Organs and Cells of Immune System

By

Prof. Dr. Batool Hassan Al-Ghurabi

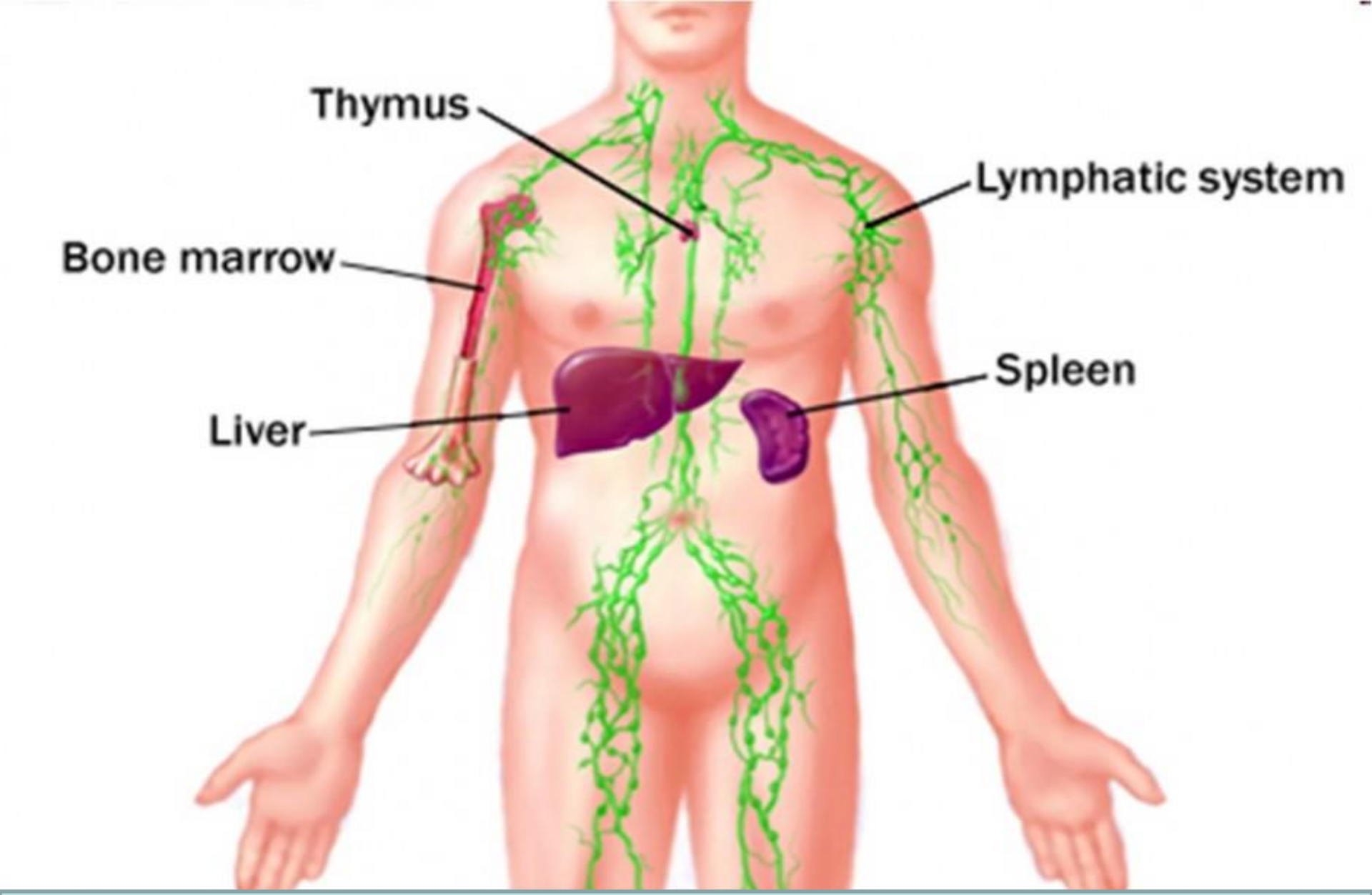
Organs and Cells of Immune System

Organs concerned with immune reactions are called lymphoid organs. They contain lymphoid cells.

Lymphoid organs are of 2 types.

1. Primary lymphoid organs

2. Secondary lymphoid organs


Thymus
Lymphatic system
Bone marrow
Spleen
Liver

1. Primary lymphoid organs

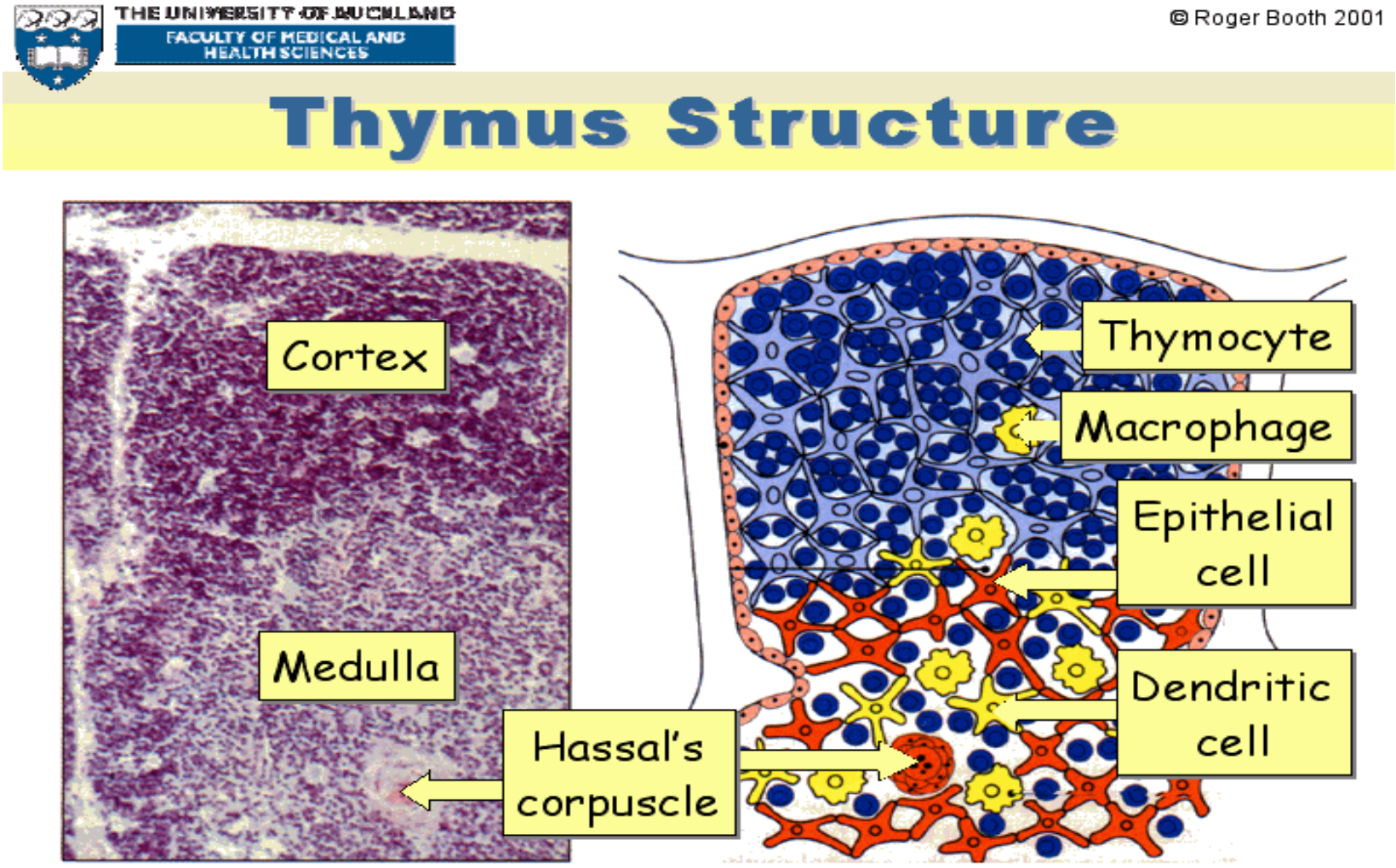
Are the major site of lymphopoiesis. The lymphoid cells proliferate, differentiate and mature in to immune competent cells in the absence of antigenic stimulation. The primary lymphoid organs are large at birth and they atrophy with age progression; major primary lymphoid organs are

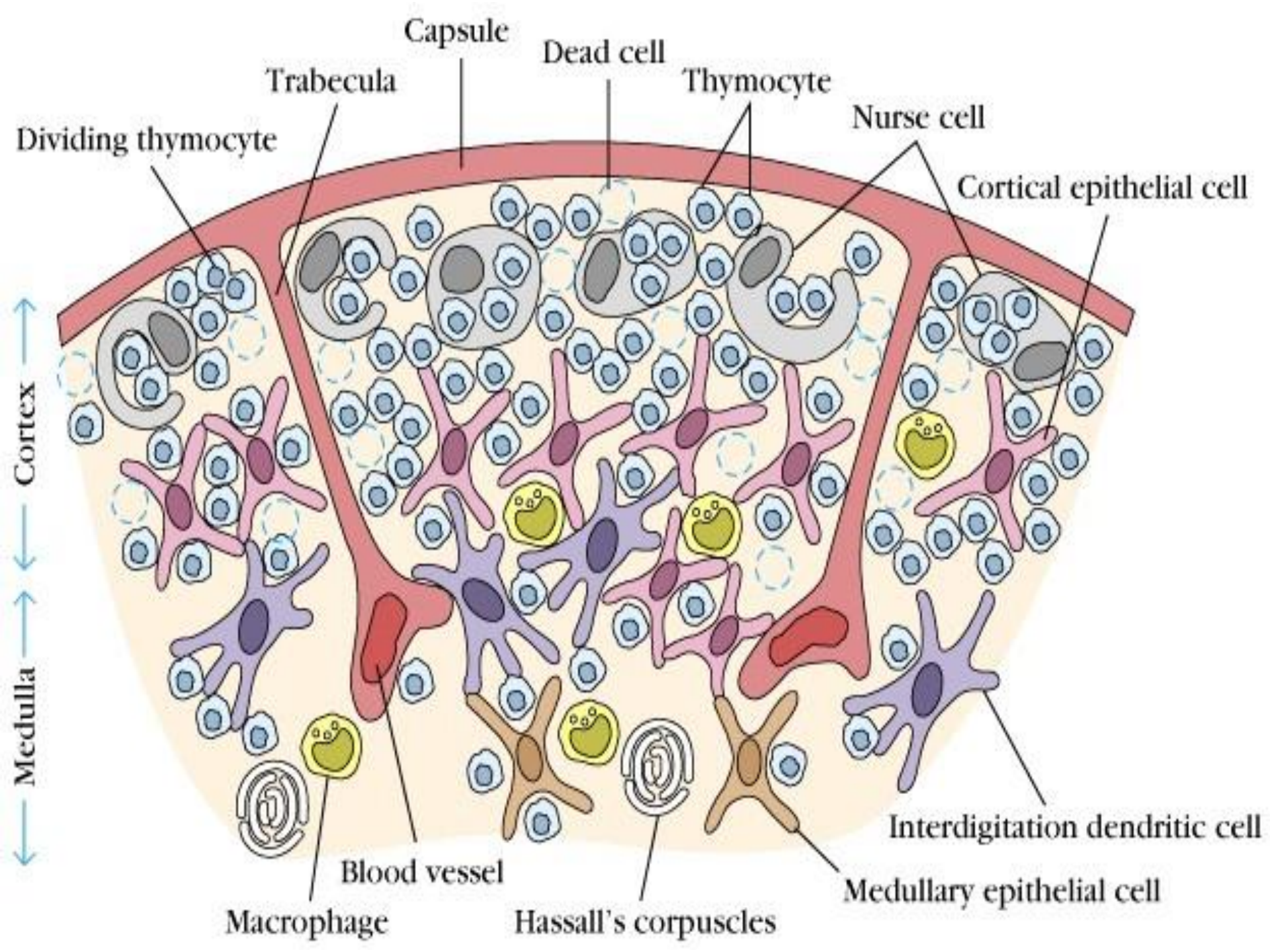
1. Thymus (site of T-cell maturation in human)

2. Bone marrow (site of B cell maturation in human)

= Bursa of fabricious (site of B-cell maturation in bird)

1.The structure of Thymus




Capsule
Dead cell
Trabecula
Thymocyte
Dividing thymocyte
Nurse cell
Cortical epithelial cell
Cortex
Medulla
Interdigitation dendritic cell
Blood vessel
Medullary epithelial cell
Macrophage
Hassall's corpuscles

Thymus: is the site of T cell differentiation and maturation, consist of the cortex and the medulla, cells found in thymus are; stroma cells, epithelial cells, macrophages, dendritic cells and thymocytes (the cells migrate from the bone marrow to the thymus and then become thymocytes).

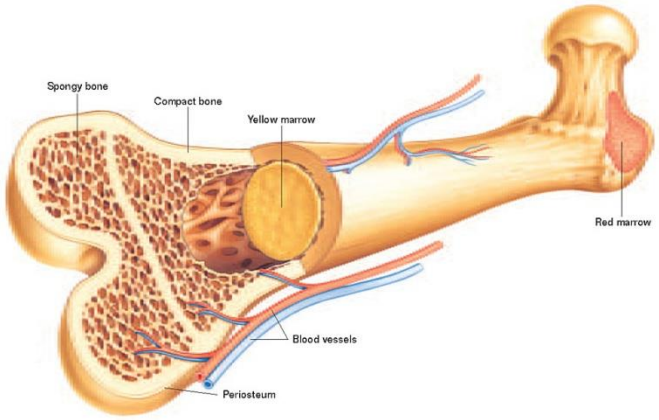
T-cells will be clustered in the cortex; these clusters will differentiated in medulla and have their own surface molecules thus called cluster of differentiated lymphocytes (CD) e.g. , CD2, CD3, CD4, CD8, CD19.

In cortex any thymocyte acquire receptors for self Ag will be killed by apoptosis (programmed cell death) this process called **negative selection**.

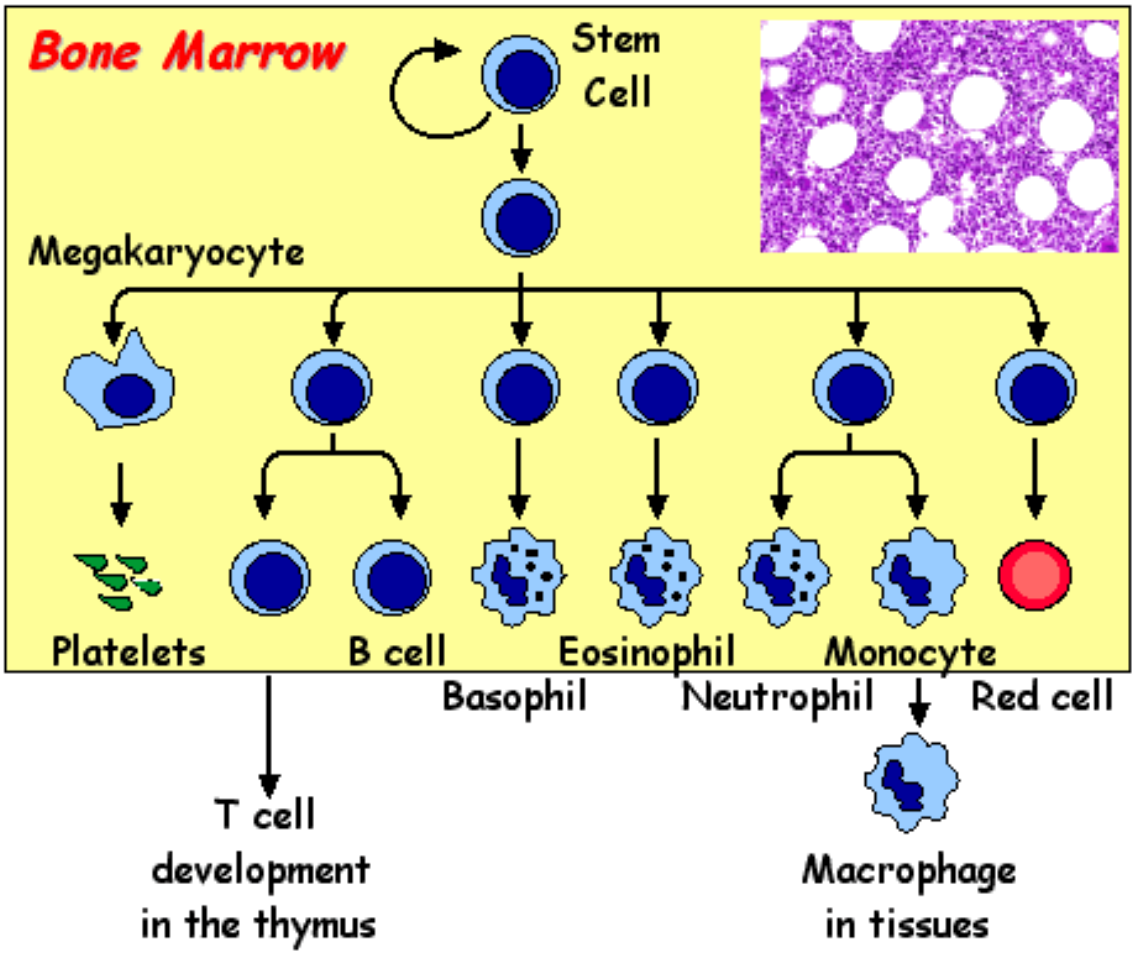
In medulla **positive selection** occur when cells acquire molecules (receptors) by which recognized Ags in association with MHC class I and II molecules. These two processes negative and positive selection are called **T-cells educations.**

Bone marrow

- **Bone marrow:** is the site of generation of all circulating blood cells in the adult, including immature lymphocytes, and is considered as the site of B cell maturation.



Blood Cell Development



2. Secondary lymphoid organs

Lymphocytes are made functional in the secondary lymphoid organs. The secondary lymphoid organs are small and poorly developed at birth and they grow progressively with age. The secondary lymphoid organs include:

1. Lymph nodes
2. Spleen
3. Mucosal associated lymphoid tissues (MALT), such as gut-associated lymphoid tissue (GALT).

Lymph nodes: are the organs in which immune responses to lymphoid-borne antigens are initiated, they have many functions.

- Filter and eliminate foreign antigens.

-Site of immune response.

-Site of lymphocytes residence and source of recirculation cells.

The spleen: is the major site of immune responses to blood-borne antigens

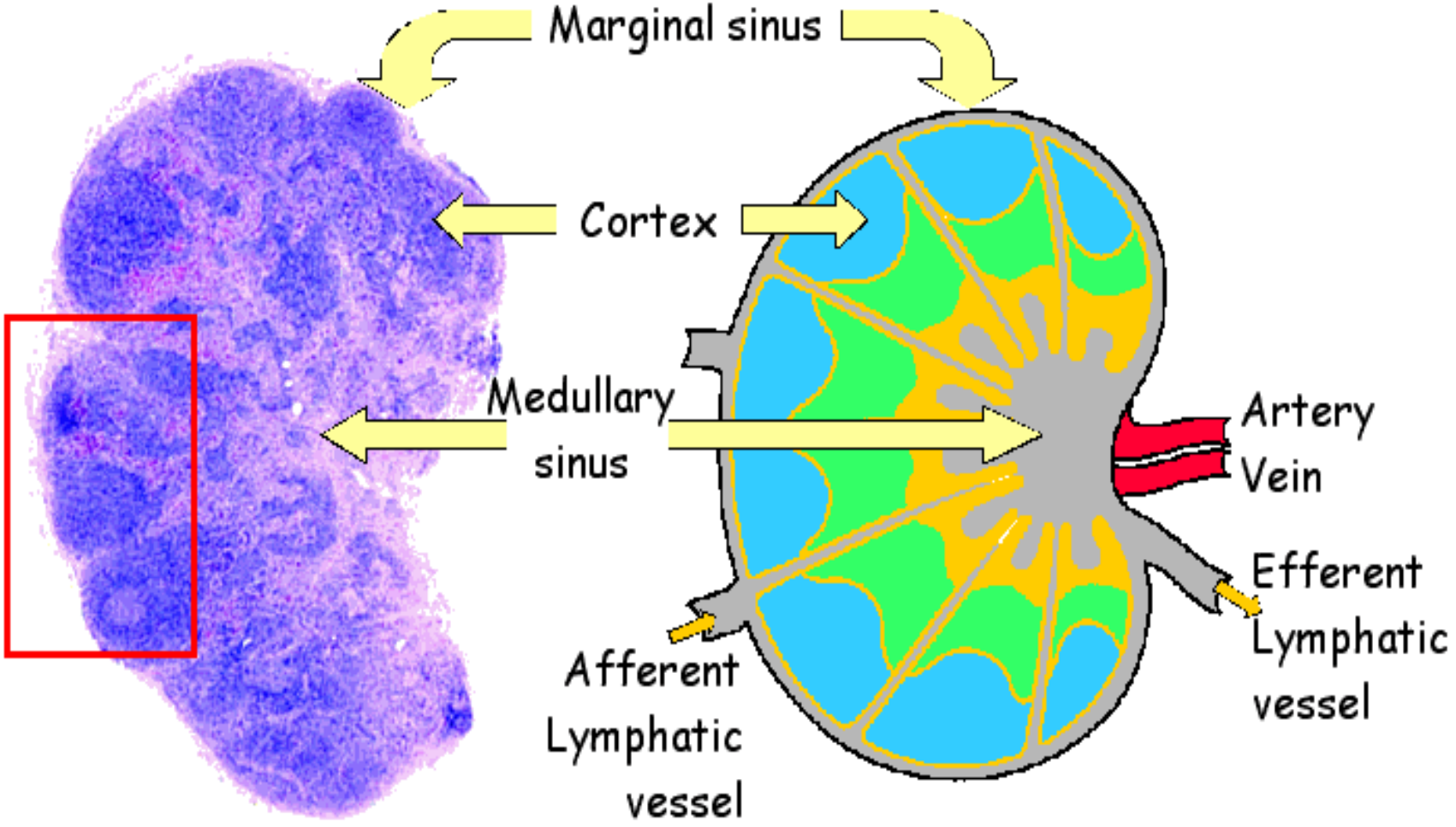
-Site of immune cell residence.

-Site of immune response.

-Produce some active substances, such as complement.

-Filtration.

A Lymph Node



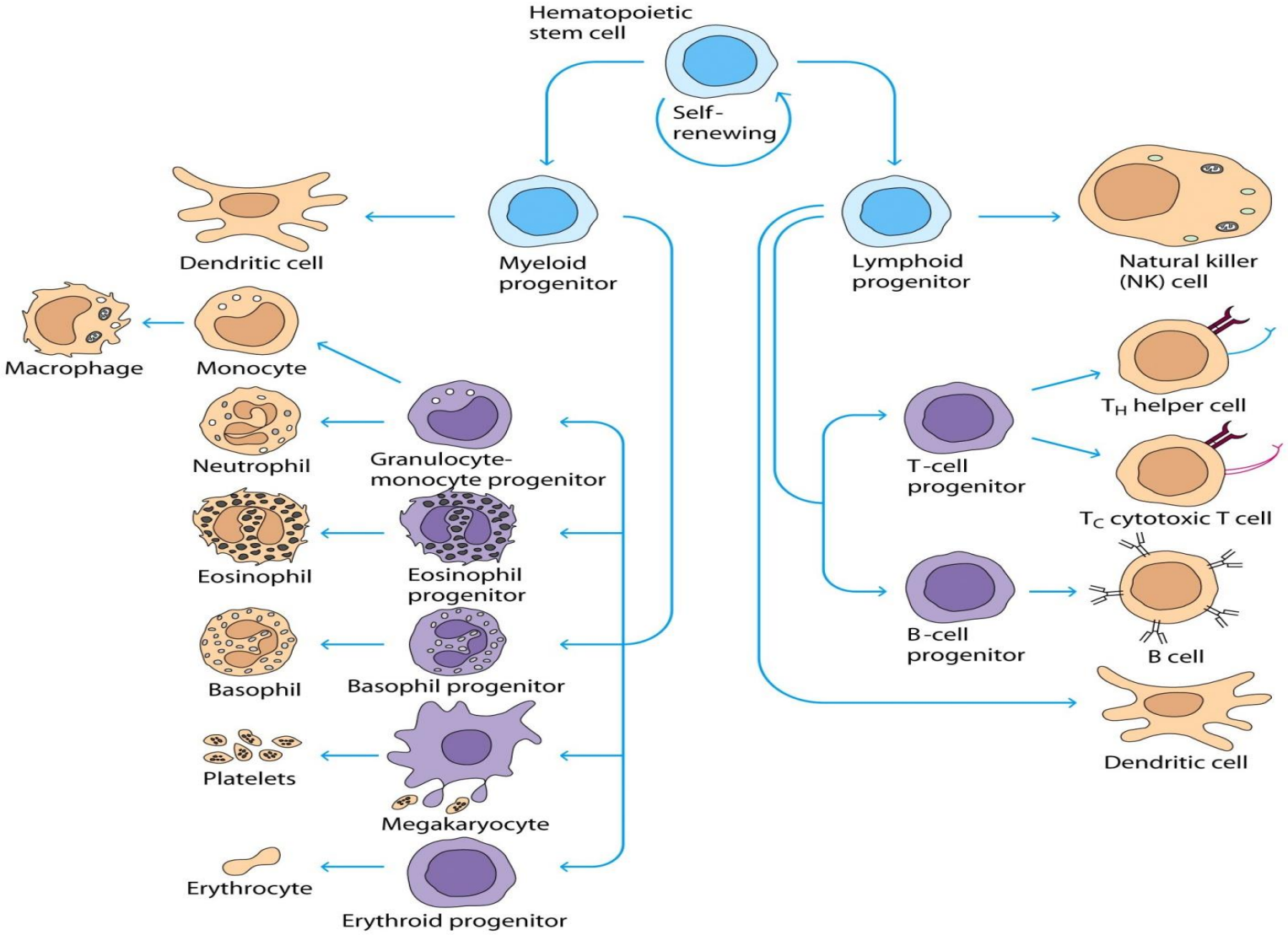
Mucosal associated lymphoid tissues (MALT)

The MALT of the gastrointestinal and respiratory tracts is colonized by lymphocytes and antigen presenting cell that initiate immune responses to ingested and inhaled antigens.

Cells of the immune system

Stem cells of the immune system originated from the yolk sack in the first six weeks of gestation, after that liver take this function, then bone marrow will be responsible for originate and proliferate stem cell under some hormones and enzymes.

Stem cells include lymphoid series (T, B and NK cells) and myeloid series (RBCs, monocytes and granulocytes).


Hematopoietic stem cell
Self-renewing
Dendritic cell
Myeloid progenitor
Lymphoid progenitor
Natural killer (NK) cell
Macrophage
Monocyte
Neutrophil
Granulocyte-monocyte progenitor
Eosinophil
Eosinophil progenitor
Basophil
Basophil progenitor
Platelets
Megakaryocyte
Erythrocyte
Erythroid progenitor
T-cell progenitor
T_H helper cell
T_C cytotoxic T cell
B-cell progenitor
B cell
Dendritic cell

1. Lymphocytes

-Lymphocytes are mononucleate, nongranular leukocytes of lymphoid tissue participating in immunity.

-They are found in blood, lymph and lymphoid tissue such as spleen, lymph nodes, tonsils and peyer’s patches.

-They are spherical or oval in shape and arise from haemopoetic stem cells.

T-Lymphocytes

- represent about **70%** of the total lymphocyte population.

- all T cells express **CD3** on their surfaces, along with T cell receptors (**TCRs**) which recognize specific antigens presented in an MHC I or MHC II molecule.

-there are numerous different T cell subtypes.

There are different types of T cells:

1. T-initiator or inducer: have CD^{+4}

2. T-helper: have $CD^{+4,}$ which have two types T-helper1 (Th1) and T-helper2 (Th2).

3. Tdh (delay hypersensitivity): have CD^{+4}.
4. T-cytotoxic: have CD^{+8}, kill viral infected cells and tumor cells .
5. T-Memory: have CD^{+4} and CD^{+8}, play a role in secondary immune response.

Maturation and development of T-cell

- The first stage in development is the arrangement of the functional T-cell receptor (**β**-TCR) to avoid death by apoptosis (programmed cell death).

- - The developing T-lymphocytes will acquire **α** and **β** T-cell receptor (TCR).

-CD+4 and CD+8 molecules define the effecter function and the MHC or (HLA) restriction of T-cells.

Mode of killing of T-lymphocytes:-

-Direct by cell to cell action (cytotoxic cell).

-Indirect by cytokines secretion (helper cell).

B-lymphocytes

Lymphocyte that matures in bone marrow and that responsible for humoral immunity is called B lymphocytes.

Mode of killing: - By secretion specific immunoglobulins.

B-cell development:-

-pro-B-cell: contain CD45 and CD19.

-Pre-B-cell: contain intra cytoplasmic μ chain.

-Immature B-cell: have surface IgM only.

-Mature B-cell: have surface IgM and IgD.

When B-cell activated it will differentiated in to plasma cell and secrete Abs (immunoglobulin).

Natural killer cells (NK cells)

They form the third population of lymphocytes. The NK cells have 2 or 3 large granules in the cytoplasm. Hence they are also called large granular lymphocytes. They destroy the cancer cells and cells infected with virus, do not need antibody for activity, are activated by interferon and interleukin-2.

Mode of killing:-

Kill by Ab dependent cell- mediated cytotxicity (ADCC): Antibodies bind to Ag via their Fab region. NK cells, attach via FC receptors, and kill these organisms not by phagocytosis but by release of toxic substances called **perforins** that found in their granules.

2. Macrophages

Macrophages are large mononuclear phagocytic cells derived from monocytes. Macrophages are concentrated in lymph nodes, spleen, bone marrow and liver.

3. Eosinophils

They are acidophilic leucocytes and called eosinophils because eosin an acid dye stains the granules of the cytoplasm of these cells . Granules are rich in hydrolytic enzymes.

4. Basophils

The cytoplasm of these cells containing granules that stains with basic dyes. The basophilic granules contain heparin, histamine, serotonin, platelet activating factor.

5. Neutrophils (microphages)

Neutrophils form the major part of the white blood cell. They are motile, short lived cells with multilobed nucleus. Major function of the neutrophil is phagocytosis.

Complement system

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Complement system is a part of the immune system that helps or complements the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the innate and adaptive immune system.

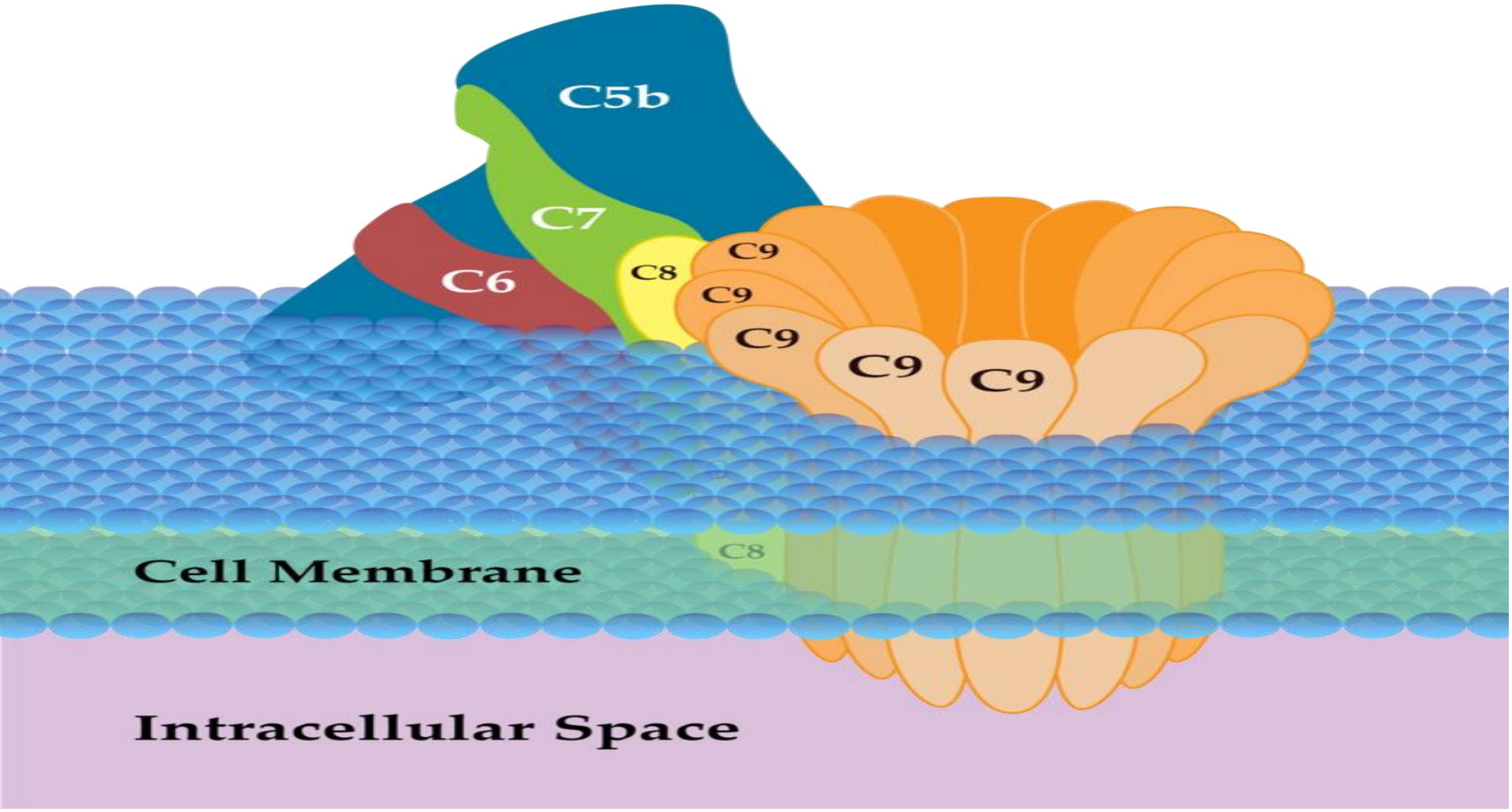
- The complement system consists of a number of small proteins (30 proteins) found in the blood. In general synthesized by the liver (hepatocytes).

- Many components are precursors (pro-proteins) which are functionally inactive until proteolytic cleavage, which removes an inhibitory fragment and exposes the active site.

When stimulated by one of several triggers, proteases in the system cleave specific proteins to activation cascade of further cleavages.

The end-result of this activation cascade is formation of membrane attack complex (MAC).

Membrane attack complex causing cell lysis



Complement Activation

There are three separate pathways which activate the complement system:

1. **classical pathway**: activated by antibody-antigen complexes (immune complexes) on pathogen surfaces.
2. mannose-binding **lectin pathway**: activated when mannose-binding lectin binds to the carbohydrate molecule mannose on pathogen surfaces.
3. **alternative pathway**: C3 reacts directly with pathogen surfaces

-All three of these pathways act to generate the enzyme C3 convertase.

-This cleaves C3 into two parts (C3a and C3b) and activates the rest of the cascade.

Classical Pathway Begins with Ag-Ab Binding

soluble Ag-Ab* or bacteria-Ab*

↓

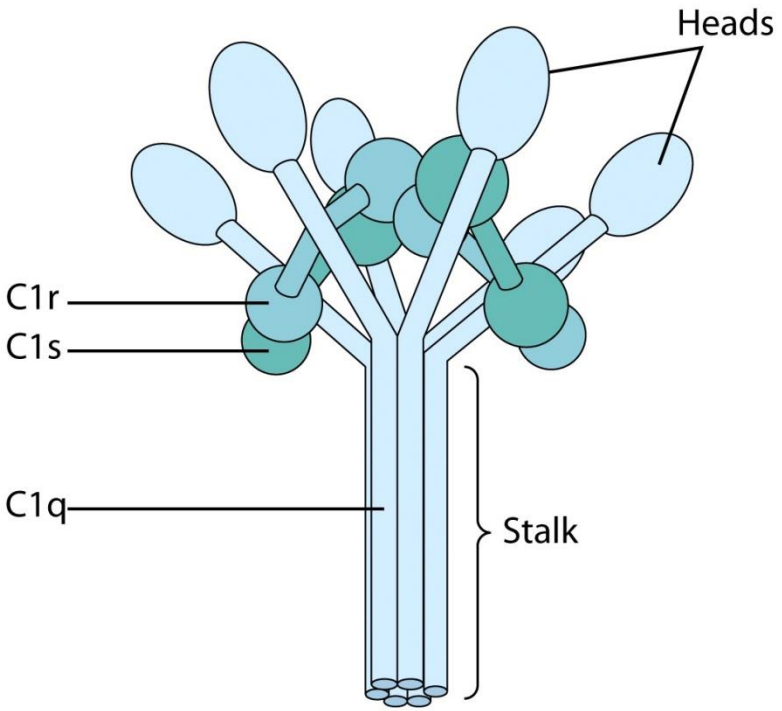
conformational changes in the Fc portion of Ig

↓

expose a binding site on the Fc portion for the C1 component of the complement system

*C1 binds to Ag-bound Ab

C1 molecule



“Classical Pathway”

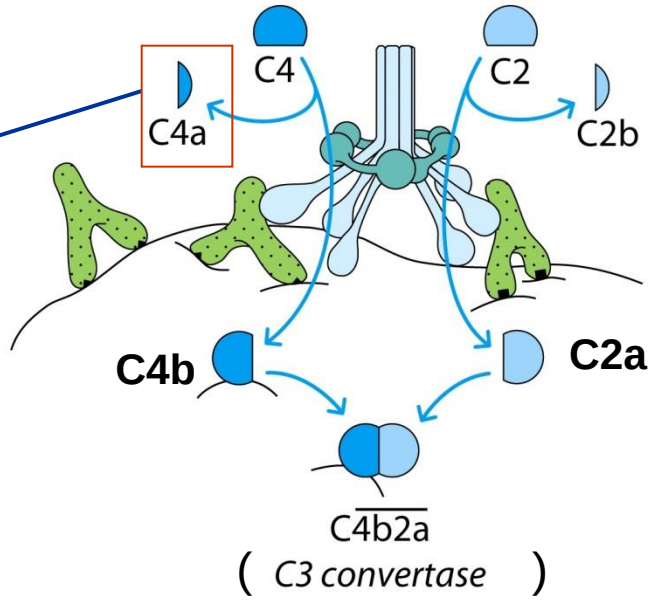
- **C1q** portion of C1 attaches to the Fc portion of an **antibody**
- Only **IgG** and **IgM** can activate complement
- Once activated **C1s** is eventually cleaved which activates C4 and C2
- C4b & C2a come together to form the **C4b2a** which is the **C3 convertase**
- C3 convertase activates C3 to C3a and C3b

C1 hydrolyzes C4 into C4a and C4b,
and hydrolyze C2 into C2b and C2a

↓

C4b and C2a form C4b2a complex, also called C3 convertase,
referring to its role in converting the C3 into an active form.

an anaphylatoxin*,
or
a mediator of inflammation



* Anaphylaxis

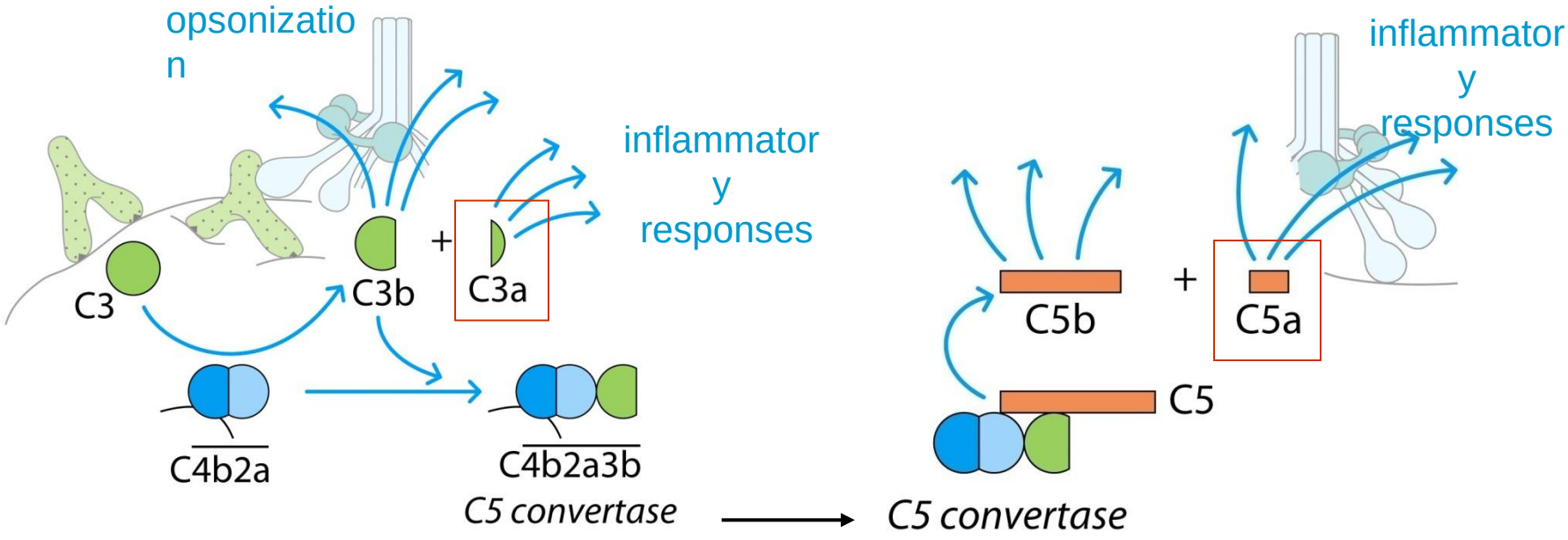
$\overline{C4b2a}$ (C3 convertase) hydrolyzes C3 into C3b and C3a

↓

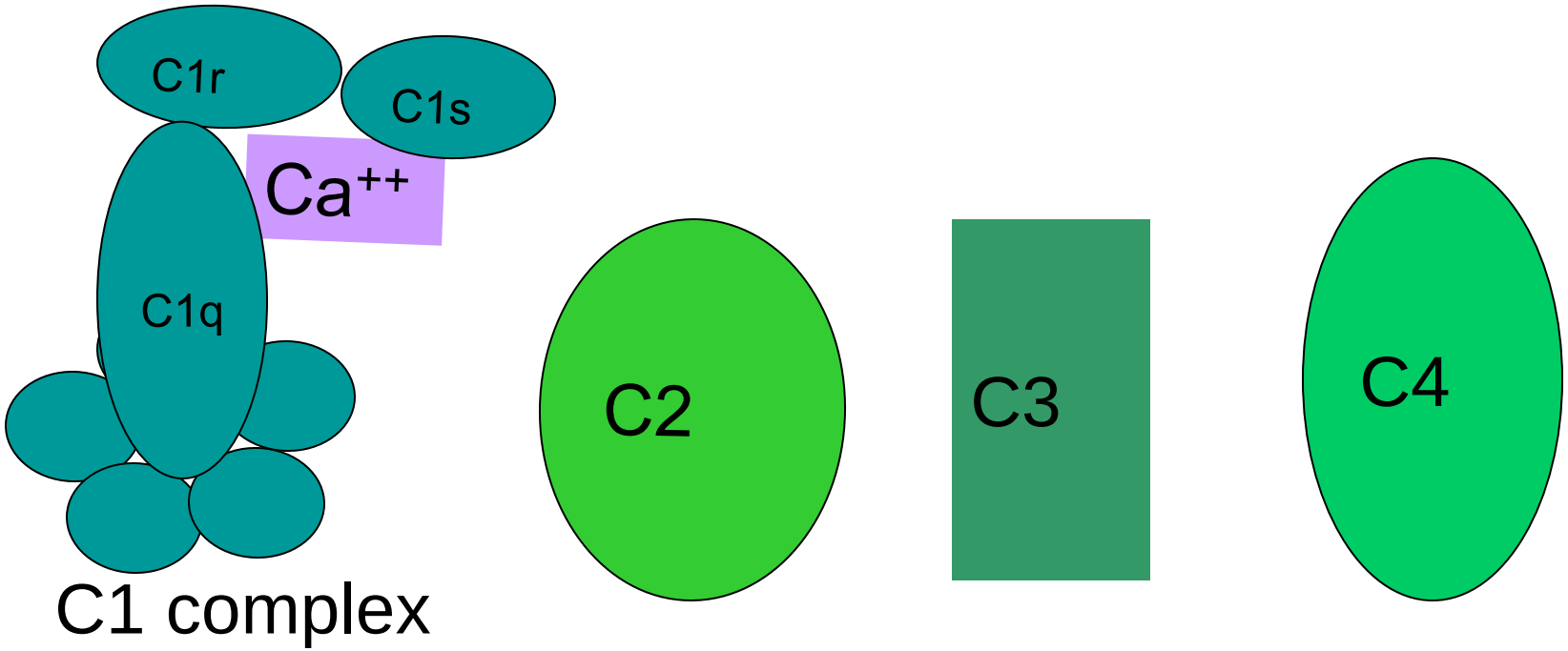
C3b binds to $\overline{C4b2a}$ and form $\overline{C4b2a3b}$ (C5 convertase)

↓

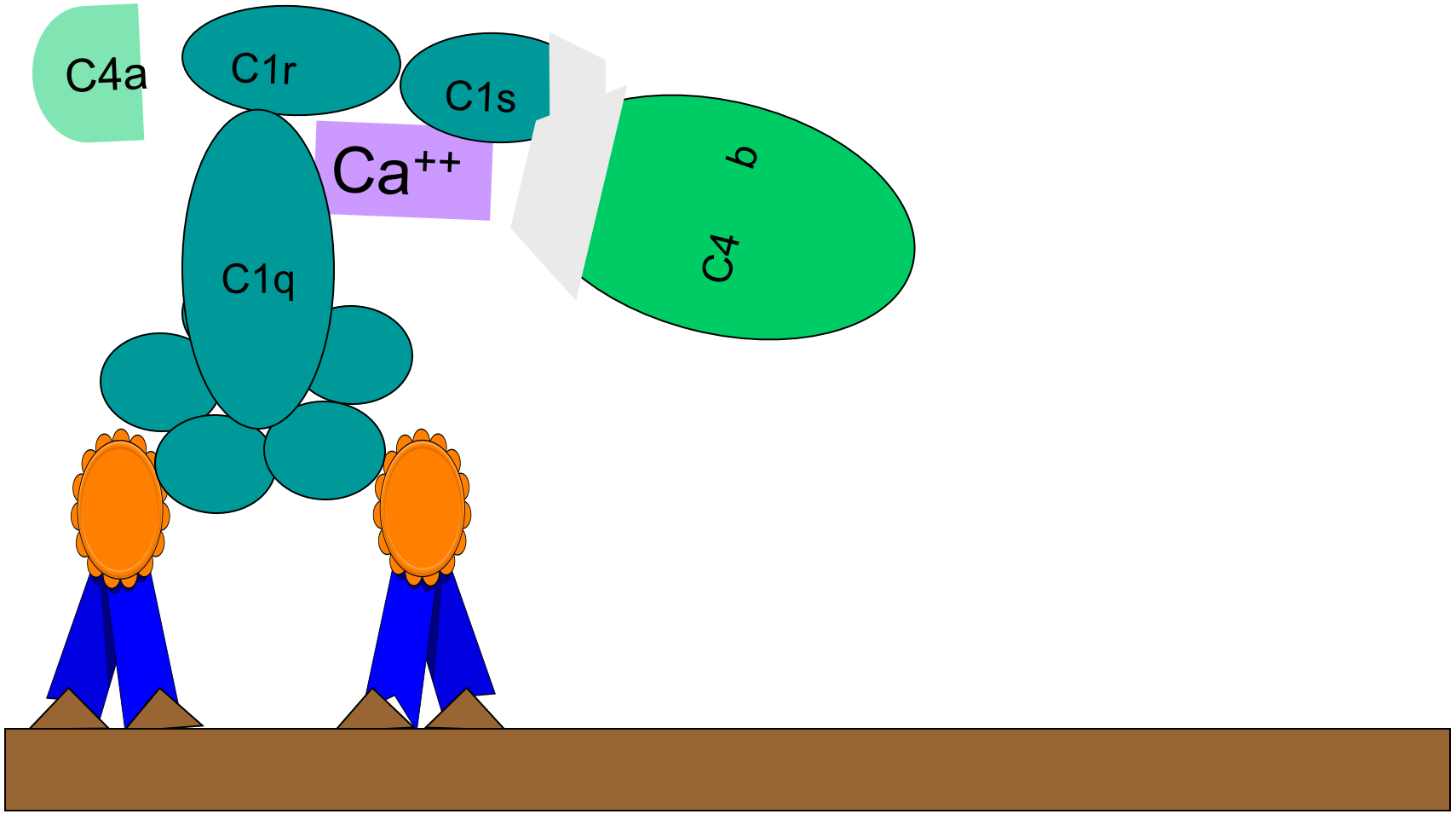
$\overline{C4b2a3b}$ cleaves C5 into C5b and C5a



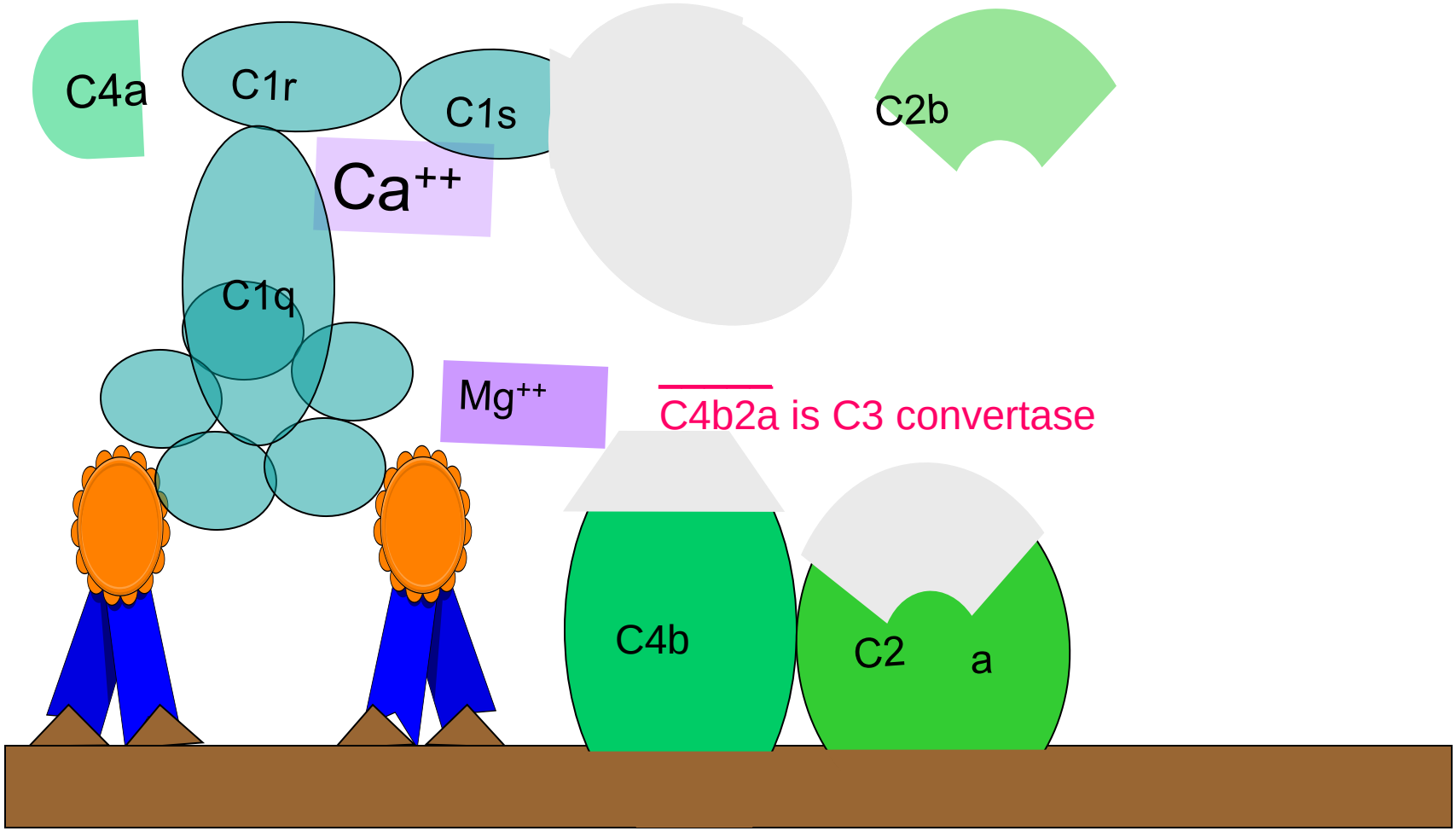
Components of the Classical Pathway



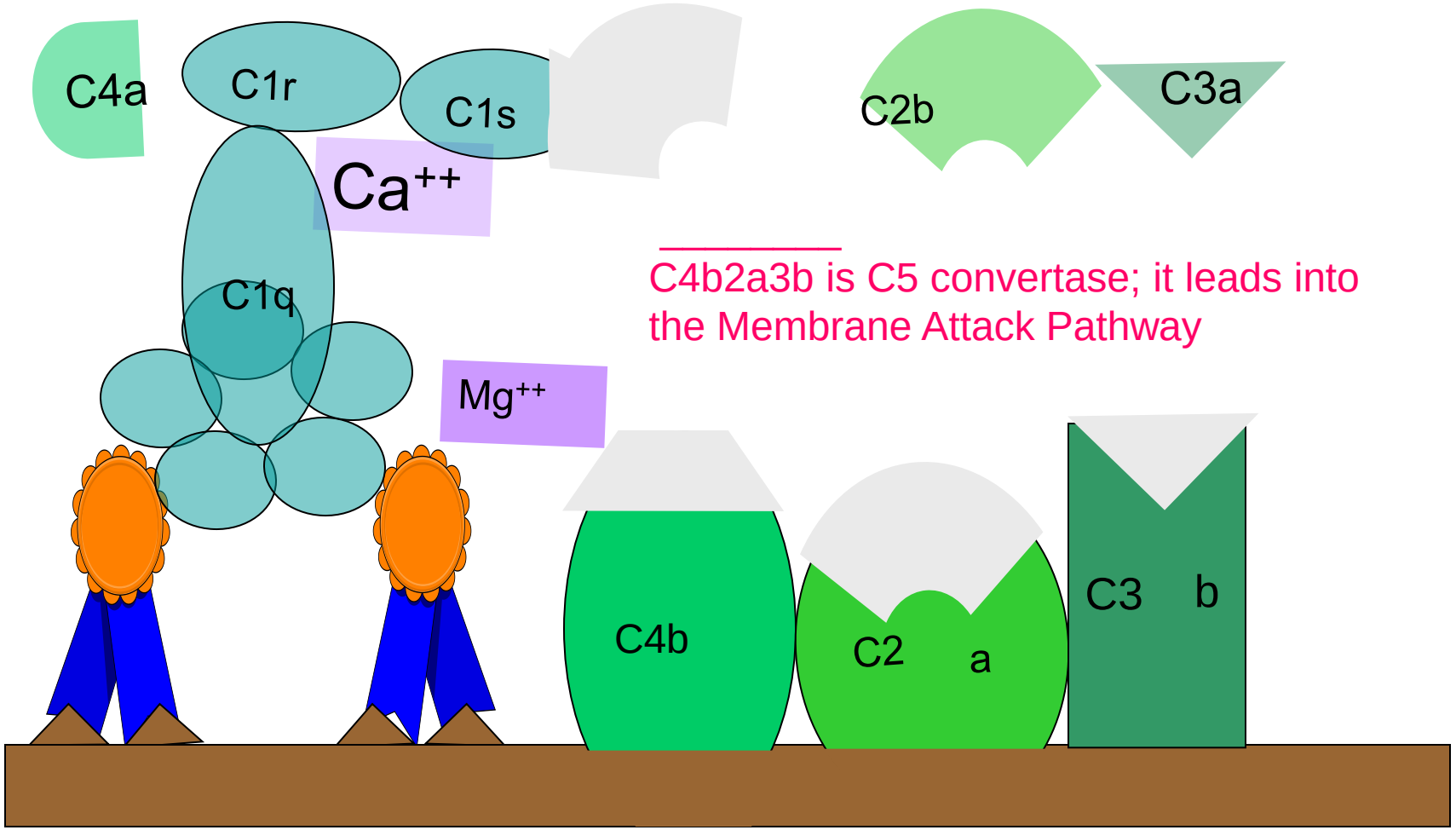
Classical Pathway
Generation of C3-convertase



Classical Pathway
Generation of C3-convertase



Classical Pathway
Generation of C5-convertase

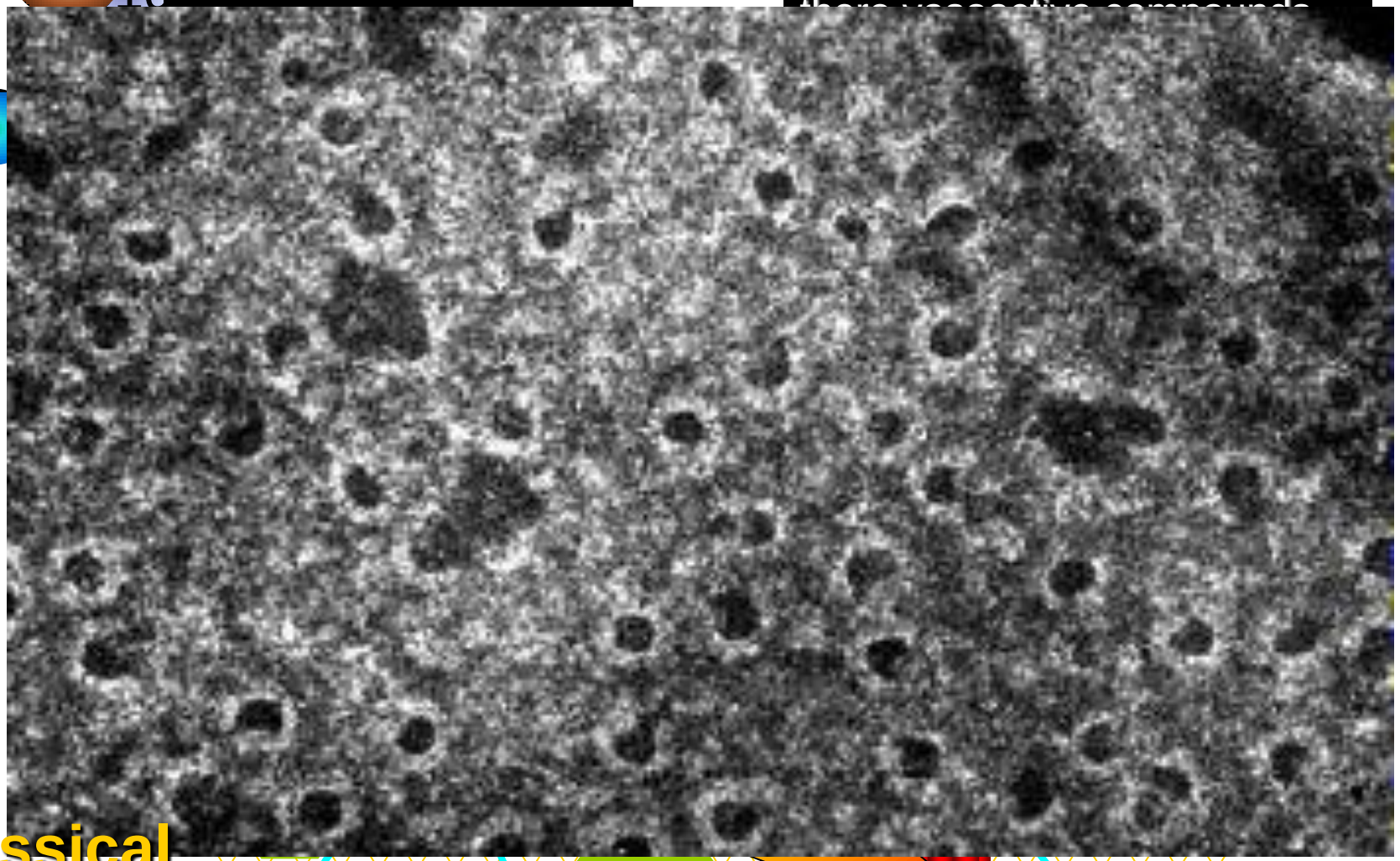


C4b2a3b is C5 convertase; it leads into the Membrane Attack Pathway

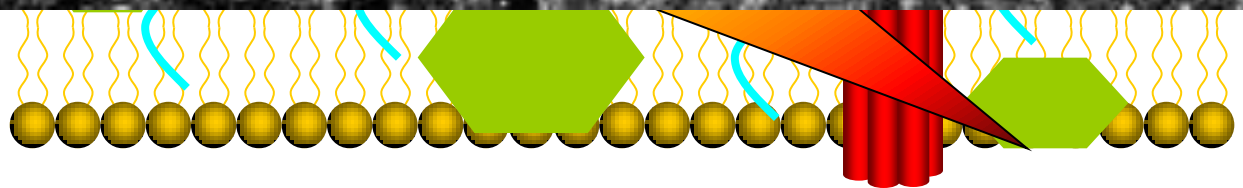
C5a is a:

1. Potent anaphylatoxin

C3a binds to receptors on **basophils** and **mast cells** triggering them to release



Classical Pathway



The Lectin Pathway

Lectin: proteins that bind to a carbohydrate

MBL (mannose-binding lectin):

(structurally similar to C1)

MASP-1 & MASP-2: - (mannose-binding associated serine protease 1 & mannose-binding associcted serine protease 2)

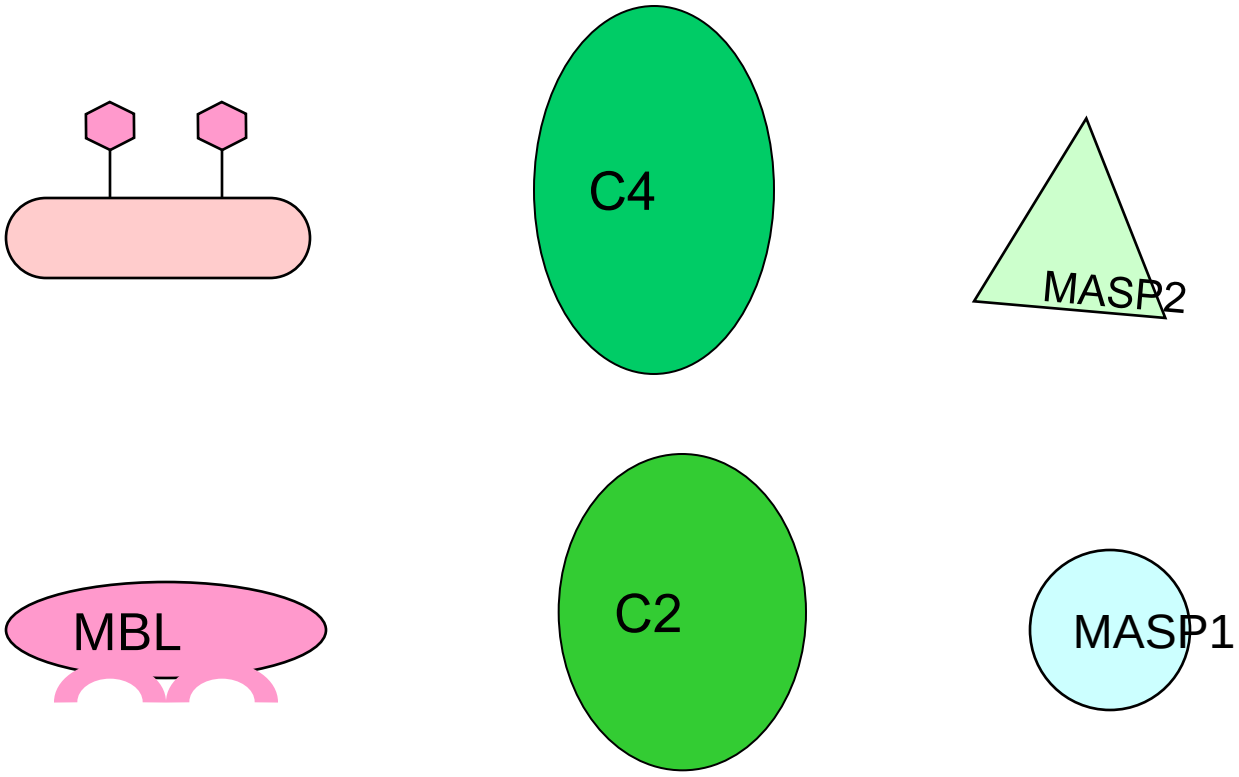
- MBL is induced during inflammatory responses.

- After MBL binds to the surface of a microbe, MBL-associated serine proteases-1 (MASP-1) and MASP-2, bind to MBL.

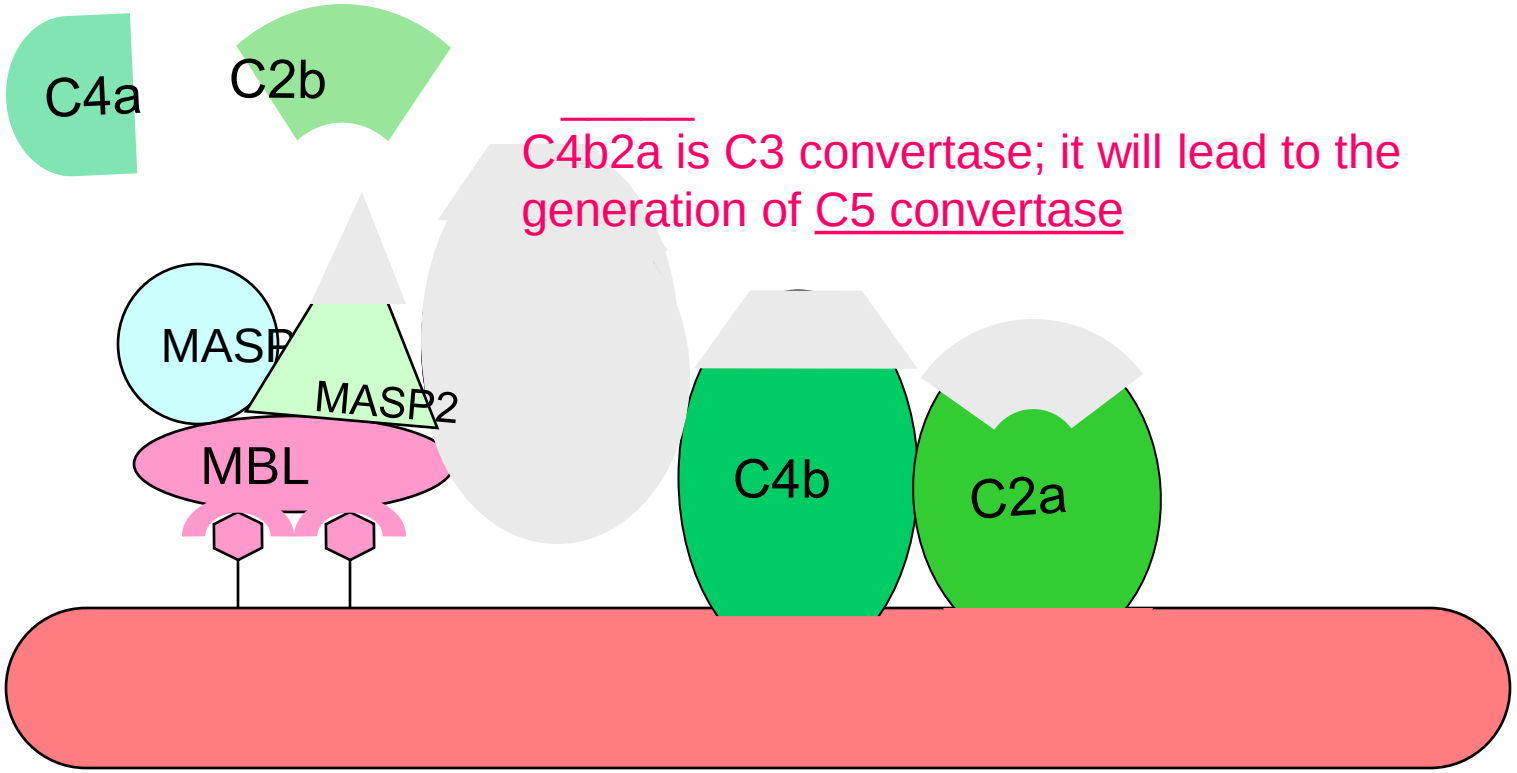
- The MBL-MASP-1/2 complex mimics the activity of C1, and causes cleavage and activation of C4 and C2.

- Thus, the lectin pathway is Ab-independent. It is an important innate defense mechanism comparable to the alternative pathway, but utilizing the elements of the classical pathway, except for the C1 proteins.

Components of mannose-binding lectin pathway



Mannose-binding lectin pathway



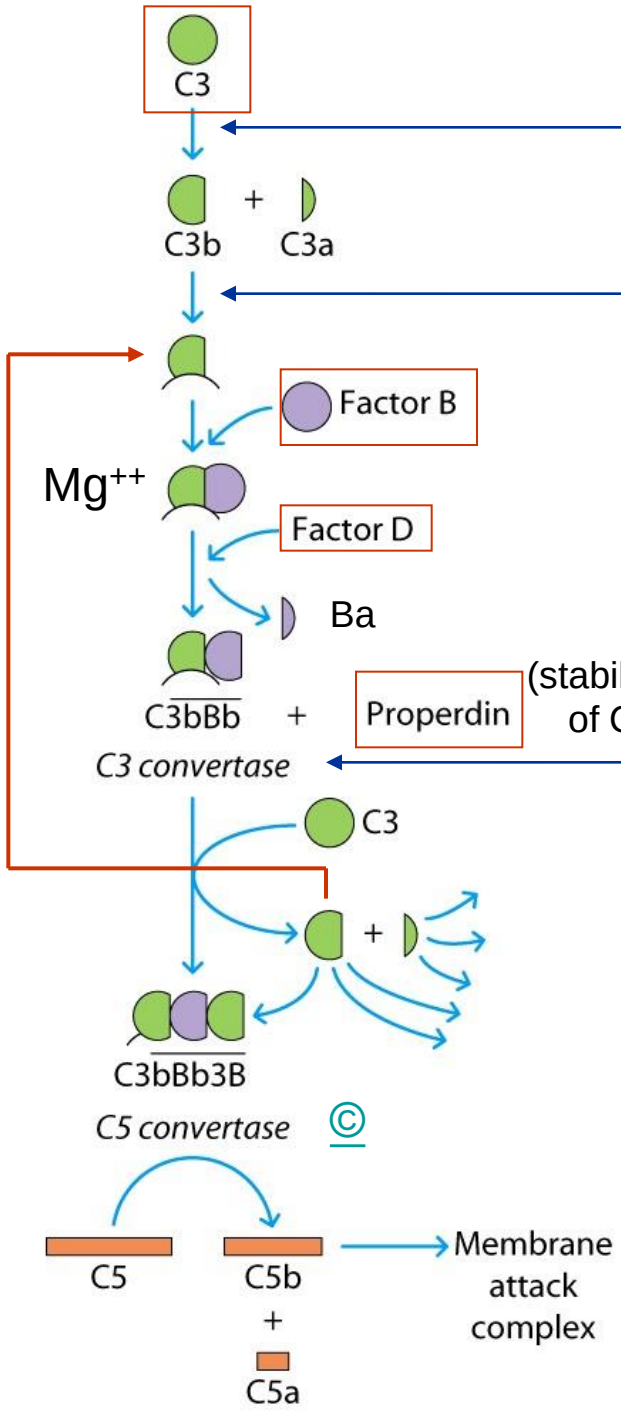
The Alternative Pathway

The activation of alternative pathway doesn’tneed Ab; thus, it is a component of the innate immune system.

- It is initiated by bacterial cell wall.

- C1, C4 and C2 are not involved in the alternative pathway.

- Four serum proteins, C3, factor B, factor D, and properdin, are involved in this pathway.



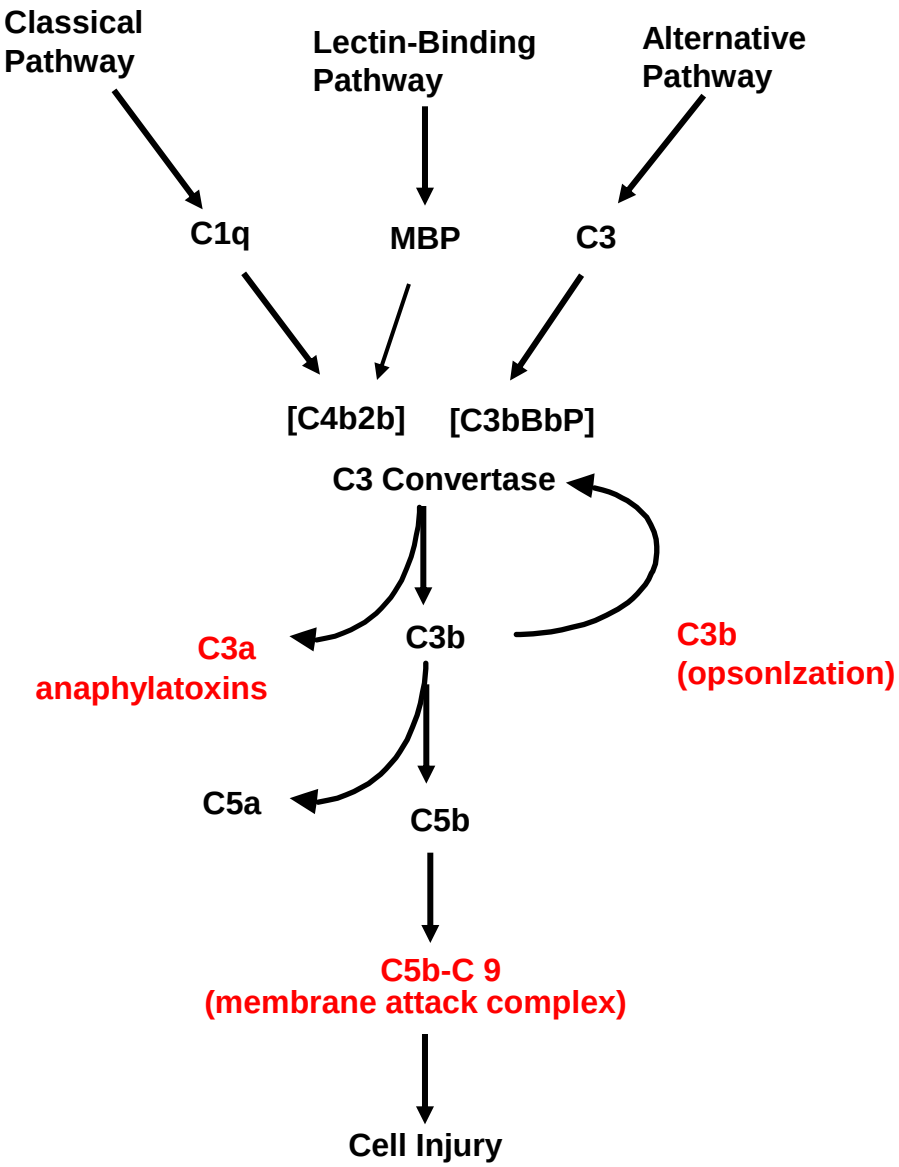
plasma C3, can be hydrolyzed spontaneously into C3a and C3b.

C3b attaches to the surface of bacteria, yeasts, viruses (or even host's own cells).

(stabilization of C3bBb)

analogous to the C4b2b complex in the classical pathway

SUMMARY OF COMPLEMENT ACTIVATION



Function of Complement

1. Cell lysis: The membrane-attack complex can lyse a broad spectrum of cells: G(-) bacteria, parasite, viruses, erythrocyte and nucleated cells (tumor cells).

2. Inflammatory response: C3a, C4a, C5a (called anaphylatoxin) bind to complement receptors on mast cells and basophils and induce degranulation with release of histamin and other mediators.

3. Opsonization: C3b is the major opsonin of the complement system

4. Clearance of immune complexes

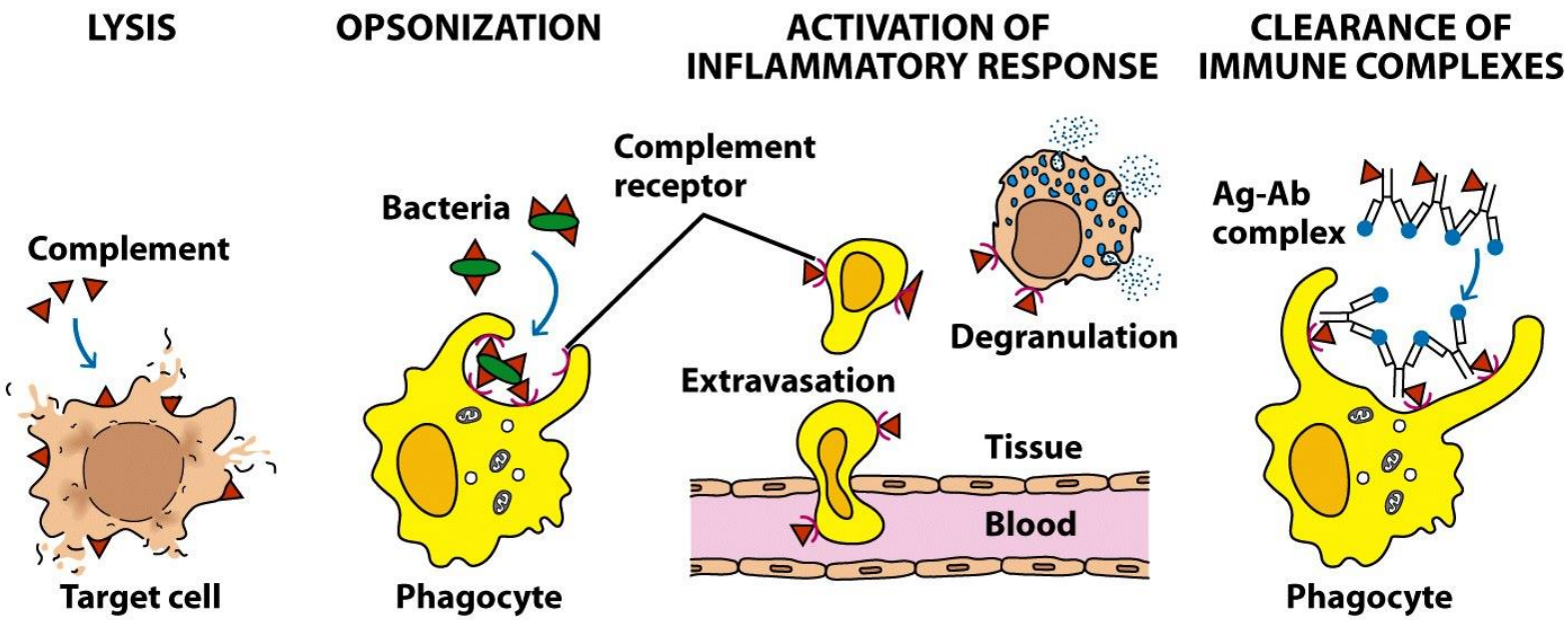


Figure 7-1
Kuby IMMUNOLOGY, Sixth Edition

Regulation of Complement

1. **C1 inhibitor (C1INA): plasma protein**

Inhibit activation of classical pathway

2. - Factor I: Plasma proteins

- decay accelerating factor (DAF): Cell membrane proteins

- membrane co-factor protein (MCP): Cell membrane proteins

Inhibit C3 convertase

3. serum carboxypeptidase N (SCPN)

Inactivate anaphylatoxins: cleave C3a and C5a

4. Protectin (CD59): cell associated protein

Inhibit MAC

Complement Deficiencies:

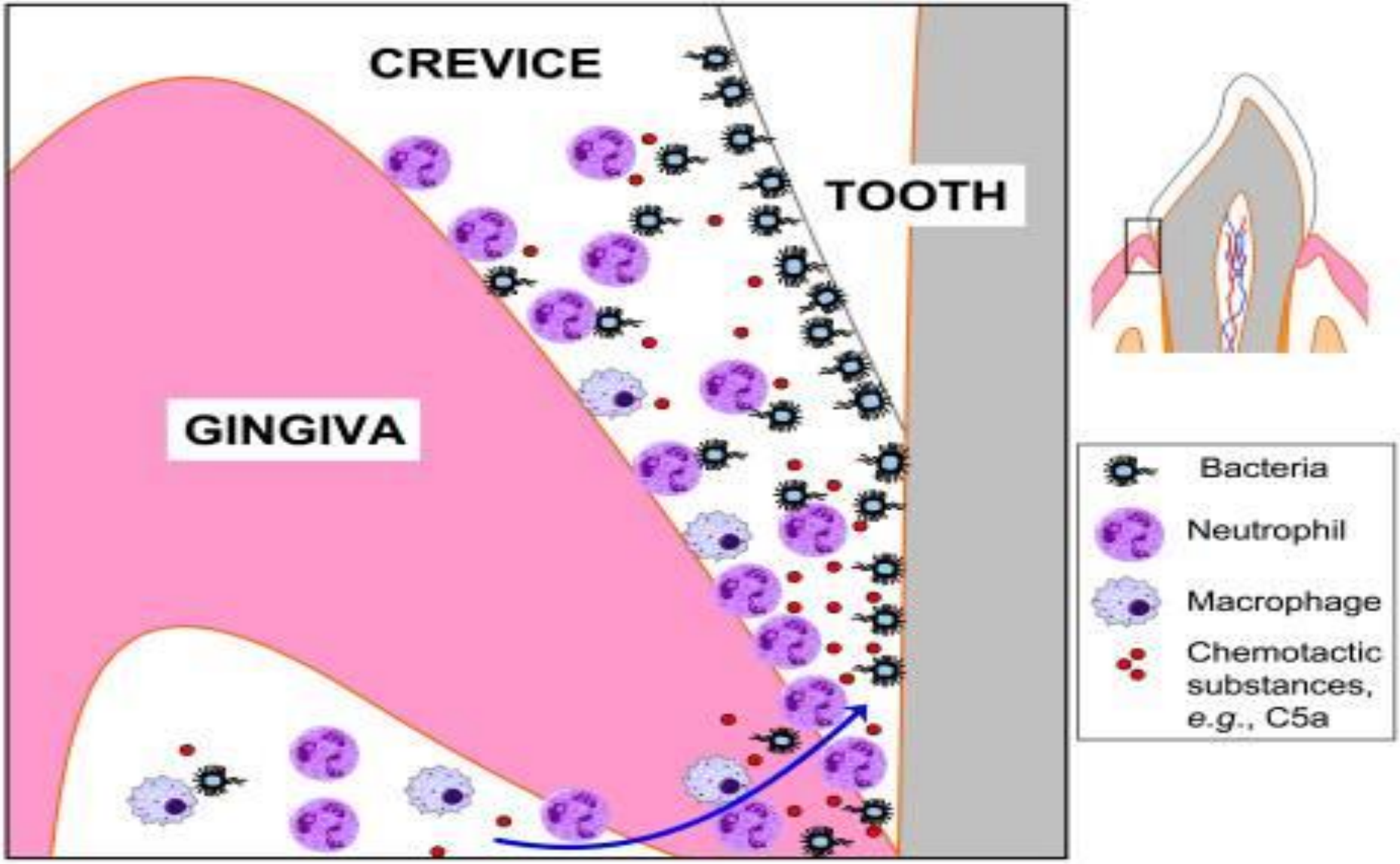
- early components deficiency: auto-immune disease
- middle and late components deficiency : pyogenic bacterial and nisseria infections
- most common congenital deficiency: C2 component
- C1inhibitor deficiency: hereditary angioedema
- DAF deficiency: hemoglobinuria

Complement and Oral Diseases

A number of clinical and histological observations suggest complement involvement in periodontitis.

- Activated complement fragments are abundantly found in the GCF of periodontitis patients, whereas absent in GCF of healthy individuals.
- The C3 gene was down-regulated following periodontal therapy

- Local complement activation may promote periodontal inflammation via C5a-induced vasodilation, increased vascular permeability and flow of inflammatory exudate, and chemotactic recruitment of inflammatory cells, especially neutrophils.


CREVICE
TOOTH
GINGIVA
Bacteria
Neutrophil
Macrophage
Chemotactic substances, e.g., C5a