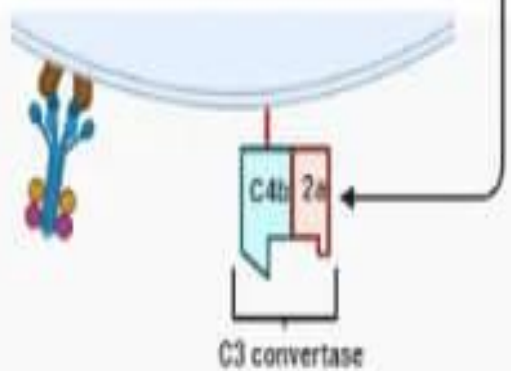
- Lectins are proteins that recognize and bind to specific carbohydrate groups.
- mannose binding lectin and ficolins (1,2,3) are lectins relevant to complement system.
- MBL recognizes mannose, fucose, and N-acetylglucosamine.
- on the other hand ficolins binds to acetylated sugars instead of mannose.

- These proteins have MBL-associated serine proteases (MASP1 and MASP2).
- These proteases are inactive until lectin bind to a pathogen surface.
- These proteases converts C4 and C2 into C4b and C2b.
- C4b and C2b forms a complex called C3 covertase.
- The remaining steps are similar to classical pathway.

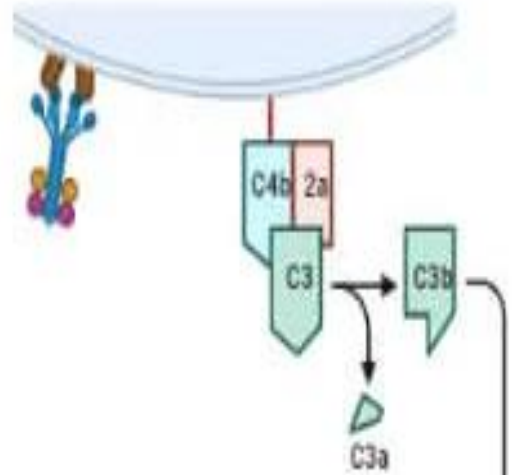
1. Binding of complement proteins to microbial cell surface or antibody



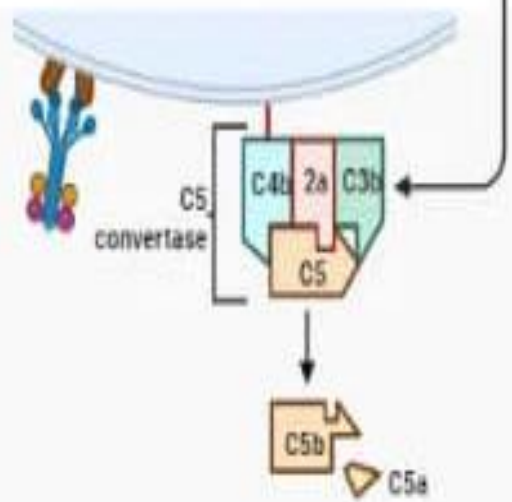
2. Formation of C3 convertase



3. Cleavage of C3 by C3 convertase



4. Formation of C5 convertase



Source : rethinkbiologynotes.com

CLONAL SELECTION THEORY:

- A theory that explains how the immune system recognizes and responds to specific antigens.
- In the 1950s, N Jerne, D Talmadge and M Burnet combined the theories of Ehrlich and Jerne, and modified them as the clonal selection theory.
- Fundamental concept in immunology, explaining adaptive immune responses.

❖**B Cells**: It develop and mature in bone marrow.
Produce antibodies against specific antigens.

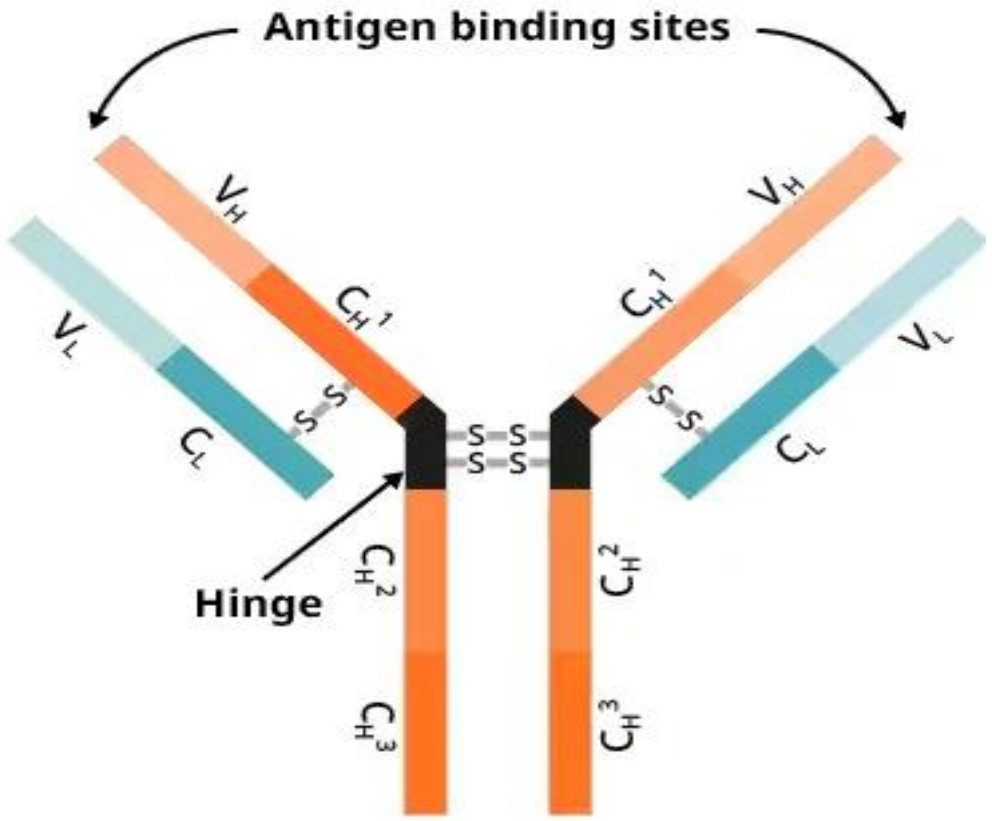
❖**T Cells**: It develop in bone marrow and mature in thymus.
Include Helper T cells (assist other immune cells) and Cytotoxic T cells (destroy infected cells).

These two cells are primarily stored in lymph nodes and spleen.

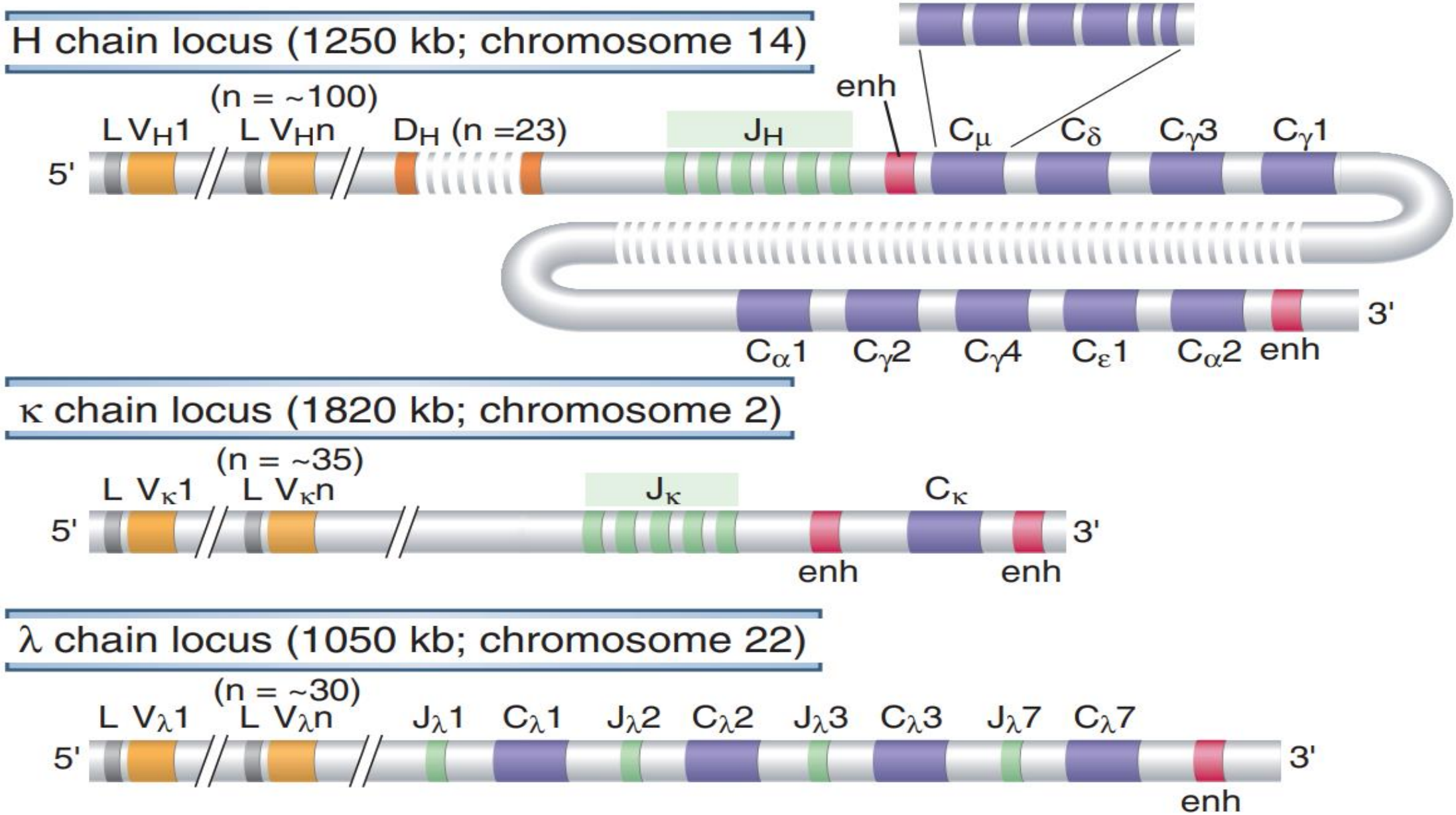
- **Antigen Encounter**: Antigens bind to specific receptors on lymphocytes.
- **Activation**: Binding leads to activation of the lymphocyte.
- **Proliferation**: Activated lymphocytes undergo clonal expansion.
- **Differentiation**: Some cells become effector cells ,others become memory cells.

ORGANISATION AND EXPRESSION OF IG:

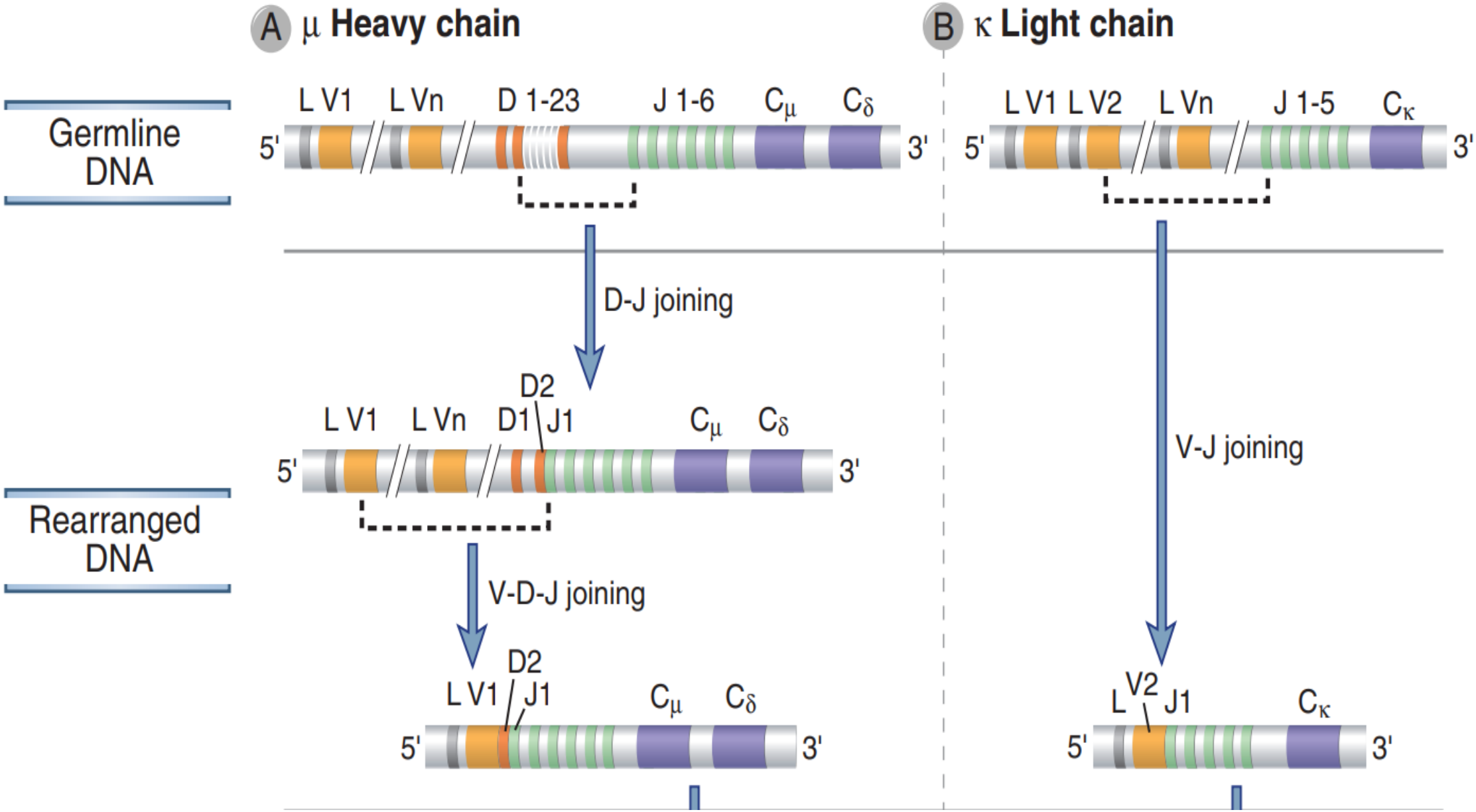
- STRUCTION OF ANTIBODY



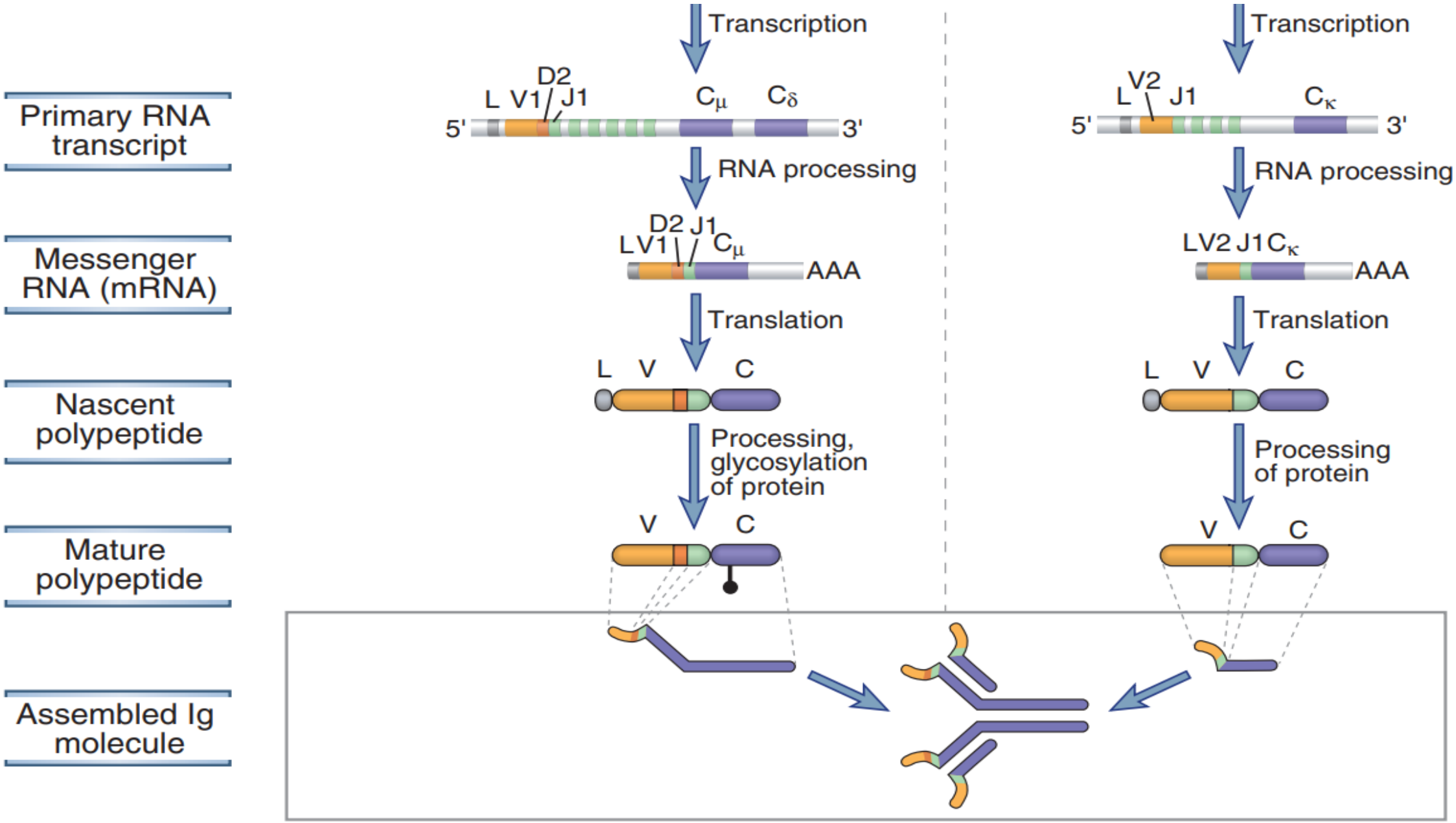
Source; abcam



Source: Jacques-Olivier Pers, 2020



Source: Jacques-Olivier Pers, 2020.



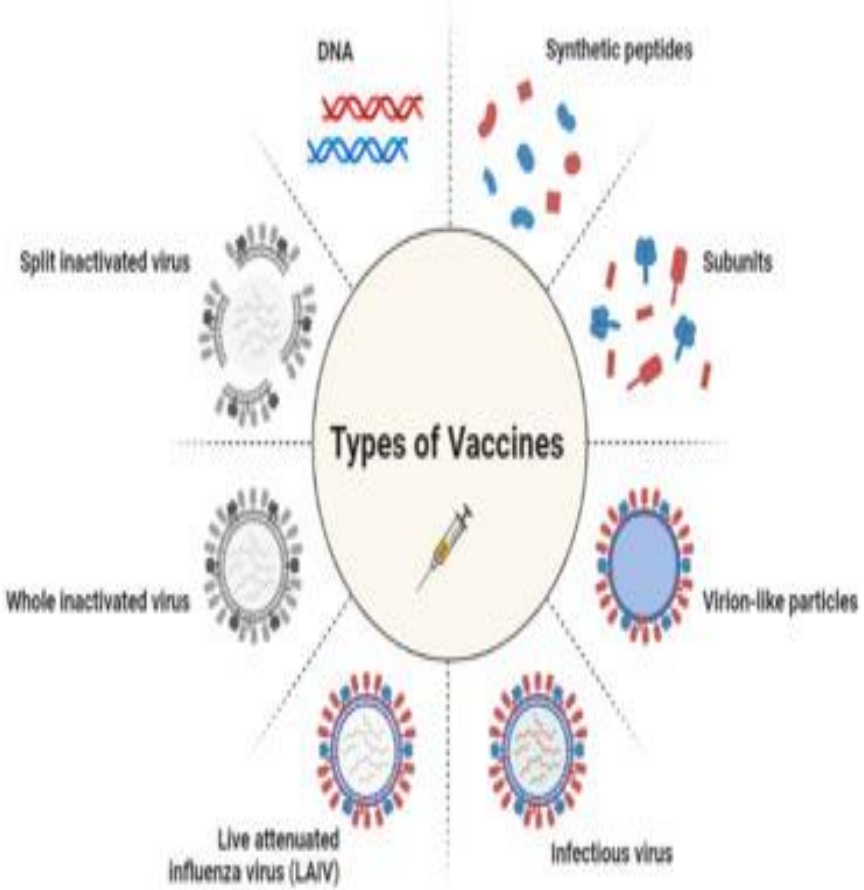
Source: Jacques-Olivier Pers, 2020.

VACCINE:

- Vaccine is a suspension of weakened, killed, or fragmented microorganisms or toxins or other biological preparation, such as those consisting of antibodies, lymphocytes, or mRNA, that is administered primarily to prevent disease.

TYPES OF VACCINE:

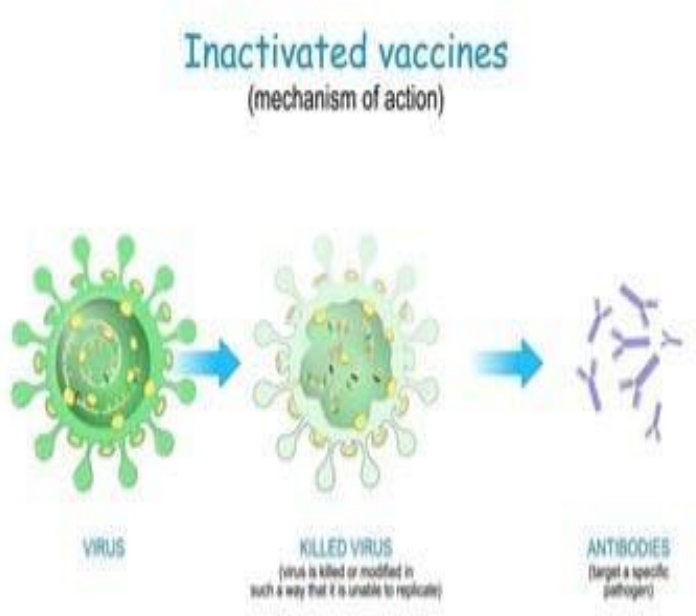
- There are several types of vaccines, including:
- Inactivated vaccines
- Live-attenuated vaccines Messenger RNA (mRNA) vaccines
- Subunit, recombinant, polysaccharide, and conjugate vaccines
- Toxoid vaccines
- Viral vector vaccines



Source: https://doi.org/10.1016/B978-0-443-18564-9.00030-8

INACTIVATED OR DEAD VACCINES:

- The disease-causing pathogen is killed or inactivated, usually through a thermal (application of high temperature) or chemical (formalin etc.) process.
- Such vaccines, when administered, elicit a robust immune response that mimics most of the responses seen during an infection.
- Examples:
- Typhoid vaccine Influenza vaccine
- Salk polio vaccine Hepatitis A vaccine



Source: dreamstime.com

PRODUCTION:

- Isolation: Isolate the pathogen from a clinical sample.
- 2. Cultivation: Grow the pathogen in large quantities.
- 3. Inactivation: Kill the pathogen using methods are Heat, Formaldehyde, Radiation , Detergents.
- 4. Purification: Remove impurities and contaminants.
- 5. Formulation: Prepare the final vaccine product (e.g., liquid, freeze-dried)
- 6. Quality Control: Test for safety, potency, and purity.

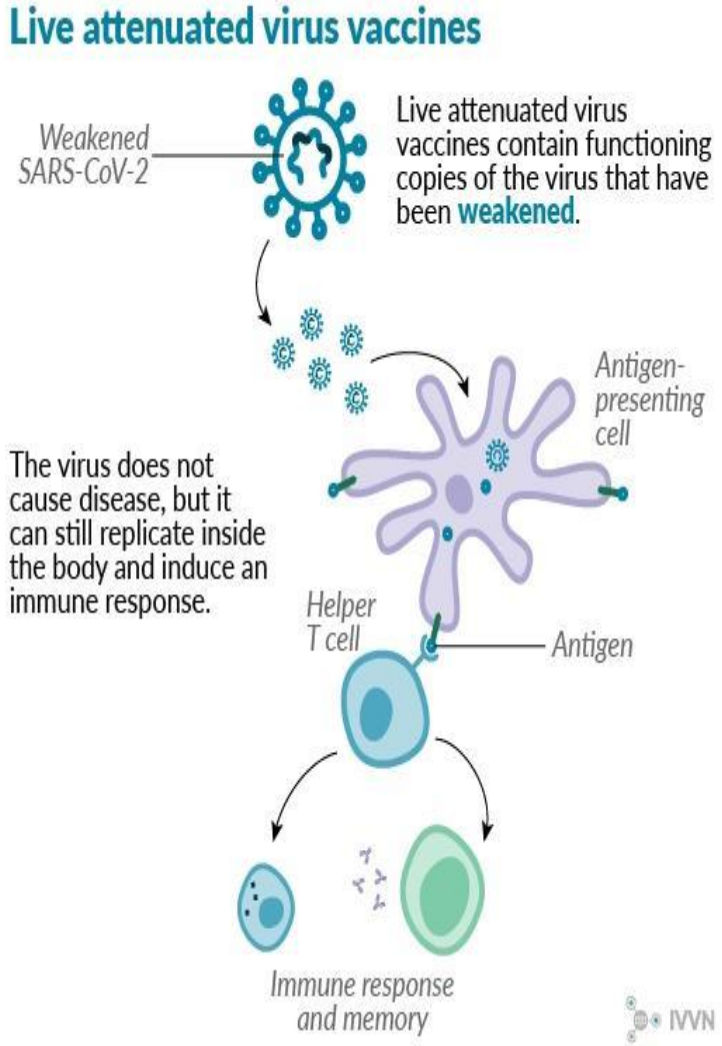
METHODS OF INACTIVATION:

- Heat inactivation
- Formaldehyde inactivation Radiation inactivation (e.g., gamma radiation)
- Detergent inactivation

- **Advantages**:
- No risk of reversion to virulence
- Suitable for immunocompromised individuals
- Easy to produce and store
- **Disadvantages**:
- May not induce strong immune response
- Require booster shots
- May contain residual toxins

LIVE ATTENUATED VACCINES

- Pathogens like virus or bacteria are weakened by genetic manipulations to limit its growth and thus do not cause disease to the host.
- In some modified versions of live vaccine an organism that is related to the pathogen is used that naturally grows poorly in humans.
- The weakened pathogen generates a broad immune response in the host similar to that shown by an infected individual with a natural pathogen.
- Examples: Oral Sabin polio vaccine ,MRV Vaccine (Measles, Mumps, Rubella, and Varicella) ,Nasal influenza vaccine



Source :http://dx.doi.org/10.54254/2753-8818/3/20220286

PRODUCTION:

- Isolation: Isolate the pathogen from a clinical sample
- Attenuation: Weaken the pathogen through various methods (e.g., passage through cell culture, mutagenesis)
- Characterization: Confirm the attenuated pathogen’s identity and stability
- Cultivation: Grow the attenuated pathogen in large quanti
- Harvesting: Collect the attenuated pathogens from the culture
- Purification: Remove impurities and contaminants
- Formulation: Prepare the final vaccine product (e.g., freeze-dried, liquid)
- Quality Control: Test for safety, potency, and purity

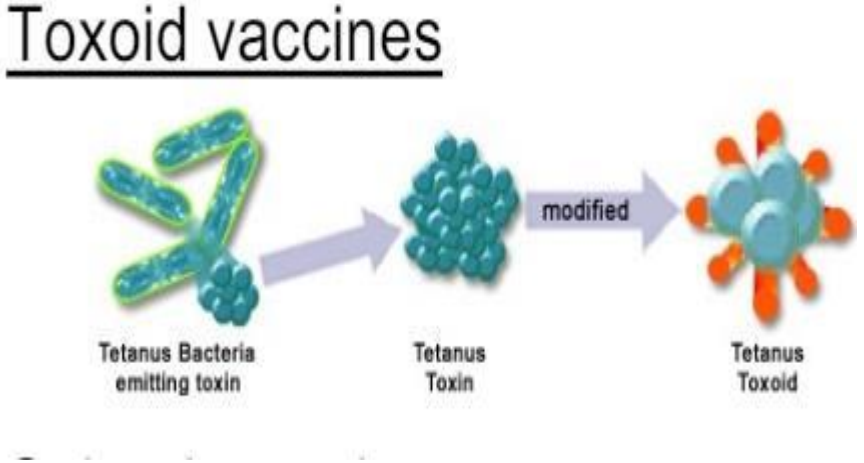
METHODS OF ATTENUATION:

- Passage through cell culture
- Mutagenesis (chemical or radiation-induced)
- Deletion of virulence genes
- Recombinant DNA technology

- **Advantages**:
- Induce strong immune response
- Mimic natural infection
- Provide long-term immunity
- **Disadvantages**:
- Risk of reversion to virulence
- May not be suitable for immunocompromised individuals
- Require careful handling and storage

TOXOID VACCINE:

- Toxoid vaccine is a type of vaccine that protects against diseases caused by bacterial toxins.
- Toxoid vaccines work by introducing a modified, harmless form of the toxin (called a toxoid) to the body, which triggers an immune response and produces antibodies that can recognize and neutralize the toxin.
- Examples of toxoid vaccines include:
- Diphtheria toxoid vaccine
- Tetanus toxoid vaccine
- Pertussis toxoid vaccine (whooping cough



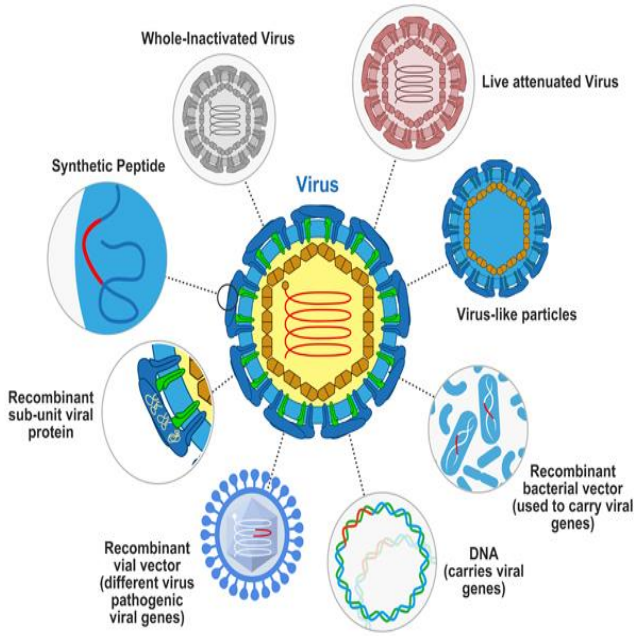
Source:https://jpabs.org/misc/diphtheria-treatment-antibiotics.html

PRODUCTION:

- Isolating the toxin produced by the pathogen (bacterium). Purifying the toxin to remove other components.
- Inactivating the toxin using: Formaldehyde , Heat ,Radiation , Chemical modification.
- Converting the toxin into a toxoid (a harmless, modified form)
- Formulating the toxoid into a vaccine product.
- Testing for safety, potency, and purity.

RECOMBINANT VECTOR VAACINE:

- Recombinant vaccines are usually produced by benefiting from bacteria, yeast, mammalian, and insect cells.
- This type of vaccine requires the insertion and transference of the DNA section responsible for encoding the antigen.
- Among the mentioned cells, bacterial expression is the most frequently utilized type that does not need modifications associated with mammalians' and insects' cells .



Source: genscript.com

PRODUCTION:

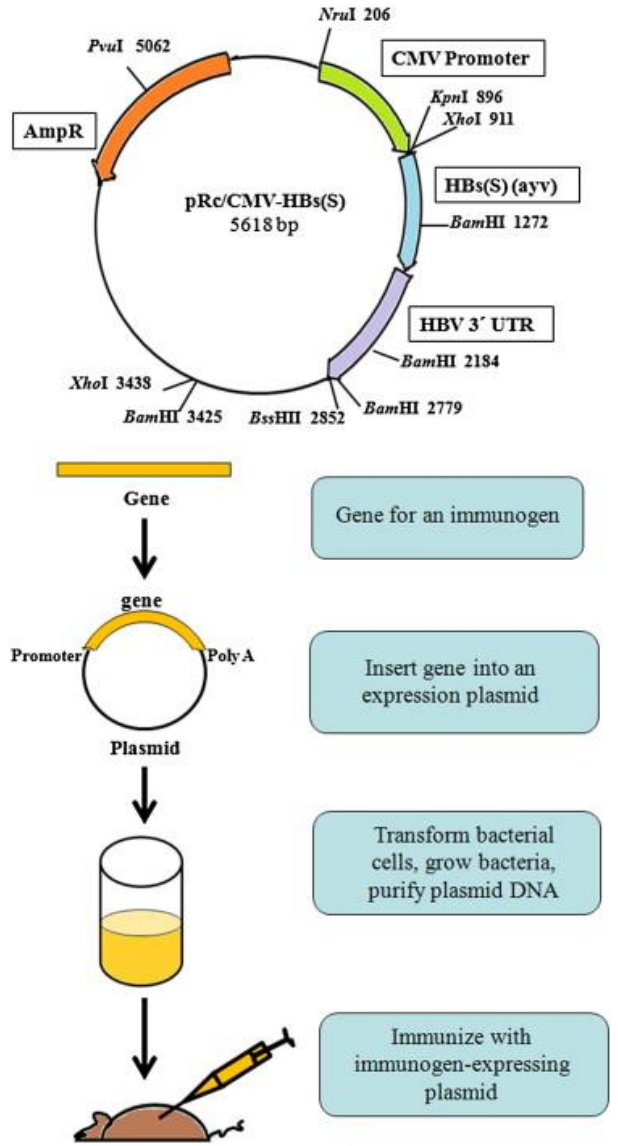
- Choosing a suitable vector (e.g., virus, bacterium, yeast) to deliver the antigen
- Cloning the gene encoding the desired antigen into the vector
- Expressing the antigen in the vector using recombinant DNA technology
- Purifying the vector-antigen complex
- Formulating the final vaccine product
- Testing for safety, potency, and purity

- **Types of recombinant vector vaccines**:
- Viral vectors (e.g., adenovirus, poxvirus, HIV)
- Bacterial vectors (e.g., Salmonella, E. Coli)
- Yeast vectors (e.g., Saccharomyces cerevisiae)
- **Advantages**:
- Flexibility in antigen design and expression
- Improved safety compared to traditional vaccines
- Enhanced immune response

DNA VACCINE:

- Naked DNA vaccines use plasmid DNA to encode and express a target protein within host cells.
- While DNA itself doesn’t trigger a strong immune response, the expressed protein can stimulate both humoral and cellular immunity.
- As of 2016, veterinary DNA vaccines exist (e.g., for West Nile Virus in horses), but human DNA vaccines are still in clinical trials for diseases like influenza and Ebola. Major safety concerns include potential DNA integration into the host genome, autoimmune reactions, and antibiotic resistance from plasmid production.

- The current evidence does not support these risks. DNA vaccines are advantageous because they are safe, stable, cost-effective, and easy to produce and store.
- Advances in delivery methods and protein expression optimization are ongoing, suggesting that human DNA vaccines may soon be available.



Source; https://doi.org/10.1016/C2011-0-05210-9

PRODUCTION:

- Designing the DNA plasmid with the desired antigen gene.
- Cloning the gene into the plasmid.
- Purifying the plasmid DNA.
- Formulating the DNA vaccine product (e.g., liquid, lyophilized).
- Testing for safety, potency, and purity.

- **Types of DNA vector vaccines:**
- Plasmid DNA vaccines
- Viral vector-based DNA vaccines (e.g., adenovirus, poxvirus)
- **Advantages**:
- Rapid development and production
- Flexibility in antigen design and expression
- Improved safety compared to traditional vaccines
- Stability and ease of storage

T-CELL, B-CELL RECEPTORS, ANTIGEN RECOGNITION-PROCESSING AND PRESENTATION TO T-CELLS, INTERACTION OF T AND B CELLS.

T cell Receptor (TCR)

- Principal component TCR was a heterodimeric 90kDa protein composed of a 40kDa and a 50kDa molecule (α and β chains)
- Surface molecule on T cells
- Recognize Ag presented in MHC context
- Similar to Immunoglobulin
- Two types of TCR
  - α β: predominant in lymphoid tissues
  - γ δ: enriched at mucosal surfaces

T cell antigen receptor: Some Fundamentals

One T-cell has *one* type of TCR

One T-cell has *one* TCR with a wholly unique specificity

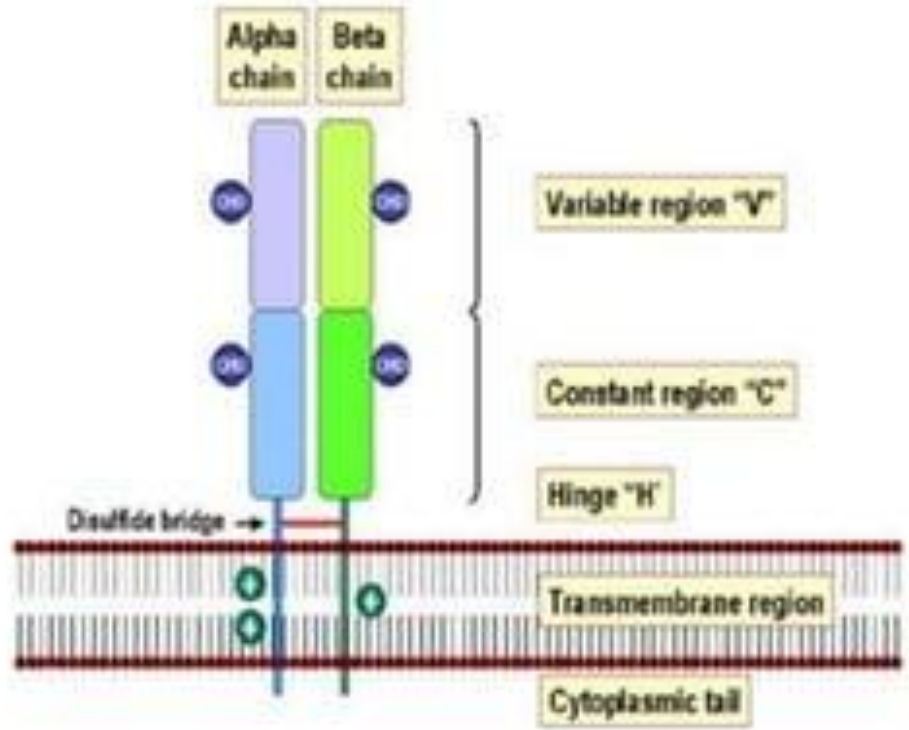
.

One T-cell has as many as 100,000 identical TCR's.

There are two important types of T-cells: T_H & T_C.

Structure of the TCR (αβ)

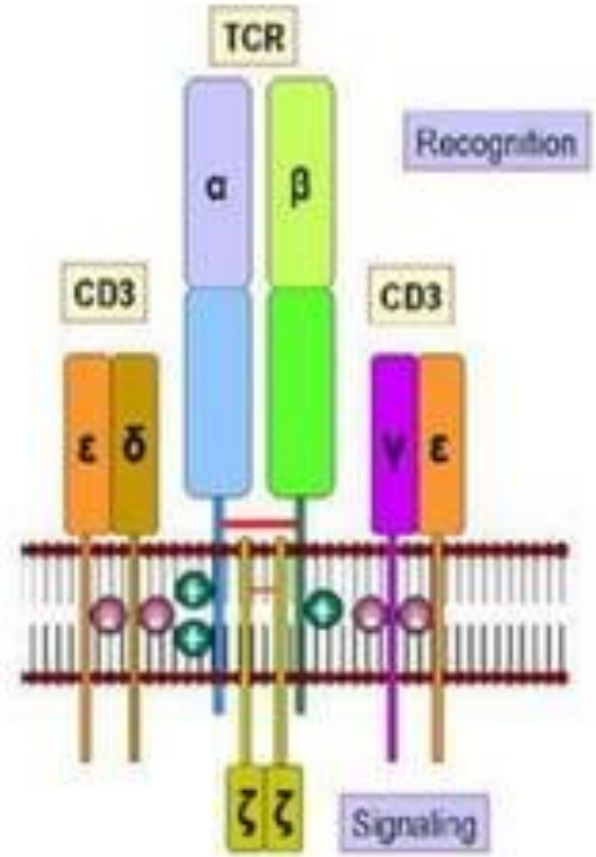
- **Regions**
  - **Short cytoplasmic tail- cannot transduce activation signal**
  - **Transmembrane with hydrophobic AAs**
  - **Both α and β have a variable (V) and constant (C) region**
  - **V region is hypervariable, determines Ag specificity**



Source:https://www.biologyexams4u.com/

TCR and CD3 complex

- TCR is closely associated with CD3 complex
  - Group of 5 proteins
  - Commonly called “invariant” chains of TCR
- Role of CD3 complex
  - CD3 necessary for cell surface expression of TCR
  - transduces signal after Ag interaction with TCR

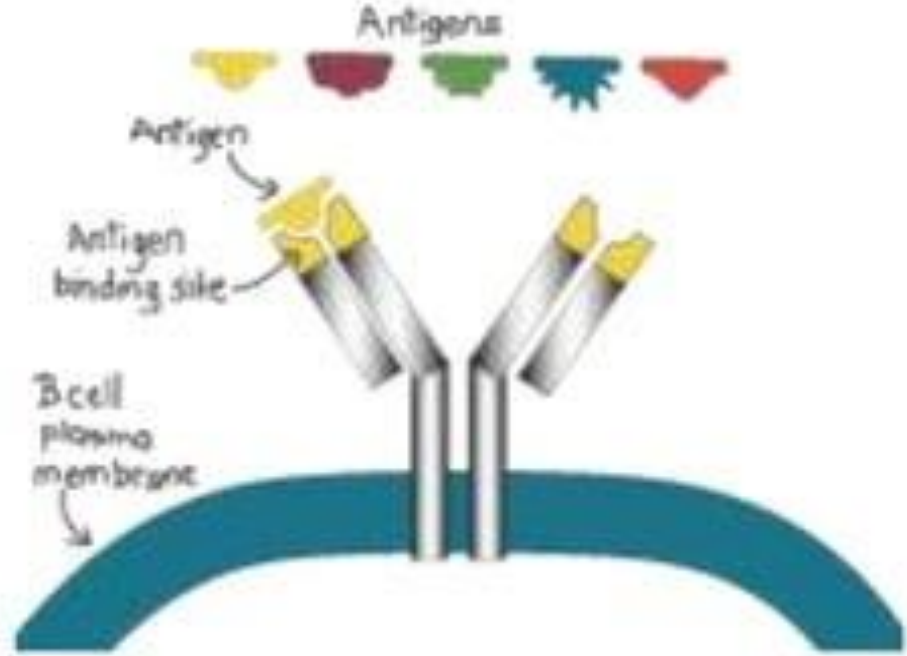


Source:https://www.biologyexams4u.com/

B cell Antigen Specific Receptor

- B-cell receptors (BCRs) are membrane-bound immunoglobulins that recognize and bind foreign proteins (antigens).

- BCRs are formed through random somatic changes of germline DNA, creating a vast repertoire of unique sequences that enable individuals to recognize a diverse range of antigens.



Source : Khan academy

What are the components of a BCR receptor?

- Each cell-surface receptor has three main components:

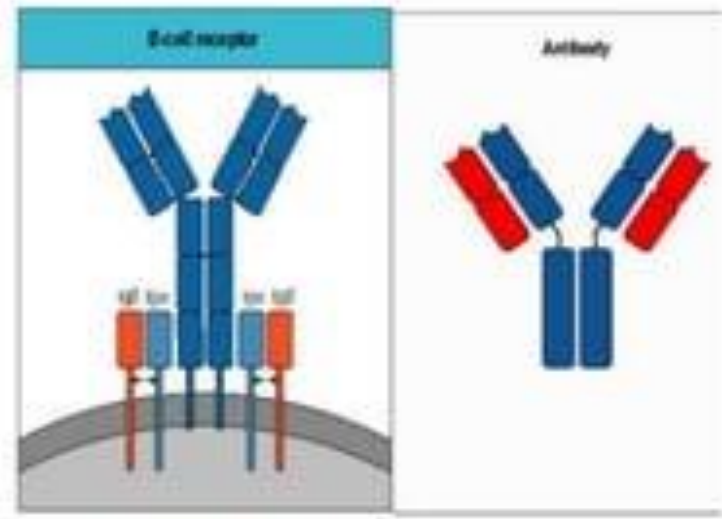
- **An external ligand-binding domain**

- **A hydrophobic membrane-spanning region**

- **An intracellular domain inside the cell.**

What activates the B cell receptor?

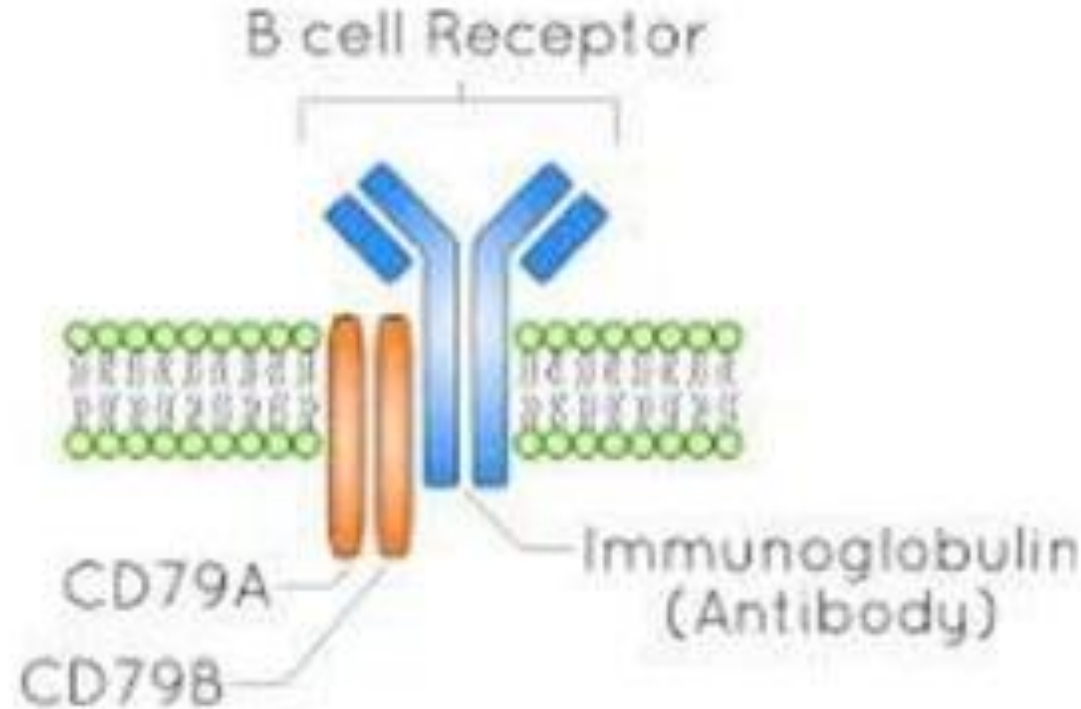
- **B-cell activation is triggered by the binding of ligand (referred to as antigen) to the B-cell receptor (BCR), which initiates a cascade of intracellular signaling leading to the internalization of antigen for processing and presentation to T cells.**



Source : Khan academy

Where is the B cell receptor (BCR) Located?

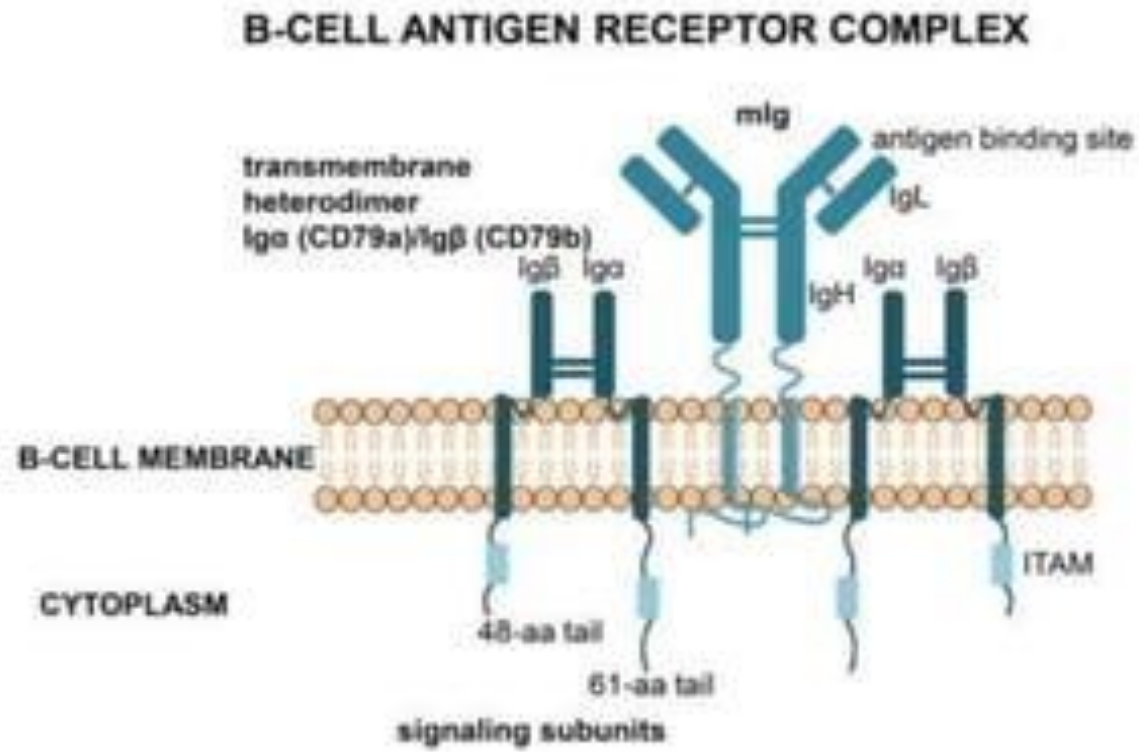
The B cell receptor is transmembrane protein composed of a immunoglobulin molecule and a signal transduction moiety.



Source: wiki

What is B cell receptor complex?

- The B-Cell Receptor complex usually consists of an antigen-binding subunit (the membrane immunoglobulin or MIg), which is composed of two IgHs (Immunoglobulin Heavy Chains) and two IgLs (Immunoglobulin Light Chains), and a signaling subunit which is a **disulfide-linked heterodimer** of Ig-Alpha (**CD79A**) and Ig-Beta (CD79B)



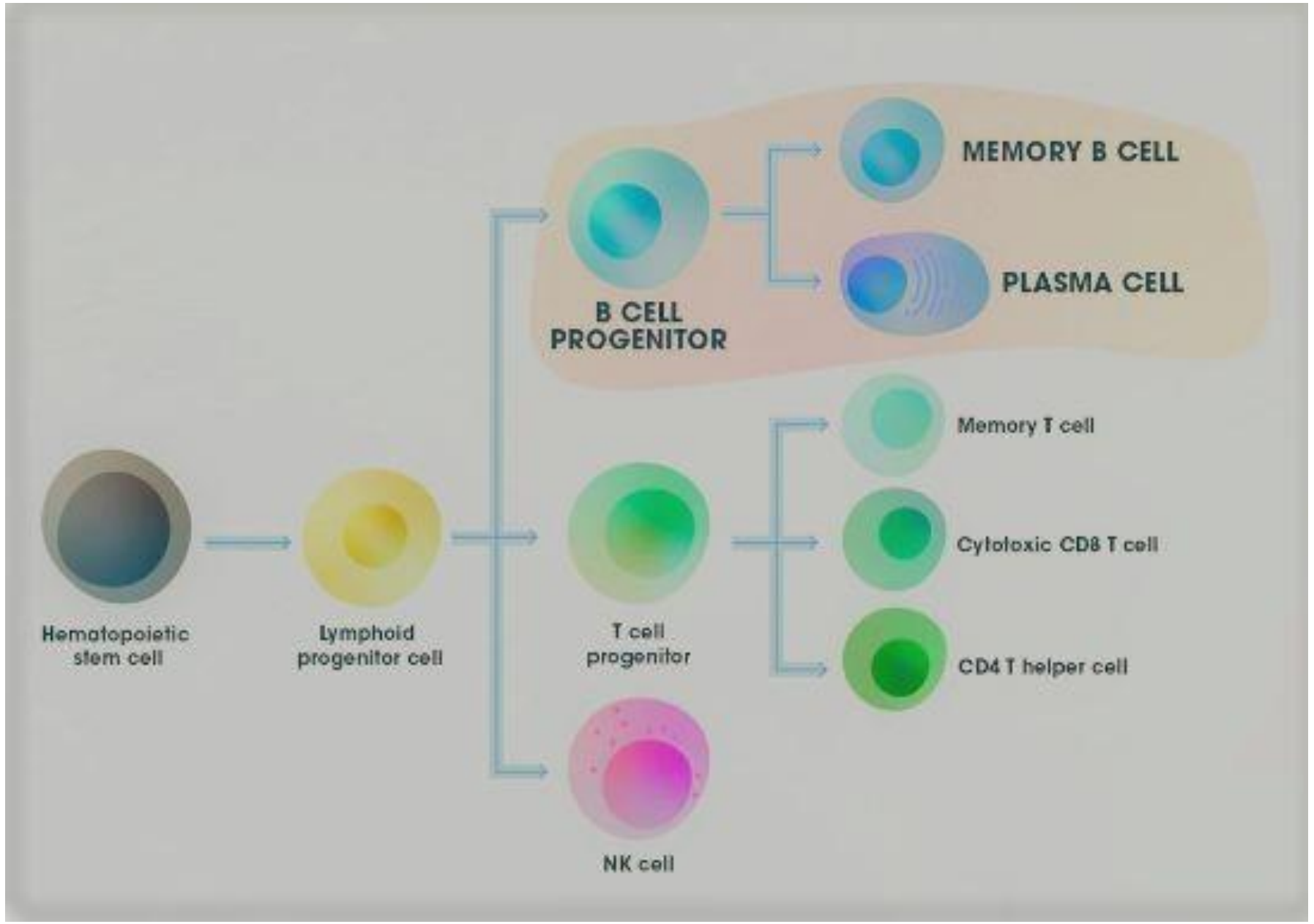
Source :bsc-int.co.jp

What is required for B cell activation?

- **Naïve B** cell activation requires antigen recognition by the Ig receptor.
- The additional signals that can come either from a **$CD4^+$ Helper T cell (thymus-dependent)**
- Or, in some cases, directly from **microbial components (T independent).**

T CELL AND B CELL

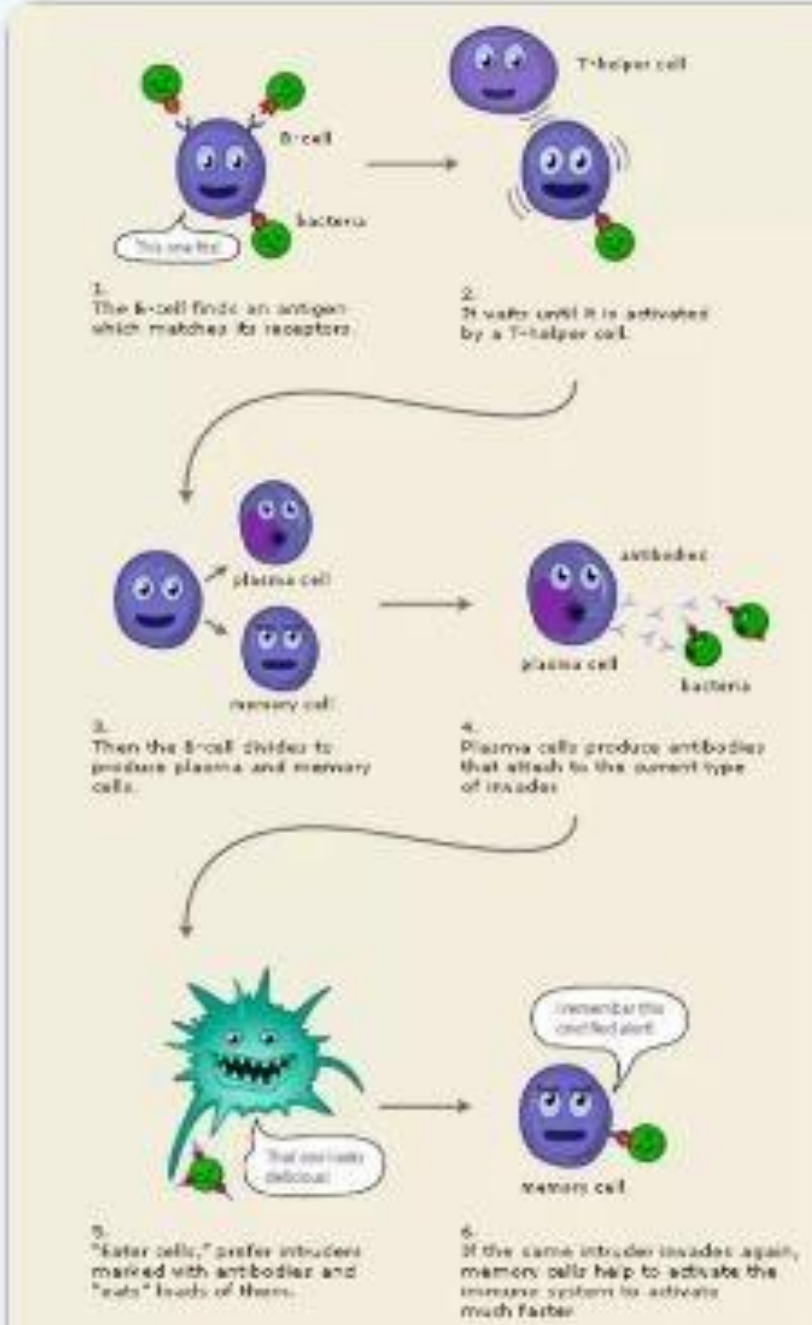
- Lymphocytes are cells that circulate in your blood that are part of the immune system.
- There are two main types lymphocytes:
- T cells and B cells.
- B cells produce antibody molecules that can latch on and destroy invading viruses or bacteria.
- T cells are direct fighters of foreign invaders and also produced cytokines which are biological substances that help activate other parts of the immune system.
- One such part is called macrophages. These macrophages act to clean up the invaders and the dead tissue after an immune response.



Source : technologynetworks

B CELL EFFECTOR MECHANISM

- These are primarily responsible for antibody-mediated immunity. Once activated, B plasma cells that produce antibodies specific to antigens. These antibodies can neut them for destruction, or facilitate their removal by other immune cells.



THE B CELLS

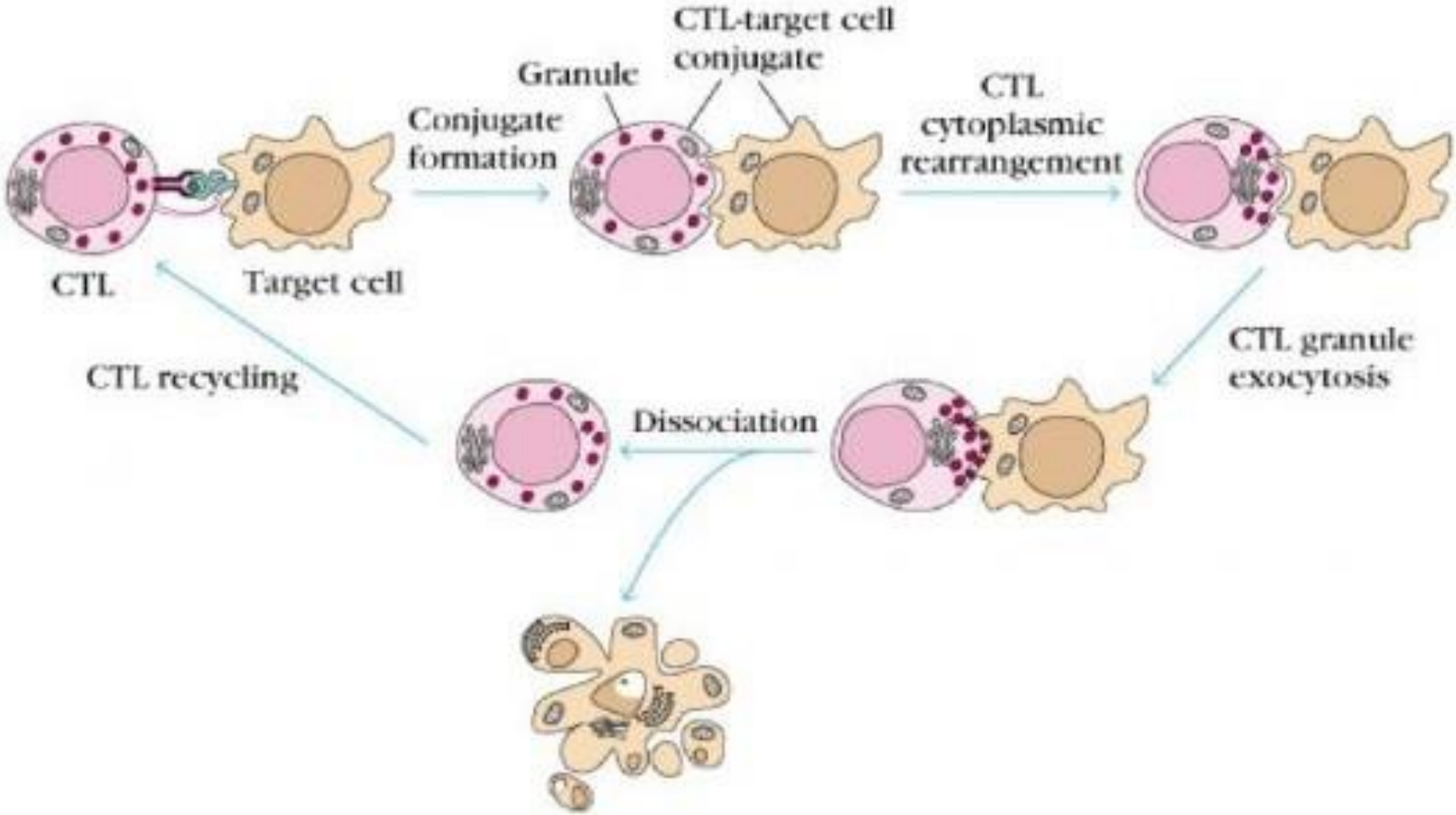
- B lymphocytes mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane
- Plasma cells live for only a few days, they secrete enormous amounts of antibody (2000/sec)

Parungao-Balolong 2011

T CELL EFFECTOR MECHANISM

T cells are involved in cell-mediated immunity. They come in several types:

- **Helper T Cells (CD4+)**: They assist other immune cells by releasing cytokines that stimulate B cells, cytotoxic T cells, and macrophages.
- **Cytotoxic T Cells (CD8+)**: These directly kill infected or cancerous cells by recognizing and binding to antigens presented by MHC class I molecules on these cells.
- **Regulatory T Cells**: They help maintain immune tolerance and prevent autoimmune reactions.


CTL-target cell conjugate
Granule
CTL cytoplasmic rearrangement
Conjugate formation
CTL
Target cell
CTL granule exocytosis
CTL recycling
Dissociation

MACROPHAGE ACTIVATION

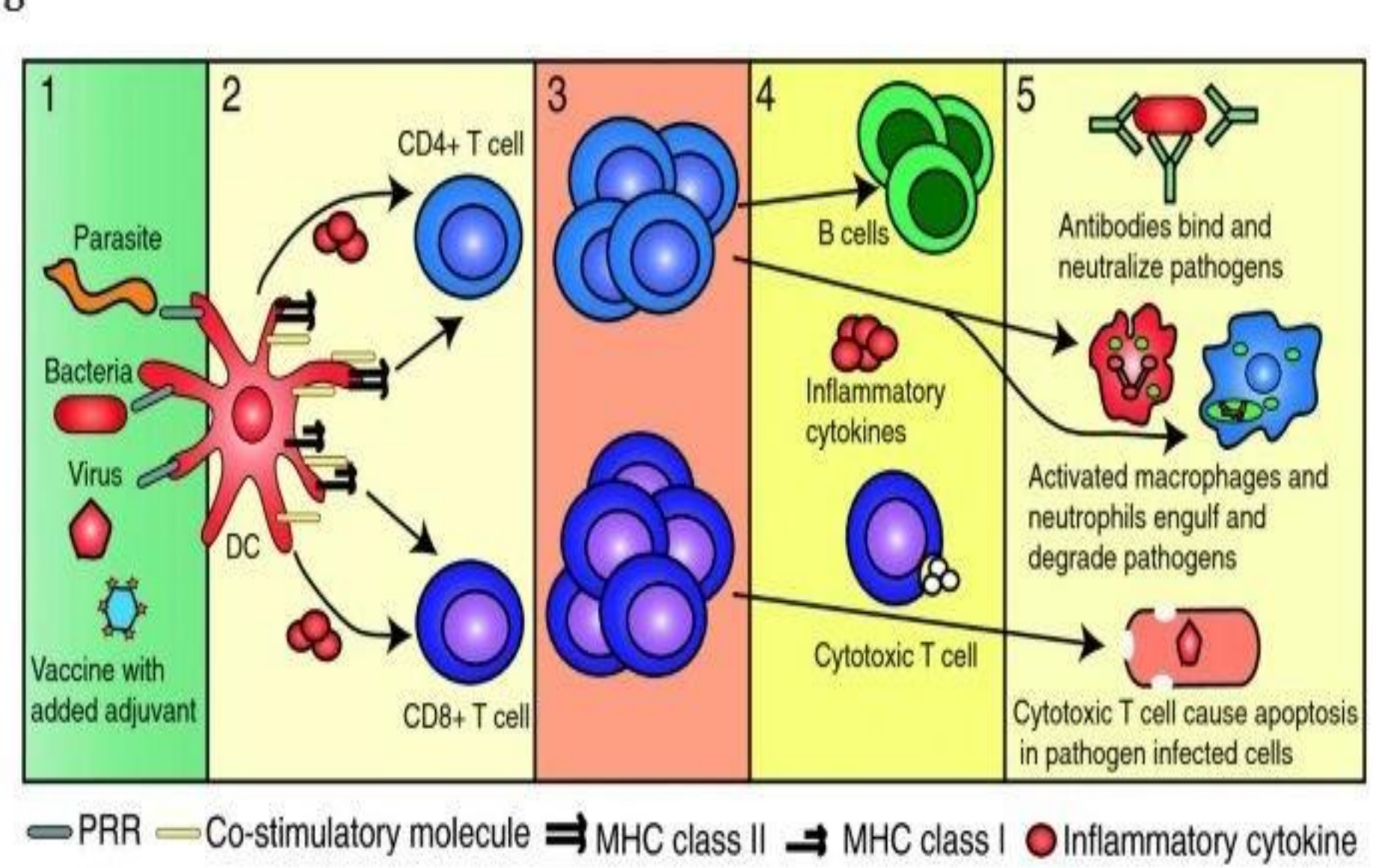
- Macrophages are versatile immune cells that can be activated by various signals, including cytokines (e.g., IFN-γ from helper T cells) and pathogen-associated molecular patterns (PAMPs).

- **Classical Activation (M1)**: Macrophages activated by IFN-γ and other signals exhibit pro-inflammatory properties, producing cytokines that enhance the ability to kill pathogens and present antigens.

- **Alternative Activation (M2)**: Typically associated with tissue repair and resolution of inflammation, M2 macrophages can also play a role in wound healing and tissue remodeling.

A dendritic cell (DC) is an antigen-presenting cell of the mammalian immune system. A DC's main function is to process antigen material

MHC stands for major histocompatibility complex, which is a group of genes that encode proteins on the surface of cells that help the immune system recognize foreign substances. These proteins include cell surface markers, antigen-presenting molecules, and other proteins that are involved in immune function.

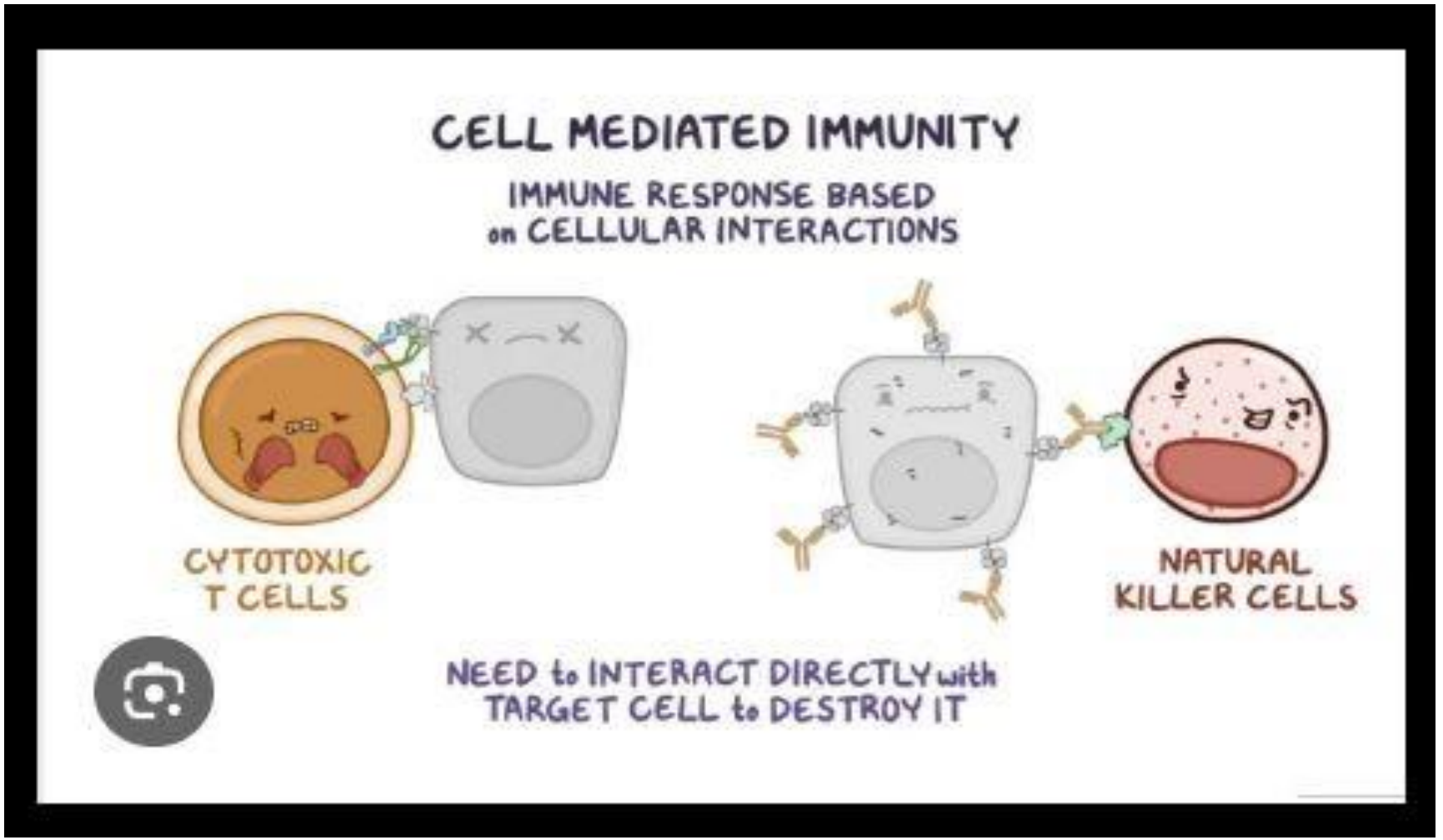


Source :http://dx.doi.org/10.1186/1741-7007-8-37

CELL MEDIATED CYTOTOXICITY :

- **Cytotoxic T Cells**: As mentioned, CD8+ T cells directly kill target cells through mechanisms like releasing perforin and granzymes that induce apoptosis in infected or cancerous cells.

- **Natural Killer (NK) Cells**: These cells also play a crucial role in cell-mediated cytotoxicity by recognizing and destroying stressed or infected cells, especially when there is a lack of MHC class I molecules on the target cell.



Source: osmosis.org

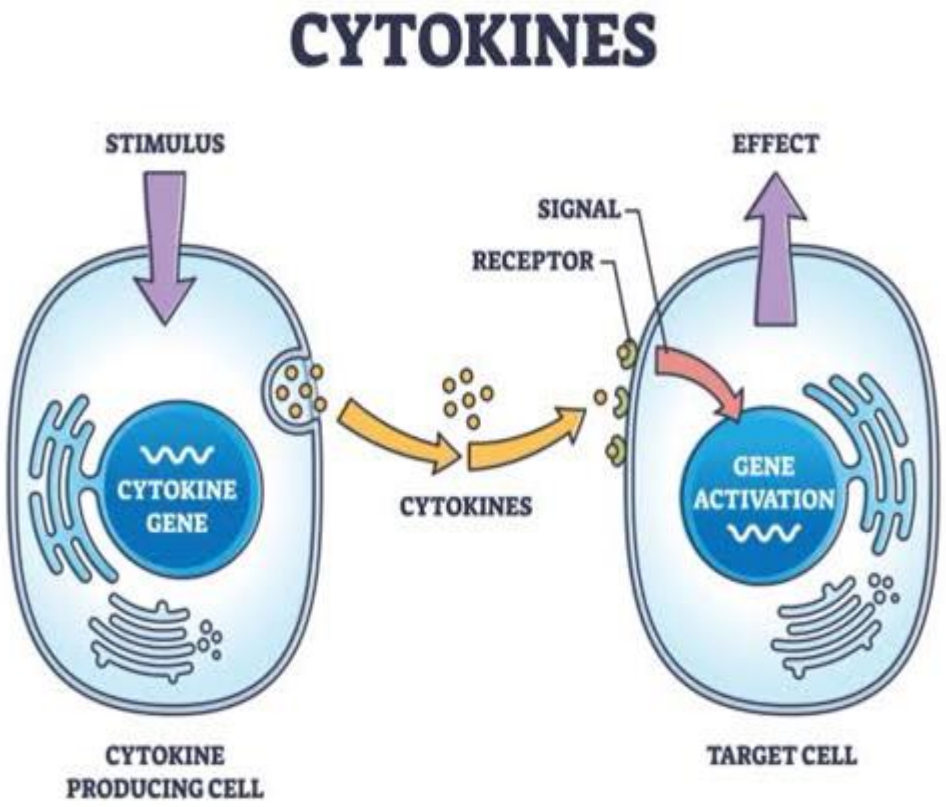
Cytokines: types regulation of immune response immune tolerance and immunosuppression

Cytokines

- The term "cytokine" is derived from a combination of two Greek words - "cyto" meaning cell and "kinos" meaning movement.
- Cytokines are small and membrane-bound protein-based cell signaling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection, and trauma.

Cytokines

- Cytokines are crucial in controlling the growth and activity of the immune system cells and blood cells.
- They also help to boost anti-cancer activity by sending signals that can cause abnormal cell death
- Cytokines are produced by various cells such as macrophages, mast cells, B-lymphocytes, T-lymphocytes, fibroblasts as well as endothelial cells,



Source:diifeology.com

Types of Cytokines

Interleukins (ILs):

- These cytokines are primarily produced by leukocytes and act on other leukocytes.
- IL-1 Family: IL-1α and IL-1β: Involved in the inflammatory response and the activation of T cells and macrophages. They also induce fever.
- IL-2: Critical for T cell proliferation. It also supports the growth and differentiation of T cells, B cells, and NK cells.

- IL-3: Supports the growth and differentiation of hematopoietic stem cells into various types of blood cells
- IL-4 : It stimulates B cell proliferation and antibody production, particularly IgE.
- IL-5: Stimulates the growth and activation of eosinophils, which are important in the immune response against parasitic infections and in allergic reactions.
- IL-6: It is involved in inflammation and the development of autoimmune diseases.

Interferons

- Interferons (IFNs) are a group of signaling proteins that are primarily involved in the immune response to pathogens, particularly viruses.
- **Type I Interferons:** IFN-α (Interferon-alpha) and IFN-β (Interferon-beta).
- Type I interferons are produced by almost all nucleated cells in response to viral infections, particularly by plasmacytoid dendritic cells.

Functions

- Antiviral Defense
- Immune Activation
- Regulation of Immune Response

- **Type II Interferon:** IFN-γ (Interferon-gamma)
- IFN-γ is primarily produced by T cells (especially Th1 cells) and NK cells.

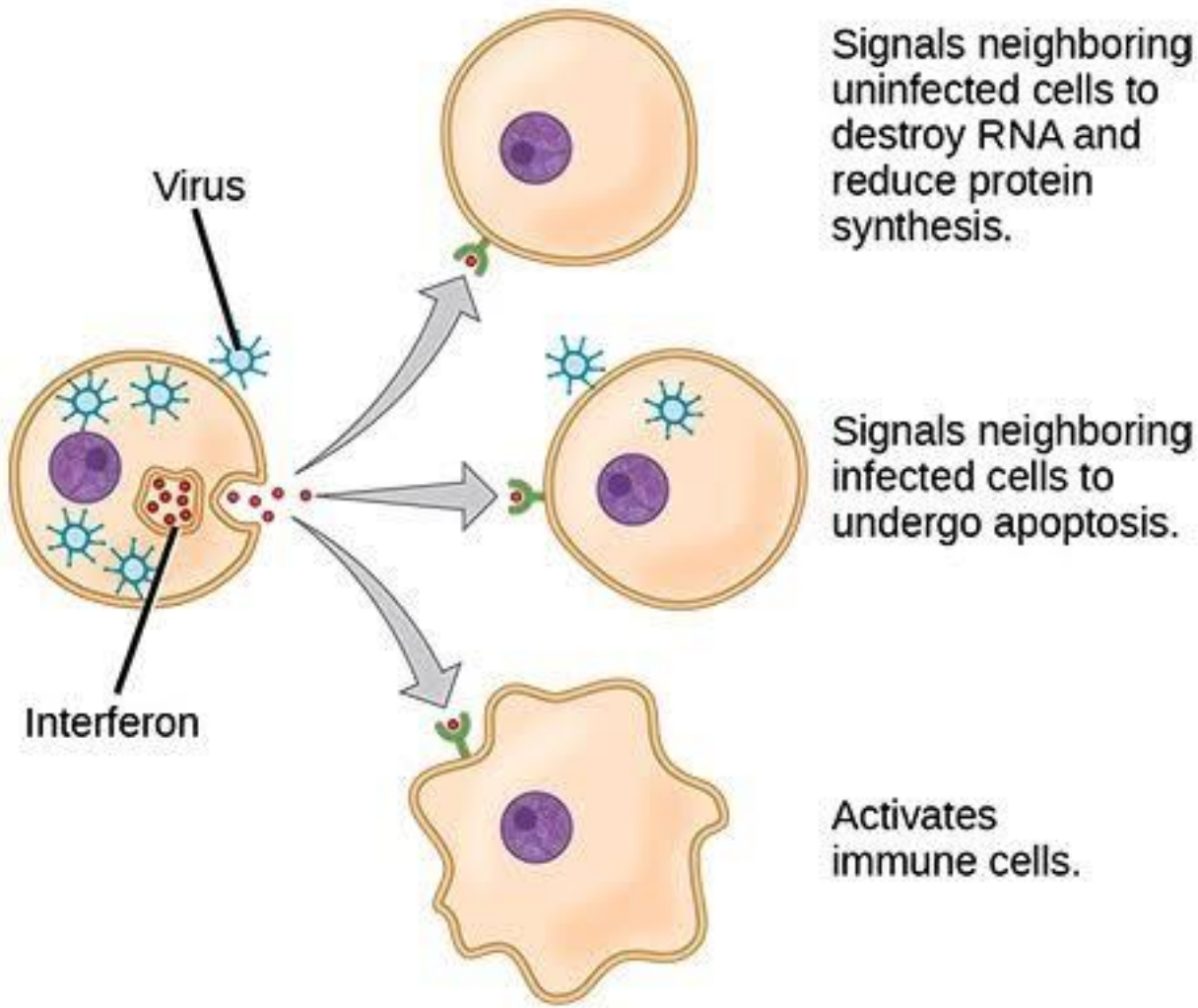
Functions:

- Macrophage Activation
- Promotion of Th1 Responses - It promotes the differentiation of native T cells into Th1 cells, which are critical for cellular immunity.

- **Type III Interferons**: IFN-λ (Interferon-lambda), including IFN-λ1, IFN-λ2, IFN-λ3, and IFN-λ4.
- Similar to Type I interferons, Type III interferons are produced by epithelial cells and dendritic cells in response to viral infections

Functions

- Antiviral Defense in Mucosal Tissues
- Regulation of Immune Response: They act similarly to Type I interferons but have a more localized effect, mainly protecting epithelial cells



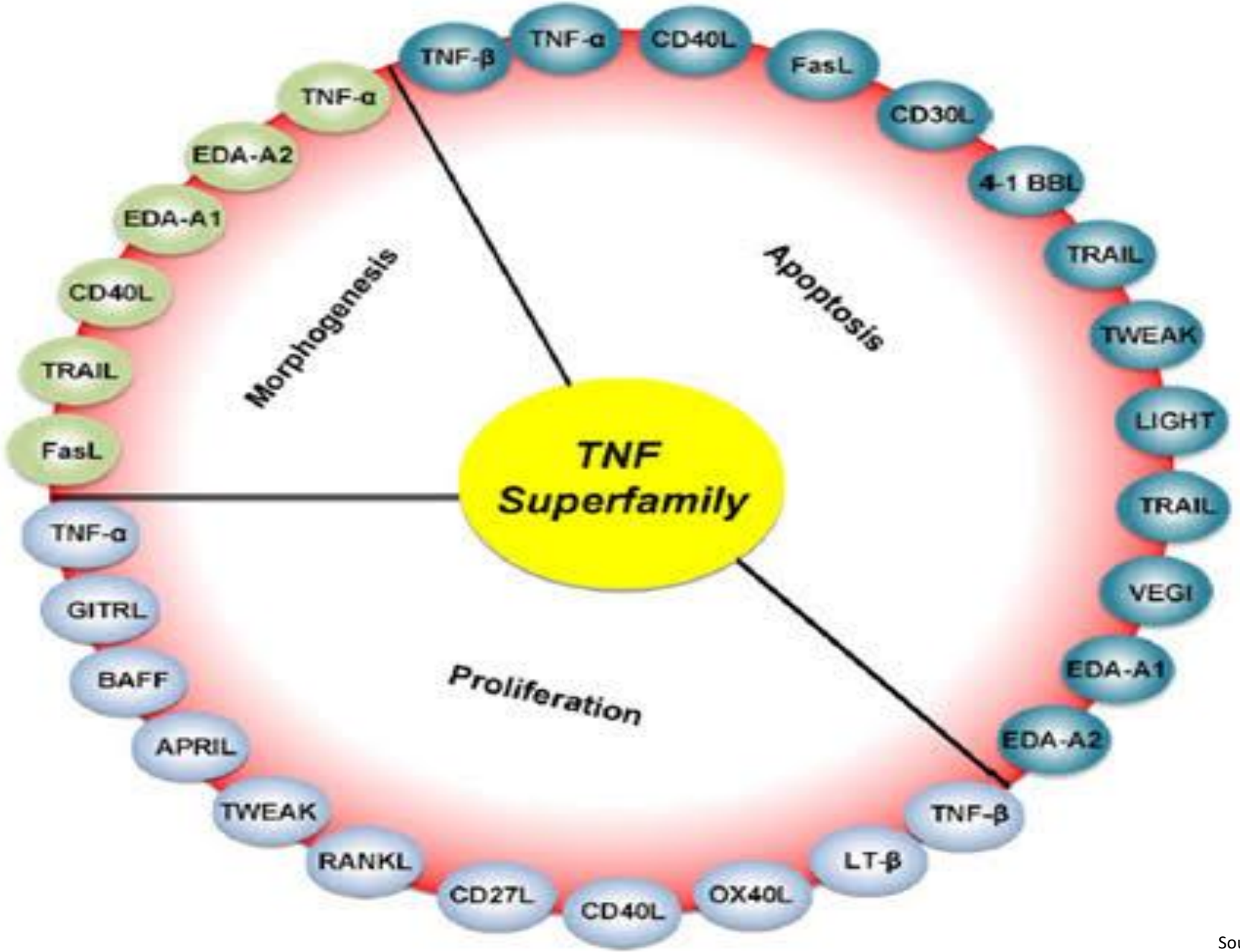
Source:nursinghero.com

Tumor Necrosis Factors (TNFs)

- Tumor Necrosis Factors (TNFs) are a group of cytokines that play a central role in inflammation and the immune response
- **TNF-α** is primarily produced by macrophages.
- Its production is often triggered by infections, endotoxins (like lipopolysaccharides from bacteria)
- It acts on the hypothalamus to induce fever as part of the acute phase response.
- TNF-α can induce cell death (apoptosis) in certain cells, which is a crucial mechanism in controlling tumor growth and eliminating infected or damaged cells.

Chronic Inflammatory Diseases: Overproduction of TNF-α is implicated in several chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, psoriasis, and ankylosing spondylitis.

Sepsis: Excessive TNF-α release during severe infections can lead to septic shock, a life-threatening condition characterized by widespread inflammation, low blood pressure, and organ failure.



Source:https://www.biologicscorp.com

Colony-Stimulating Factors (CSFs)

- Colony-Stimulating Factors (CSFs) are a group of cytokines that play a crucial role in hematopoiesis

Granulocyte Colony-Stimulating Factor (G-CSF):

- G-CSF (e.g., filgrastim, pegfilgrastim) is commonly used in patients undergoing chemotherapy to boost neutrophil counts

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF):

- GM-CSF (e.g., sargramostim) is used to accelerate recovery of the immune system after bone marrow transplantation

Macrophage Colony-Stimulating Factor (M-CSF)

- Specifically stimulates the production and differentiation of macrophages

Multi-CSF (Interleukin-3, IL-3)

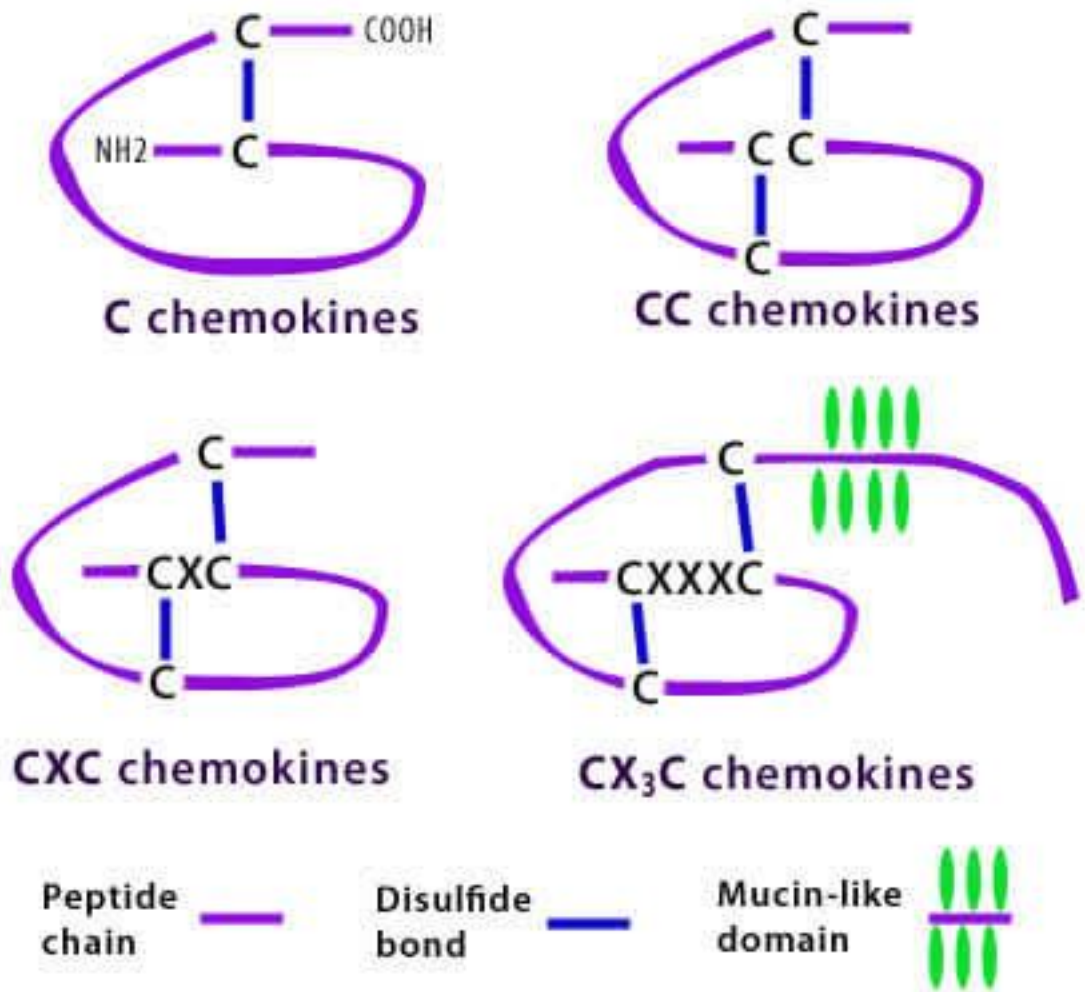
- A broader acting CSF that stimulates the production of various types of blood cells, including erythrocytes (red blood cells), platelets, and different white blood cells

Chemokines

- Chemokines are a specialized subset of cytokines that primarily function as **chemoattractants**, guiding the migration of immune cells to sites of infection, inflammation, or injury.
- Chemokines are small proteins, typically 8-10 kDa in size, characterized by the presence of conserved cysteine residues that form disulfide bonds

Examples of Chemokines

- **CXCL8 (IL-8):** Attracts neutrophils to sites of infection or injury. Also involved in angiogenesis.
- **CCL2 (MCP-1):**Recruits monocytes, memory T cells, and dendritic cells to sites of inflammation.
- **CX3CL1** (Fractalkine):Exists both as a soluble chemokine and as a membrane-bound protein, facilitating adhesion and migration of leukocytes.



Source:https://www.technoconcept.co.in/chemokines

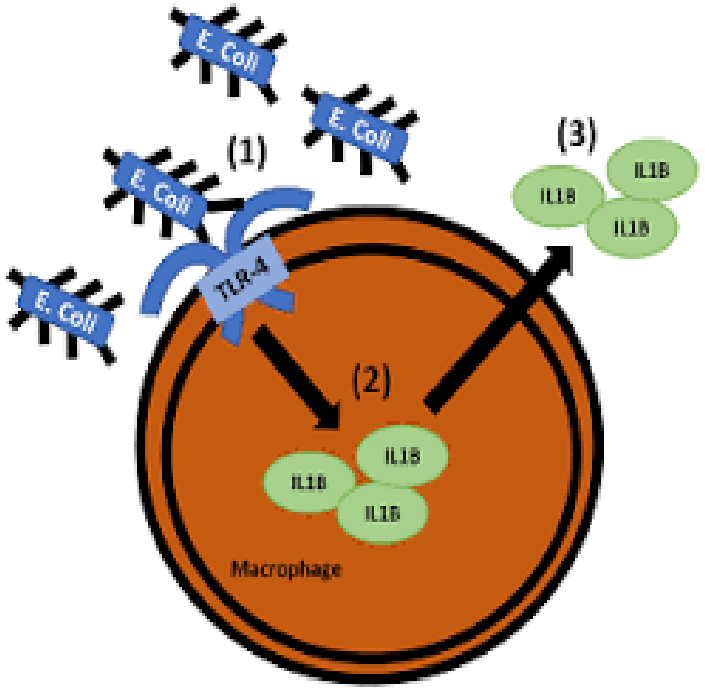


Figure 1. Representation of a pro-inflammatory cytokine response

(**1**) When *Escherichia Coli* (*E. Coli*) enters our system, lipopolysaccharide (LPS) in the outer membrane of *E. coli* is recognized by Toll-like receptor 4 (TLR-4) abundant on the surface of macrophages. (**2**) Once the LPS-TLR4 complex is formed, intracellular signaling pathways lead to Nuclear factor-κB (NF-κB) activation and upregulation of IL1-β, a key cytokine involved in pro-inflammatory responses. (**3**) IL1-β is then secreted from the cell and can propagate the pro-inflammatory response.

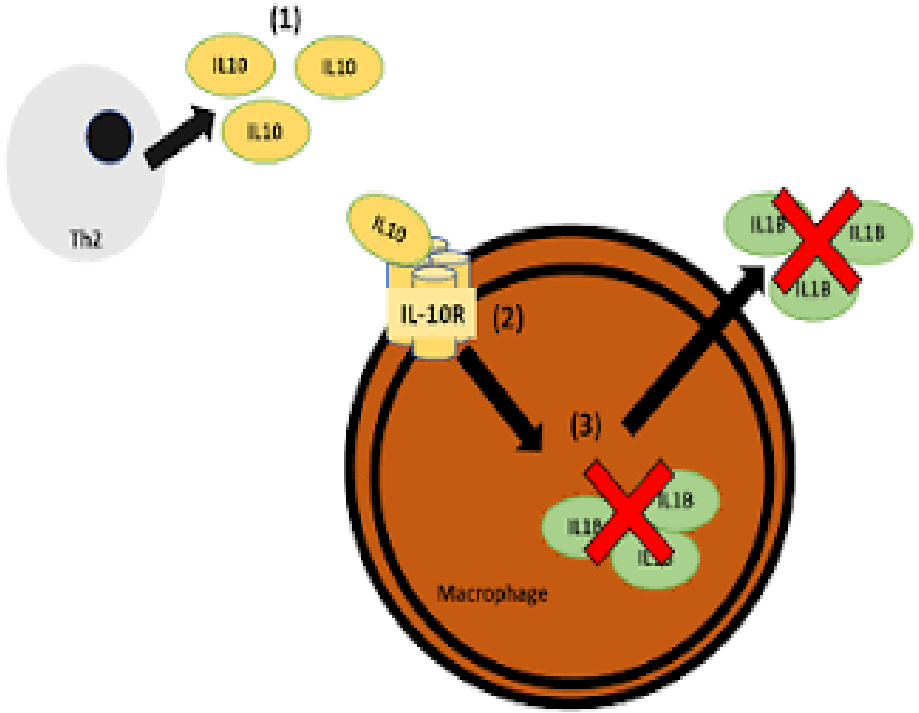


Figure 2. Representation of an anti-inflammatory cytokine response

(**1**) In response to the pro-inflammatory signaling, T-Helper Cells (Th2) produce and release IL-10. (**2**) IL-10 binds to the IL-10 receptor (IL-10R) located on the surface of many immune cells (including macrophages), (**3**) which leads to down-regulation of pro-inflammatory cytokines by intracellular JAK/STAT signaling. This process helps regulate the inflammatory response and restore homeostasis to the system.

Source:https://www.chondrex.com/cytokine-detection

Immune tolerance

- Immune refers to the immune system's ability to distinguish between the body's own cells and foreign entities, thereby preventing it from attacking the body's own tissues

Central tolerance in T cells

Thymic Development:

- Positive Selection: T cells undergo maturation in the thymus, where they are tested for their ability to recognize self-MHC (Major Histocompatibility Complex) molecules. Only those T cells that can moderately bind to self-MHC molecules receive survival signals and proceed to the next stage. This ensures that T cells are functional and can recognize antigen-presenting cells (APCs) in the body.

- Negative Selection: T cells that strongly bind to self-antigens presented by self-MHC molecules are targeted for apoptosis (programmed cell death). This process removes T cells that are likely to cause autoimmunity. It ensures that T cells which might attack the body's own tissues are eliminated before they enter the peripheral circulation.

Central Tolerance in B Cells

Bone Marrow Development:

- Immature B Cell Testing: B cells develop in the bone marrow and undergo a selection process. They are tested for their reactivity to self-antigens.
- Negative Selection: Immature B cells that bind strongly to self-antigens are either eliminated through apoptosis or undergo a process called receptor editing. Receptor editing involves rearrangement of the B cell receptor (BCR) genes to change specificity away from self-antigens.

Peripheral Tolerance

- Anergy: T cells that recognize self-antigens in the periphery (outside the thymus) without the necessary co-stimulatory signals become anergic. These T cells remain alive but are functionally inactive.
- Regulatory T Cells (Tregs): These cells are essential for maintaining tolerance. Tregs suppress the activation and proliferation of self-reactive T cells. They play a critical role in preventing autoimmune diseases and maintaining homeostasis.
- Deletion: Self-reactive T cells that escape central tolerance may be deleted in peripheral tissues through apoptosis if they recognize self-antigens.

Immune suppression

Cytokine Regulation:

- Inhibitory Cytokines: Cytokines like IL-10 and TGF-beta play a crucial role in dampening immune responses. They can inhibit the production of pro-inflammatory cytokines and suppress the activation of immune cells.

Immune Checkpoints:

- Checkpoint Proteins: Proteins such as CTLA-4 and PD-1 on T cells regulate immune responses by providing inhibitory signals. These checkpoints help prevent overactivation of the immune system and maintain self-tolerance.