THE COMPLEMENT SYSTEM

Dr. Tola FARAJ

MA 210 Immunology - Spring term

Lecture #03 2025

Course topics and content [14 weeks program], **Spring term**

Theoretical Sessions

Immune Theory topics [Spring Term]

1. What is an **Antibody**? Classes, Structure, and Functions of Immunoglobulin(s)
2. **Opsonization**
3. The **Complement** System
4. Overview of Immune Responses to **Microbes**
5. Immunological **Tolerance** [T and B Lymphocyte Tolerance]
6. Tolerance to **Commensal Microbes** in the Intestines and Skin
7. Tolerance to **Fetal Antigens**
8. Midterm Exam
9. **Autoimmunity**
10. Immune Responses Against **Tumors and Transplants**
11. **Hypersensitivity**
12. Congenital and Acquired **Immunodeficiencies**
13. Final Exam
14. Final Exam

Curriculum

Spring term

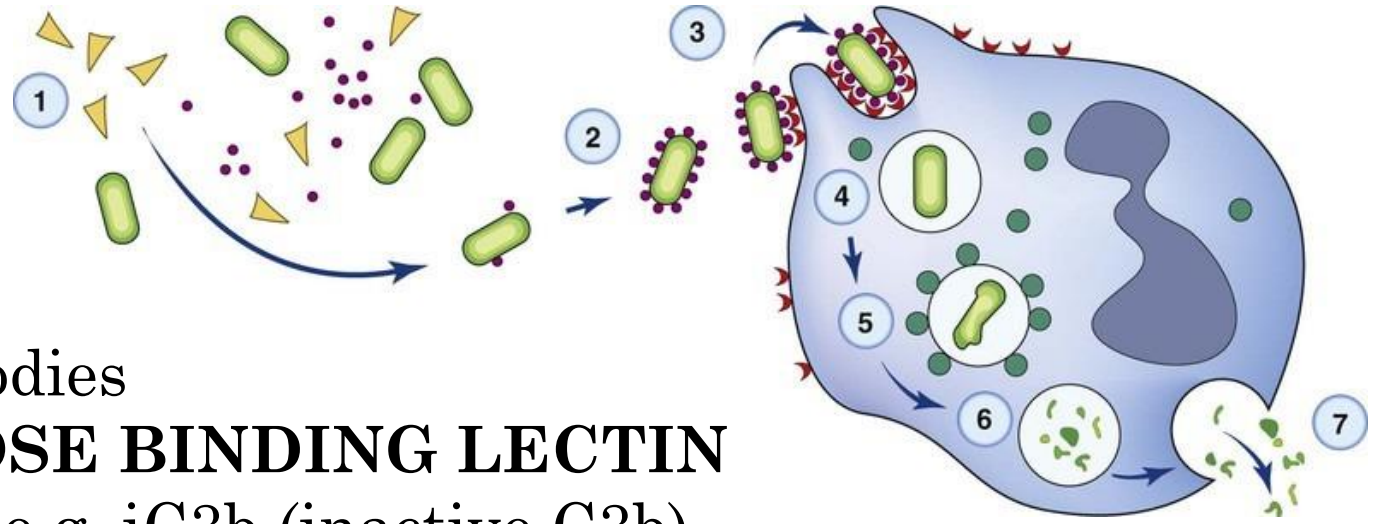
Dr. Tola FARAJ

Outline

- What is the Opsonization process?
- What are the major types of Opsonins?

- What is the Complement System? And what are the main functions of it?
- Pathways of the Complement System.
- What is the function of c3a, c4a, and c5a?

- **OPSONIZATION** The process whereby Opsonins make an invading microorganism more susceptible to phagocytosis.
- **OPSONIN** An *antibody* or *complement* protein that enhances phagocytosis by marking an antigen.

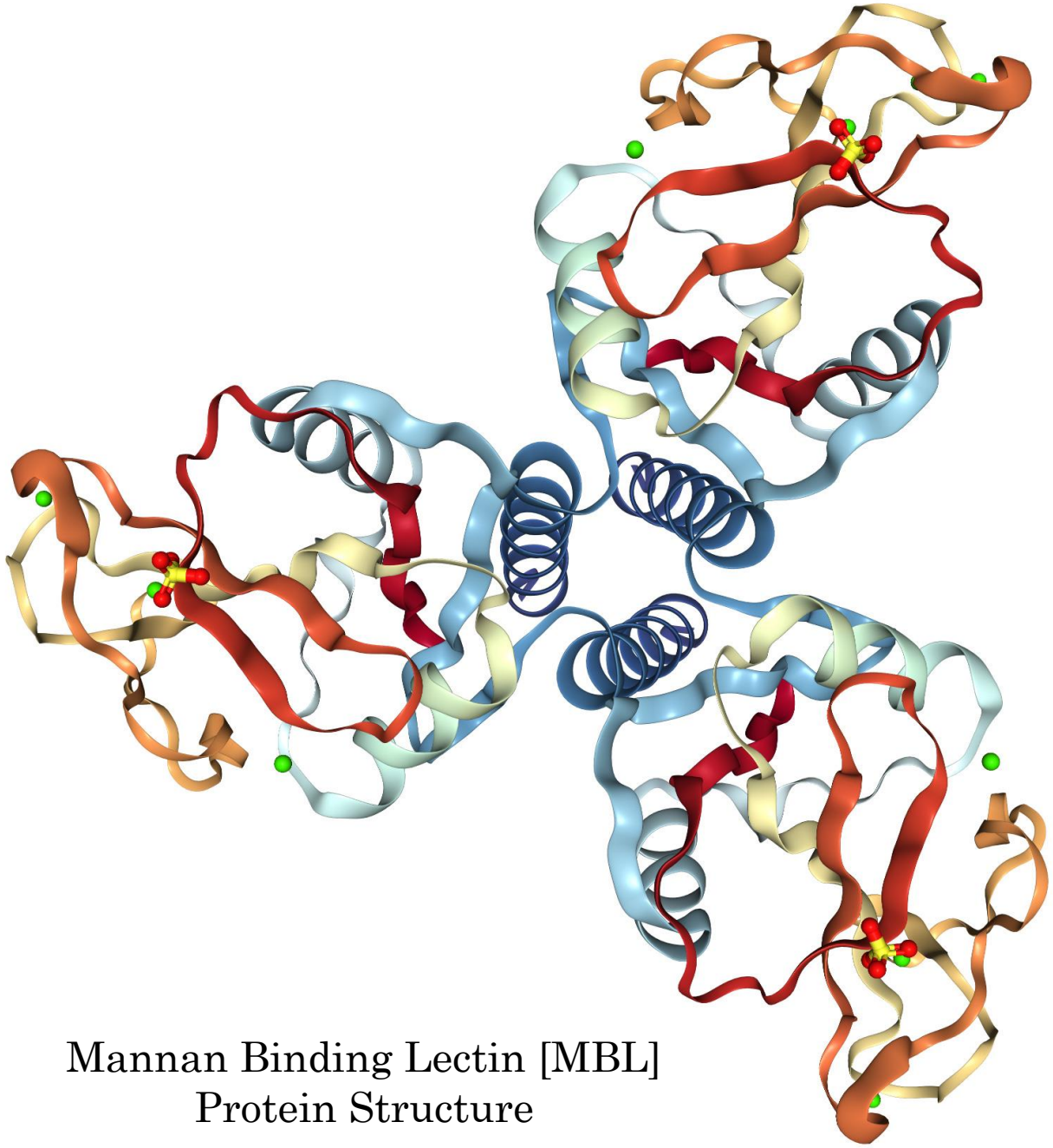


- Major opsonins are:

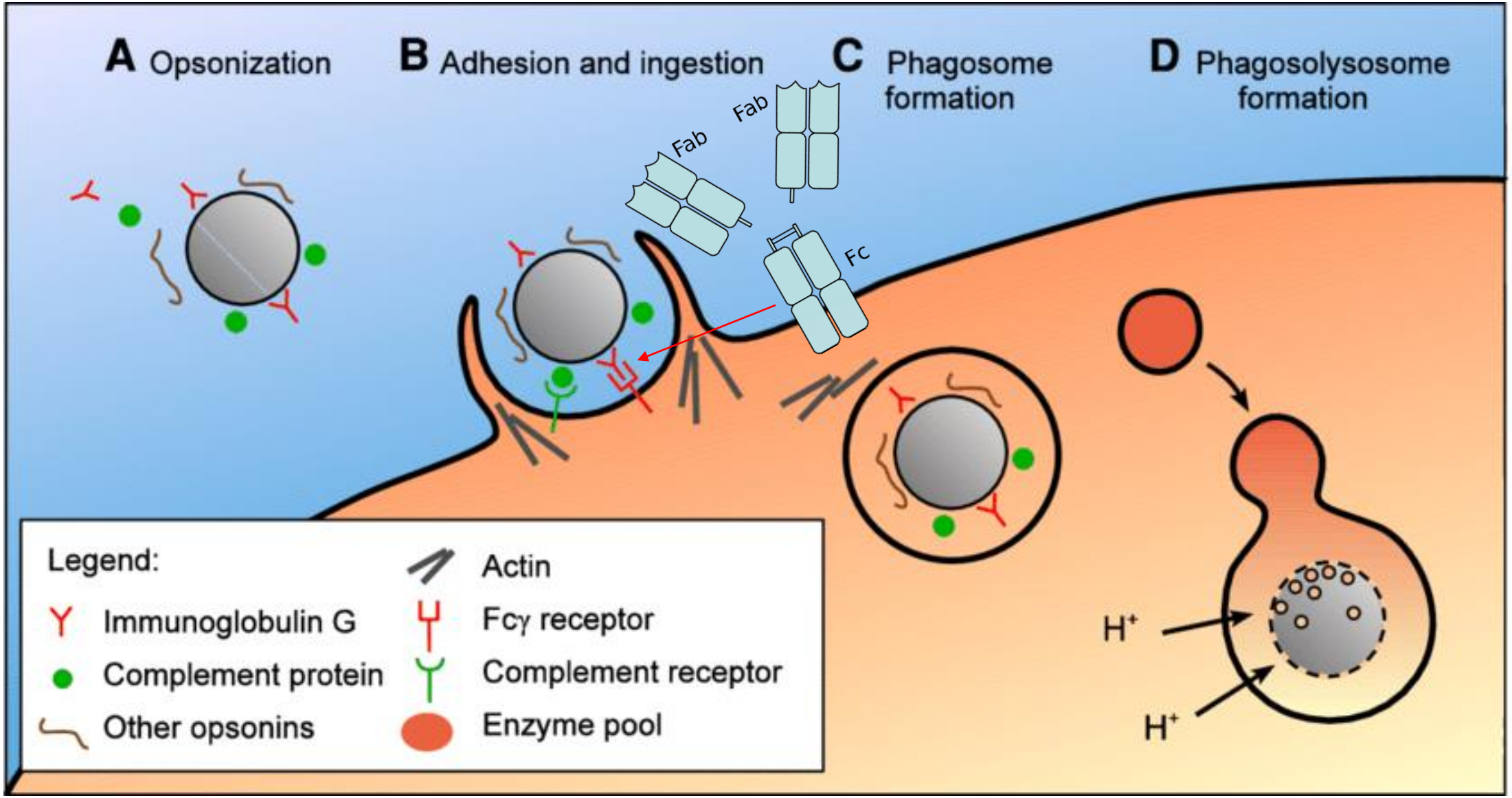
1. **Immunoglobulin** (Ig)G antibodies
2. Certain plasma lectin **MANNOSE BINDING LECTIN**
3. **C3b** and it's cleavage products e.g. iC3b (inactive C3b)

- **Opson** in ancient Greece referred to the **delicious side-dish** of any meal.

- Mannose-binding lectin (MBL) is an important component of the innate immune system. MBL is primarily produced by the liver, circulates throughout the body, and is able to recognize a wide array of common pathogens.



Mannan Binding Lectin [MBL] Protein Structure

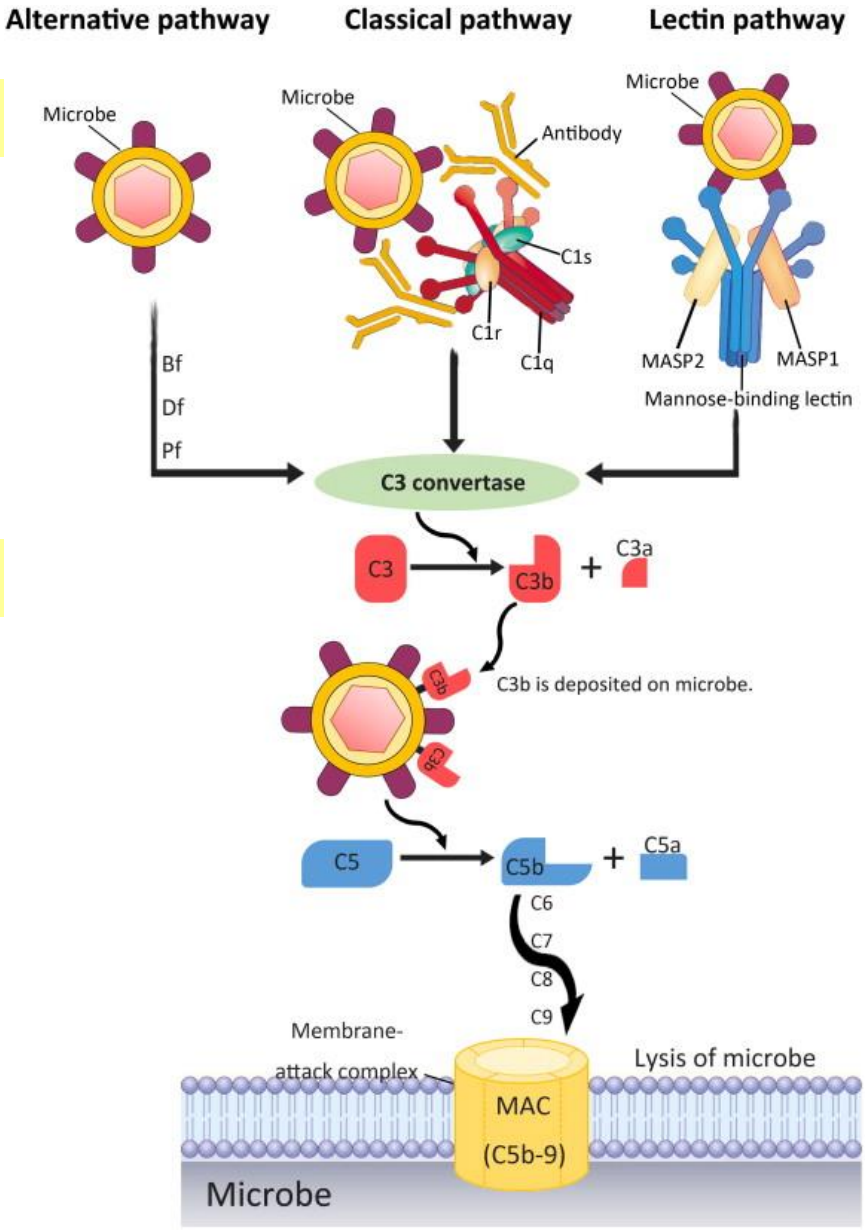

A Opsonization
B Adhesion and ingestion
C Phagosome formation
D Phagosolysosome formation
Fab
Fab
Fc
H+
H+
Legend:
Immunoglobulin G
Complement protein
Other opsonins
Actin
Fcγ receptor
Complement receptor
Enzyme pool

Complement System

- Complement is component of normal plasma that causes the **[1] opsonization** and **[2] killing of bacteria**.
- The complement system refers to a series of proteins, circulating in the blood and tissue fluids.
- Most of the proteins are normally **inactive**, but in response to the recognition of **molecular components of microorganisms** they become sequentially **activated** in an **enzyme** cascade – the activation of one protein enzymatically cleaves and activates the next protein in the cascade.

- **Complement** is a system of plasma proteins that can be activated **directly** by pathogens or **indirectly** by pathogen-bound antibody, leading to a cascade of reactions that occurs on the surface of pathogens and generates active components with various effector functions.

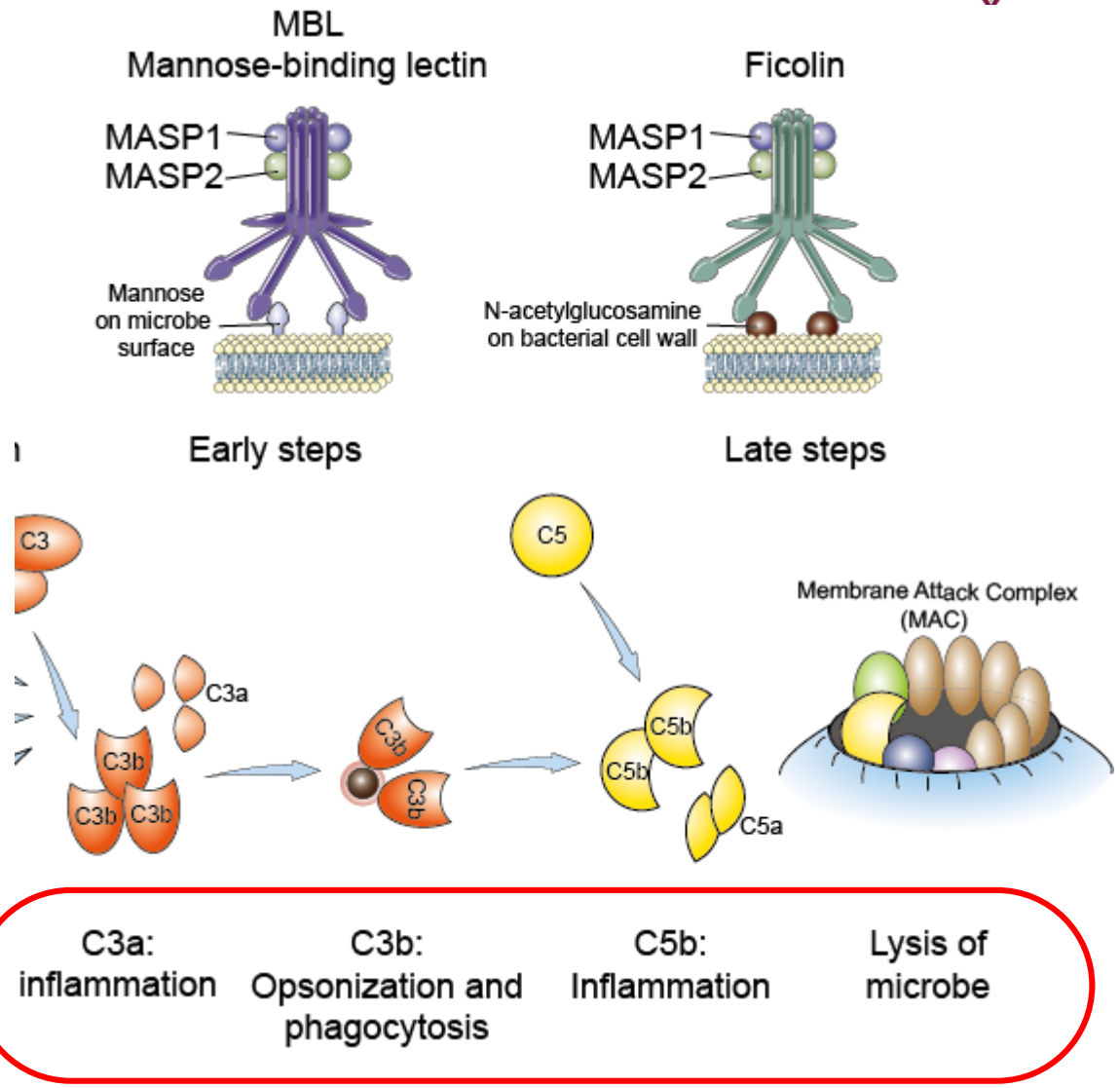
- The complement system is covered by **nine central components** of the cascade (C1 to C9), multiple activation products (such as C3a and C3b), regulators and inhibitors (e.g. Factor H and C4BP), **proteases** and newly assembled enzymes (e.g. C4b2a and Factor B), or effector molecule receptors (such as C3aR and C5aR).



- The **main function** of complement proteins is to:

[1]aid in the destruction of pathogens by piercing their outer membranes (cell lysis) or;

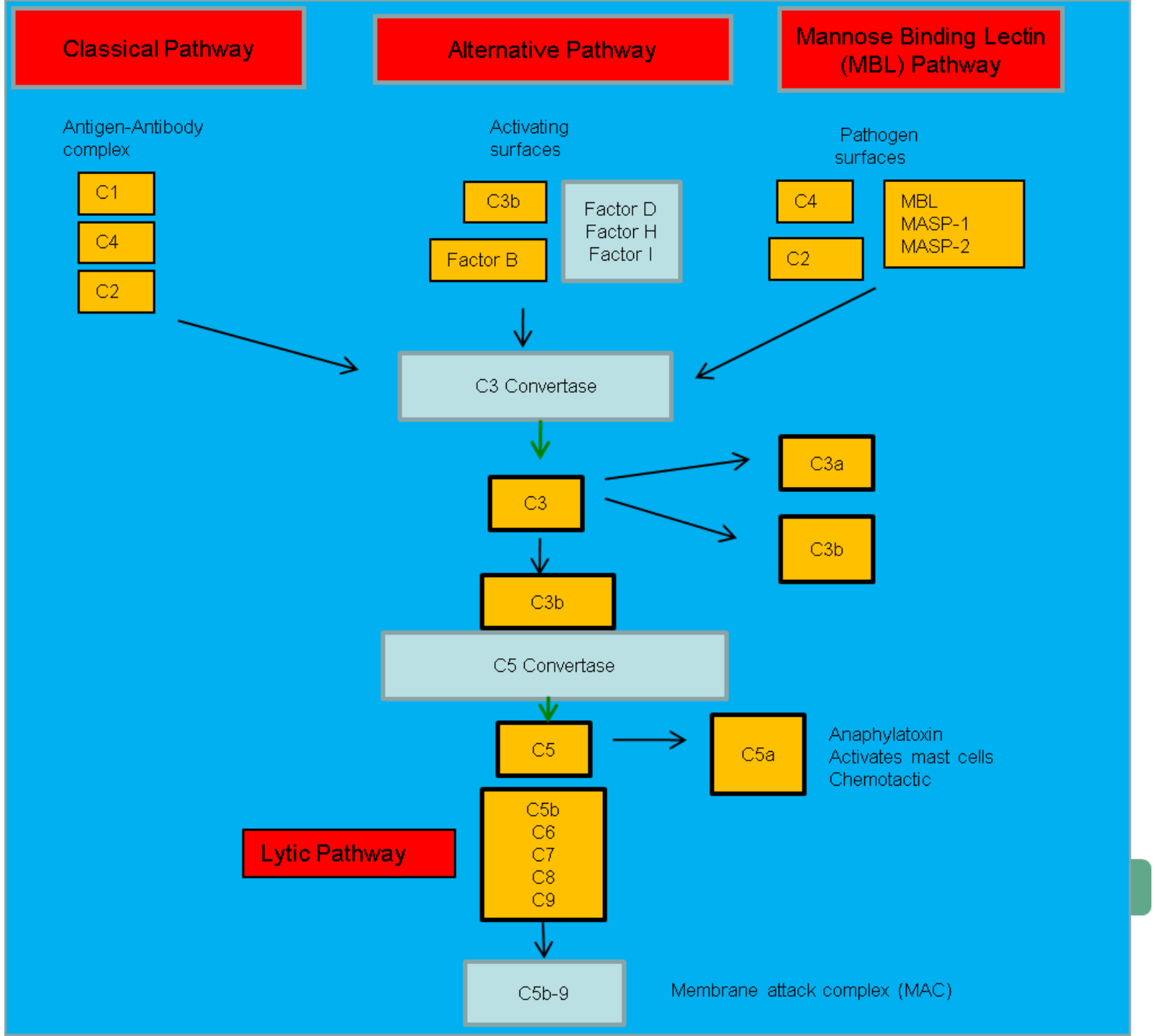
[2]by making them more attractive to phagocytic cells such as macrophages (a process known as opsonization).



Complement System

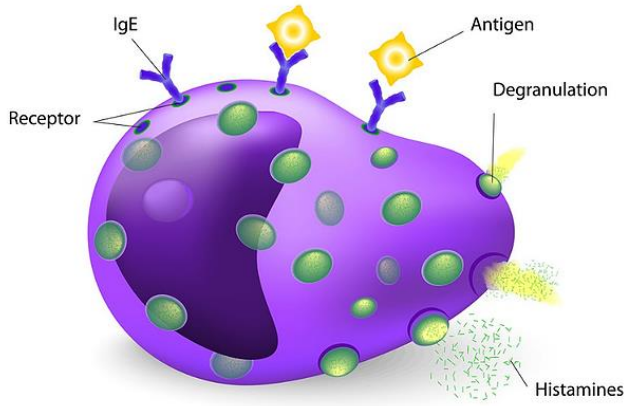
- Complement can be **activated** via **three different pathways**, which can each cause the activation of **C3**, cleaving it into a large fragment, C3b, that acts as an **opsonin**, and a small fragment C3a that promotes **inflammation**.
- Activated C3 can trigger the lytic pathway, which can **damage the plasma membranes of cells and some bacteria**.
- C5a, produced by this process, **attracts macrophages and neutrophils**.

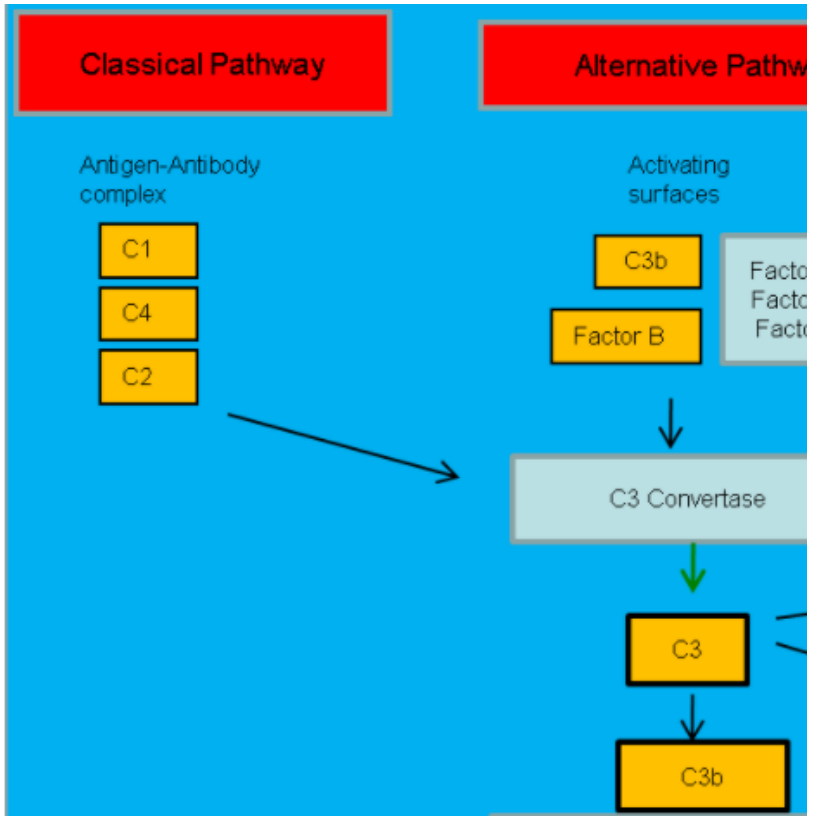
Complement System



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.



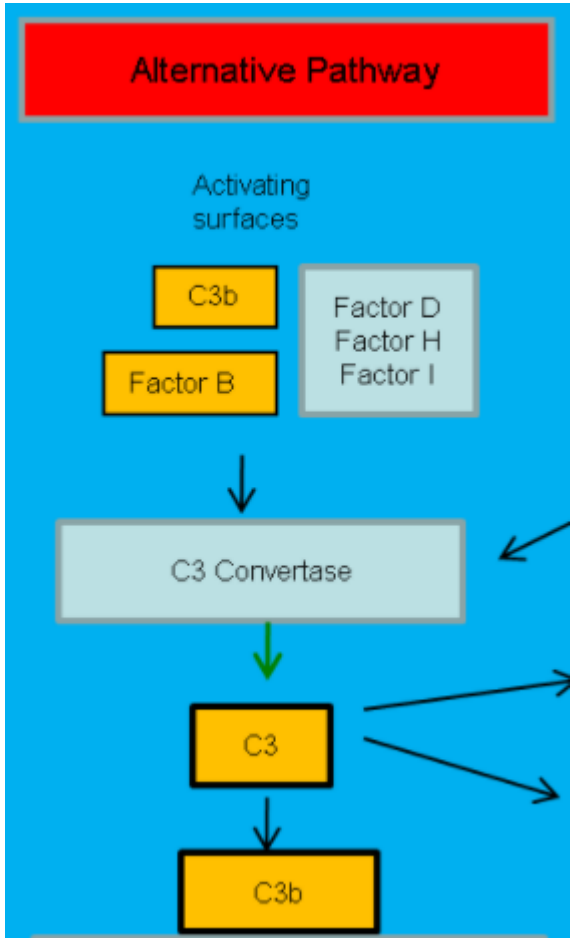


- Histamine increases the vasodilatation, and also increases the vascular permeability, involved in the inflammatory reaction.

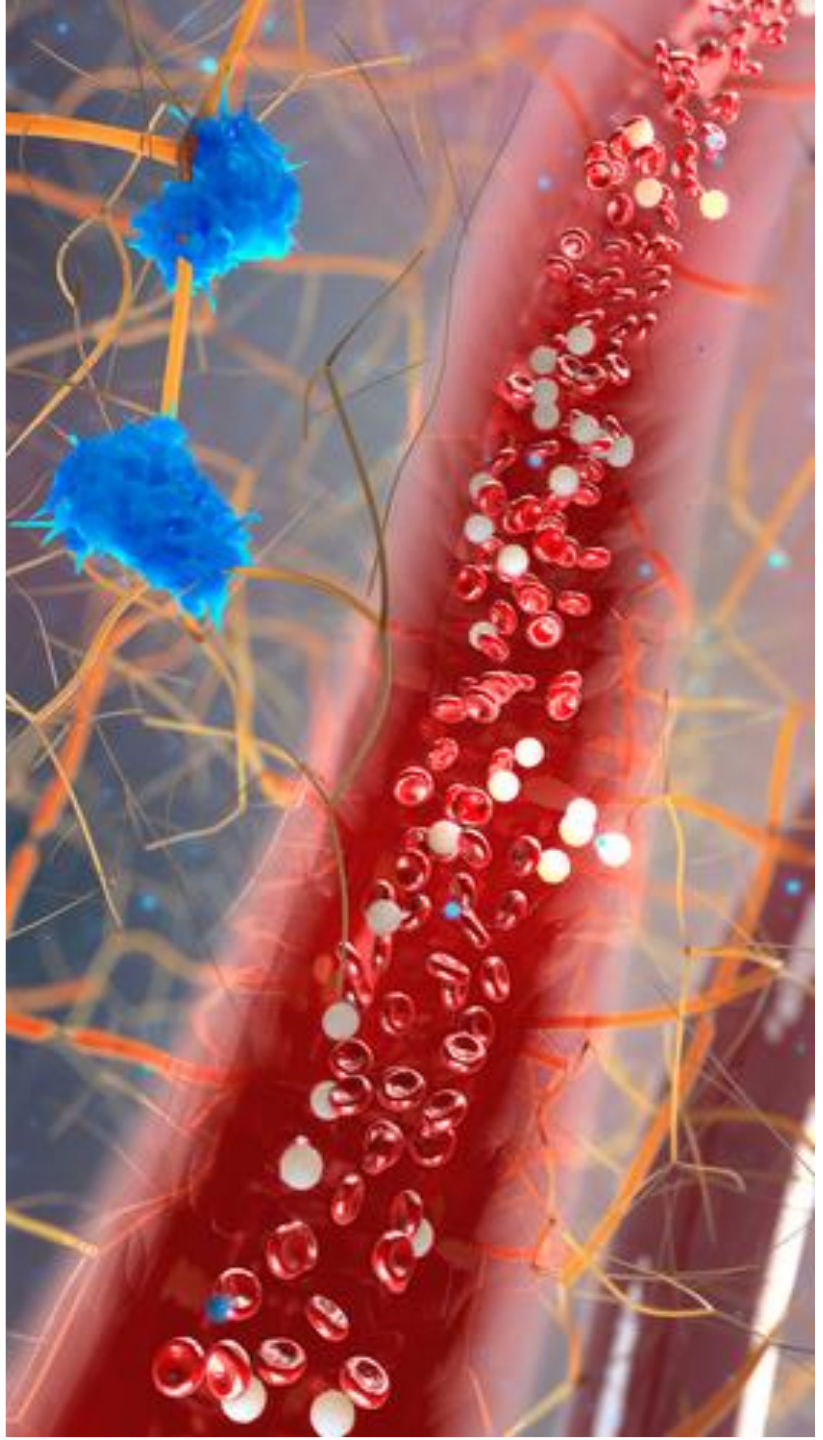
Alternative Pathway

This 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.

The alternative pathway is one of three complement pathways that opsonize and kill pathogens. The pathway is **triggered** when the **C3b protein directly binds a microbe**.



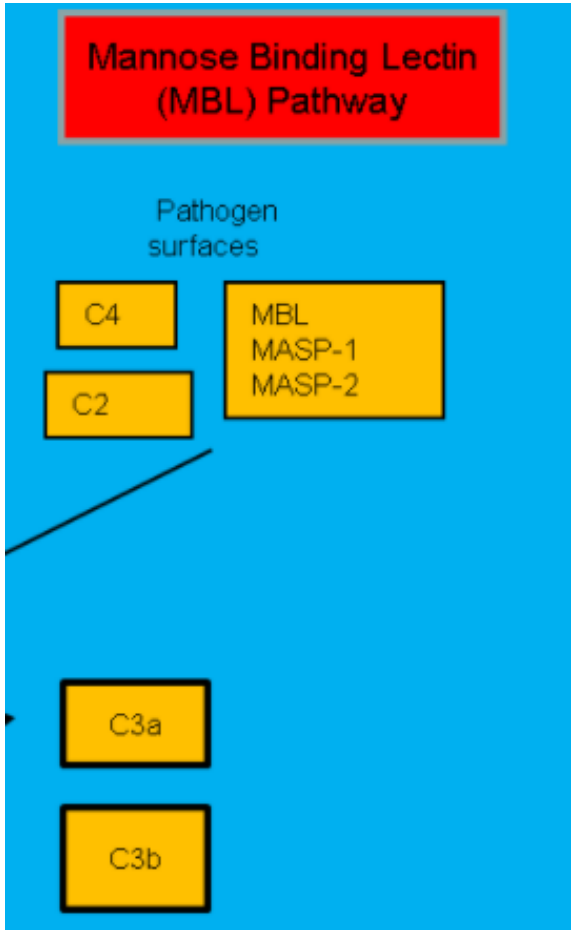
- The amplification loop is the balance between two competing cycles both acting on C3b: the C3 **feedback** cycle which enhances amplification and the C3 **breakdown** cycle which downregulates it.



Mannose-binding Lectin Pathway

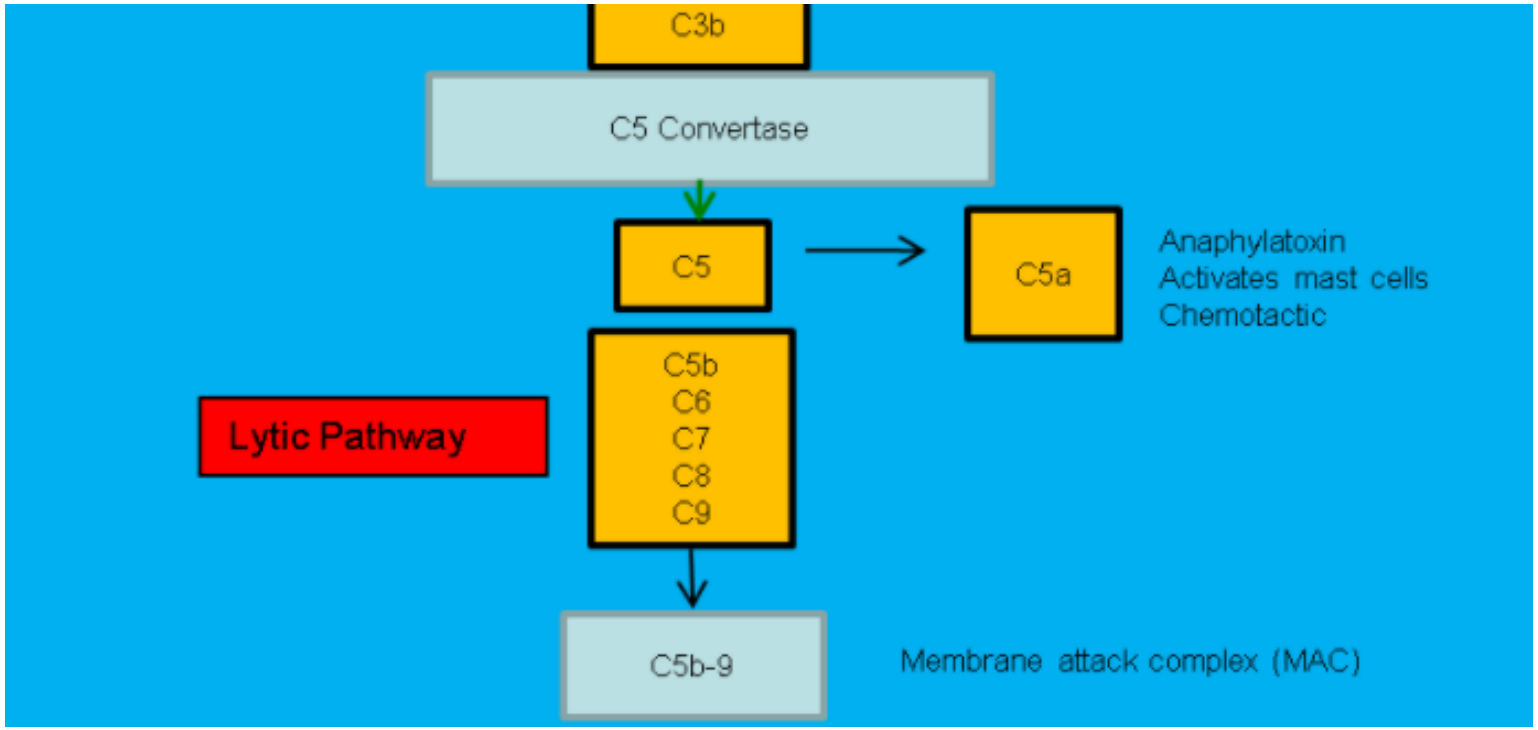
This pathway is activated by the binding of **mannose-binding lectin** (**MBL**) to mannose residues on the pathogen surface. This in turn activates the MBL-associated serine proteases, **MASP-1** and **MASP-2**, which activate **C4** and **C2**, to form the C3 convertase, **C4b2a**.

- Mannose-binding lectin plays an important role in the body's immune response by **attaching to foreign invaders** such as bacteria, viruses, or yeast and turning on (activating) the complement system.



Lytic Pathway

This pathway is initiated by the splitting of **C5**, and attachment of **C5b** to a target. **C6, C7, C8** and **C9** unite with C5b, and this **membrane-attack complex** (**MAC**), when inserted into the outer membrane of some bacteria, can contribute to their death by lysis.



What is the function of c3a, c4a, and c5a?

C3a, C4a, and C5a trigger the degranulation of mast cells and basophils, which release the vasoactive amines that cause the **increased vascular permeability** and smooth muscle contraction characteristic of **inflammation (Anaphylatoxins)**.

Thank You!