Innate

Immunity

Components

✔ Anatomical and chemical barriers

✔ **Cell associated Pattern Recognition Receptors**

- Toll-Like Receptors (TLRs)
- NOD-Like Receptors (NLRs)
- RIG-I-Like Receptors (RLRs)
- STING-associated CDS

Cellular effectors of innate immunity

- Phagocytes
- ILCs and NK cells

Soluble effectors of innate immunity

- the complement system
- pentraxins
- collectins and ficollins

Effector system of innate immunity and humoral immunity (Bordet)

Identified by Jules Bordet in the 1890's

Immunized Sheep with *Vibrio cholerae*

Mixed antiserum with *Vibrio cholerae* and observed that bacteria were lysed

Heating at 56°C eliminated lysis

Could restore lysis activity to heated serum by adding non-immune serum

A heat-sensitive activity that "completes" or <u>complements</u> the ability of antibody to neutralize bacteria

Soluble effectors of innate immunity

Present in the blood and extracellular fluids

Three main mechanism of action:

1 - **Opsonization** and induction of phagocytosis

2 - **Direct killing** of microbes

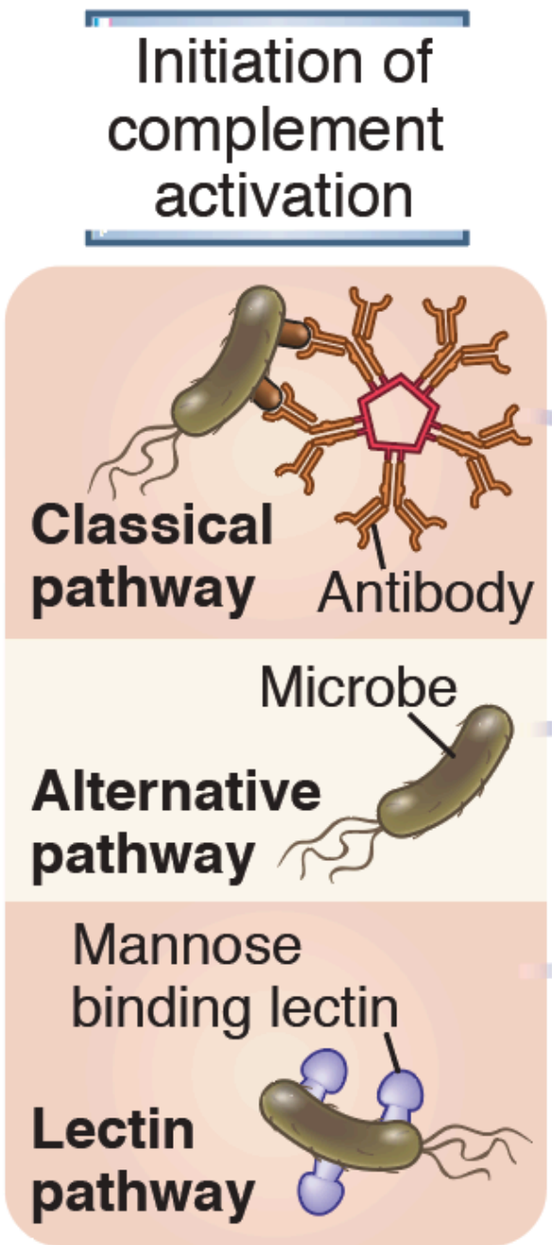
3 - Induction of **inflammatory response**

3 Stages of Complement Cascade

- Initiation – beginning the reaction
- Amplification – producing cascade effect
- Membrane attack – kills microorganisms

The complement system

Serum and surface proteins that interact in a regulated manner with other molecules of the immune system to generate products that function to eliminate microbes.



A group of plasma proteins, proteases (**C** or **F**-factor), inactive, but that can be activated by proteolysis

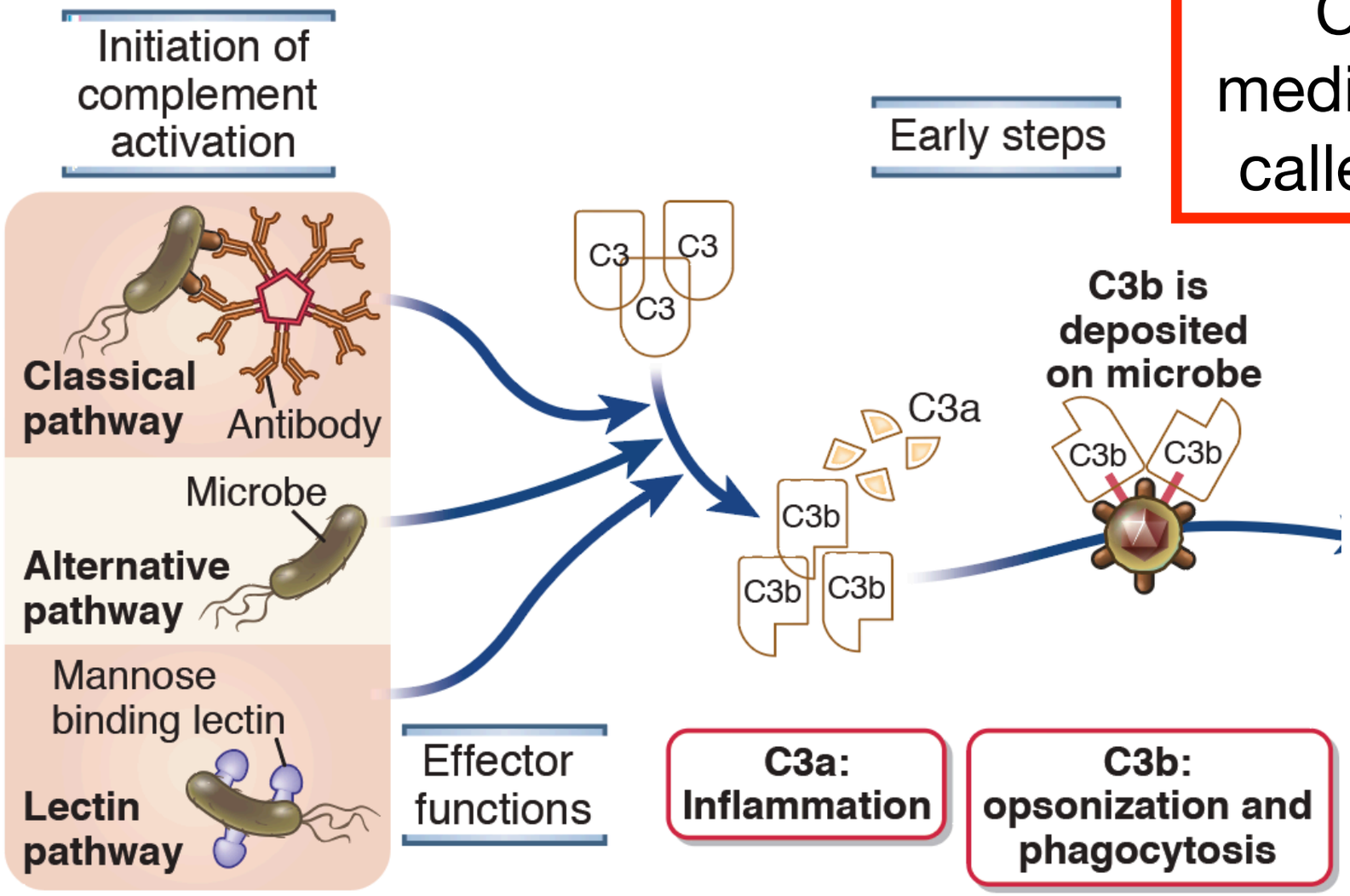
Proteolytic cascade to activate zymogens

Attack concentrate on microbe surfaces (microbes, Ab, apoptotic cells)

Three different activation pathways

What do they have in common?

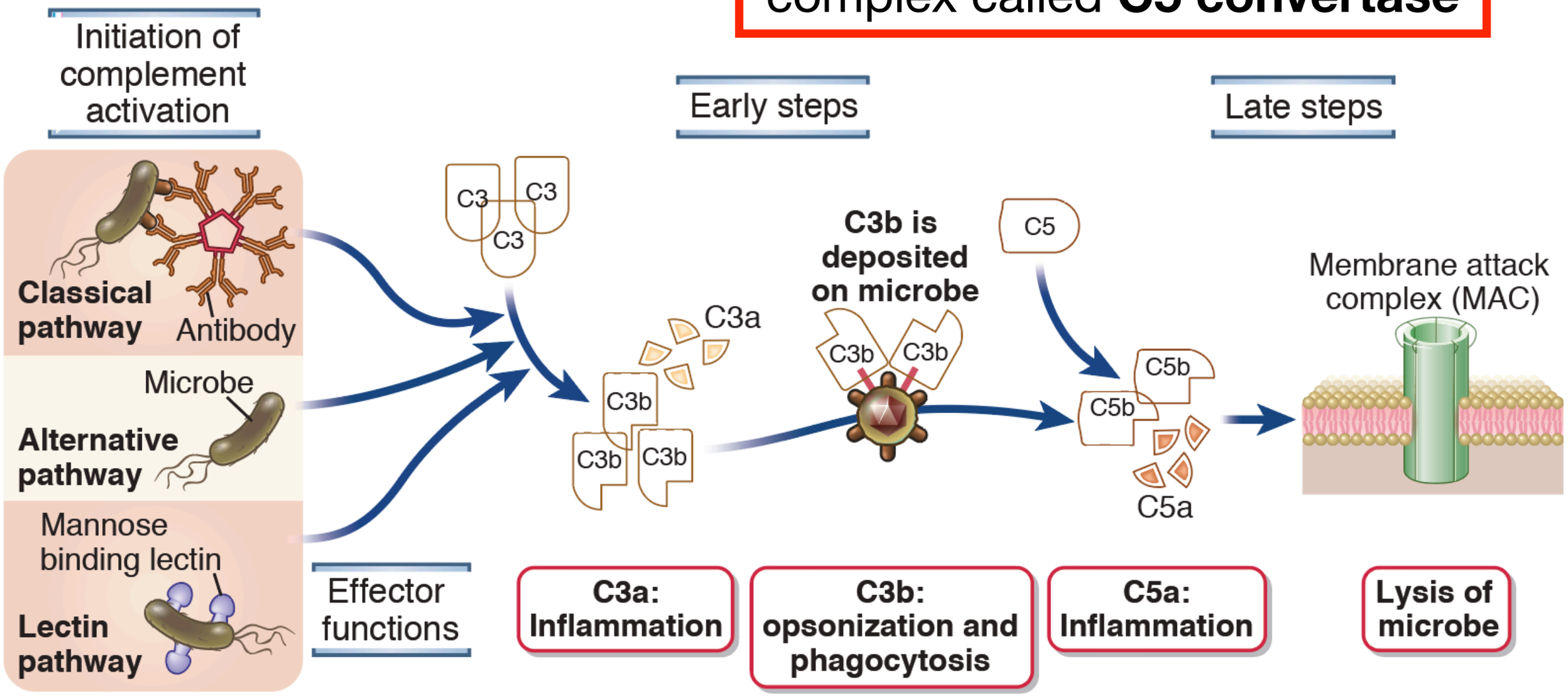
C3 is activated by proteolysis in two fragments: C3a and C3b



General rule for complement proteins:
a = smaller product
b = larger product

C5 is activated by proteolysis in two fragments: C5a and C5b

C5 proteolysis is mediated by a complex called **C5 convertase**



covalent bond

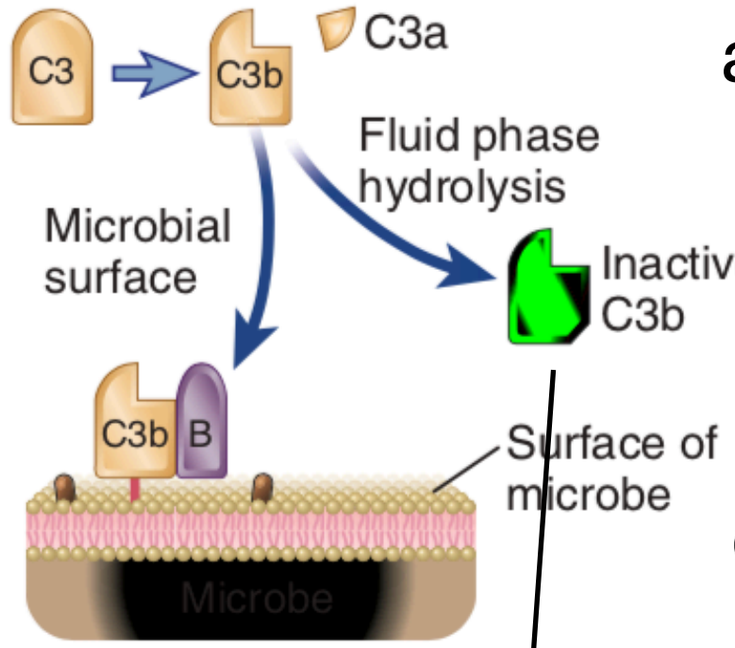
The complement system

THE ALTERNATIVE PATHWAY

Spontaneous cleavage of C3

Hydrolysis and inactivation of C3b in fluid phase

C3b binds covalently to microbial surfaces, binds Factor B



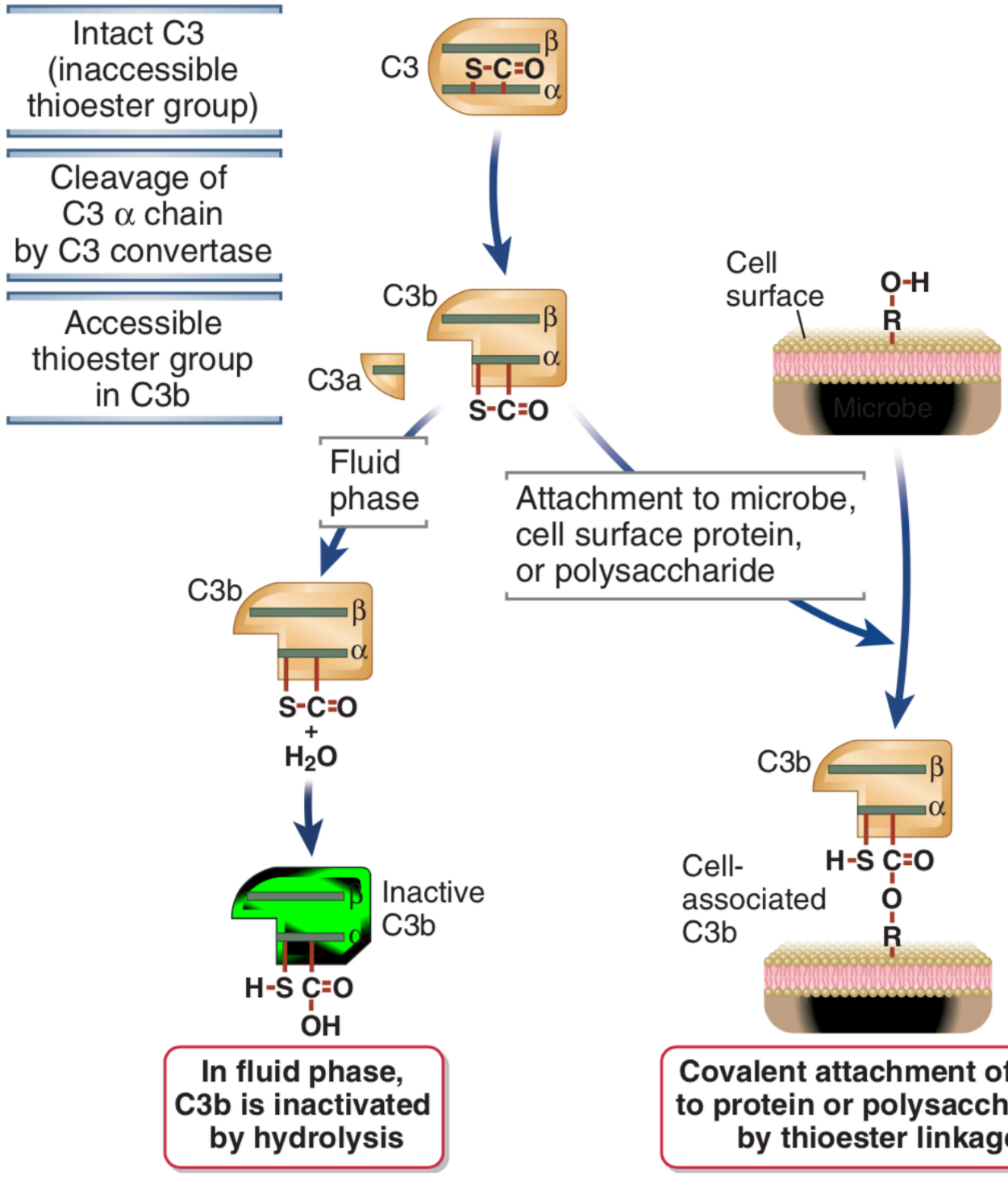
C3 is continuously cleaved at a low rate (**C3 tickover**).
1-2% h

Cleavage induce exposure of the **C3b thioester domain**, carrying a reactive thioester that can bind covalently surface of microbes

Ab absence

Hydrolysis of thioester and inactivation

C3 thioester

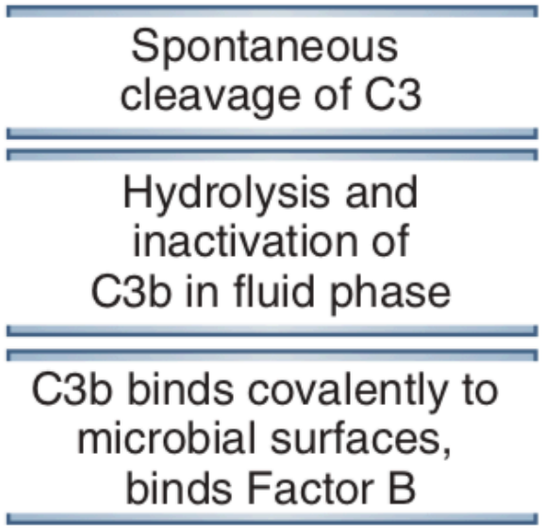


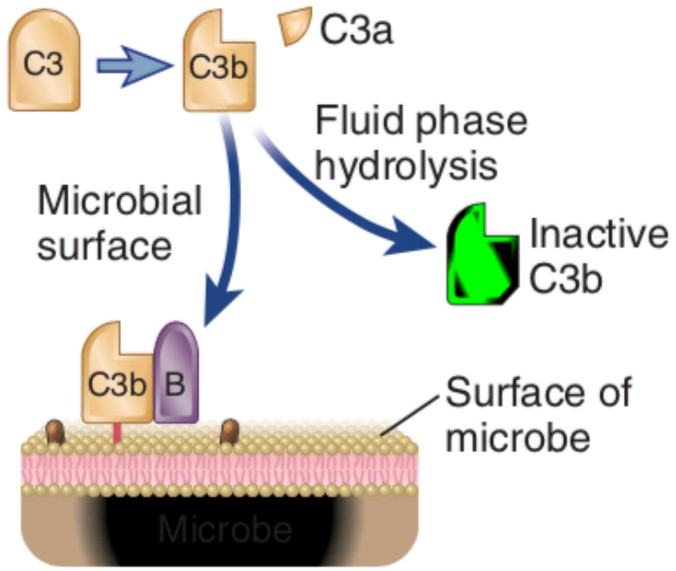
Reactivity with OH (shown) or NH_2

Ester (shown) or amide

The complement system

THE ALTERNATIVE PATHWAY





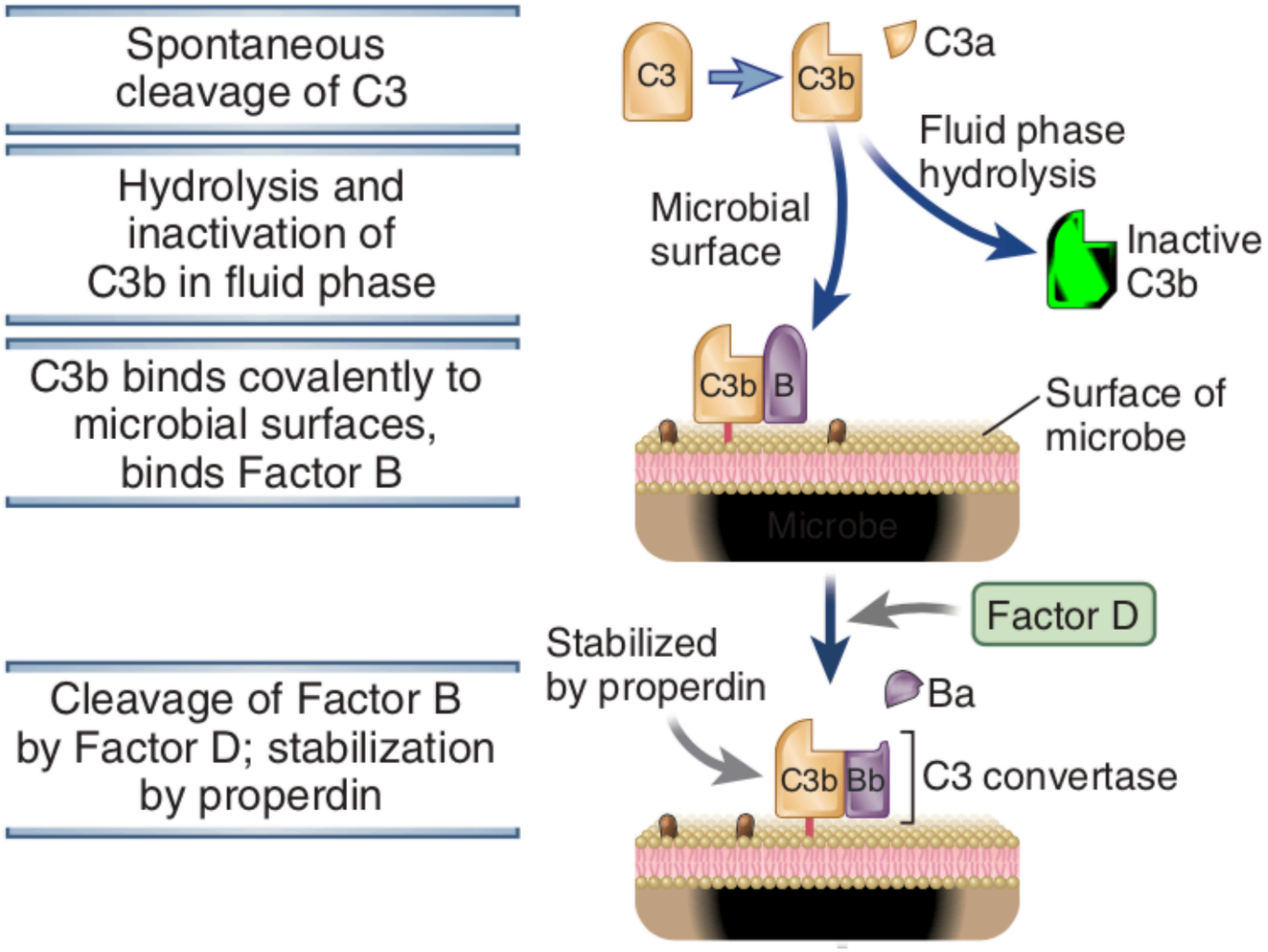
C3 is continuously cleaved at a low rate (**C3 tickover**)

Cleavage induce exposure of the **C3b thioester domain**, carrying a reactive thioester

Cleavage also induce exposure in C3b of the **Factor B binding site**

The complement system

THE ALTERNATIVE PATHWAY



C3 is continuously cleaved at a low rate (**C3 tickover**)

Cleavage induce exposure of the **C3b thioester domain**, carrying a reactive thioester

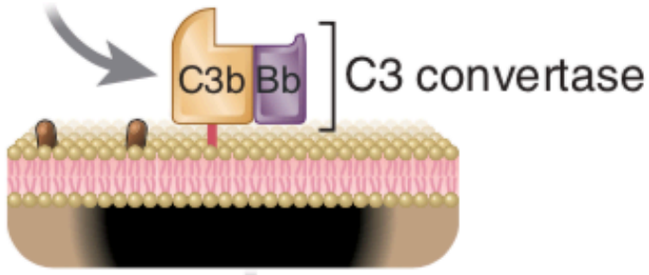
Cleavage also induce exposure in C3b of the **Factor B binding site**

Factor B is cleaved by **Factor D**

Properdin: made by neutrophils

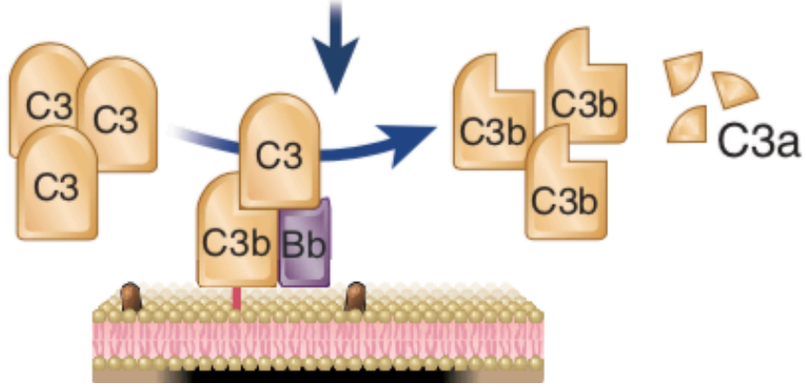
The complement system

THE ALTERNATIVE PATHWAY



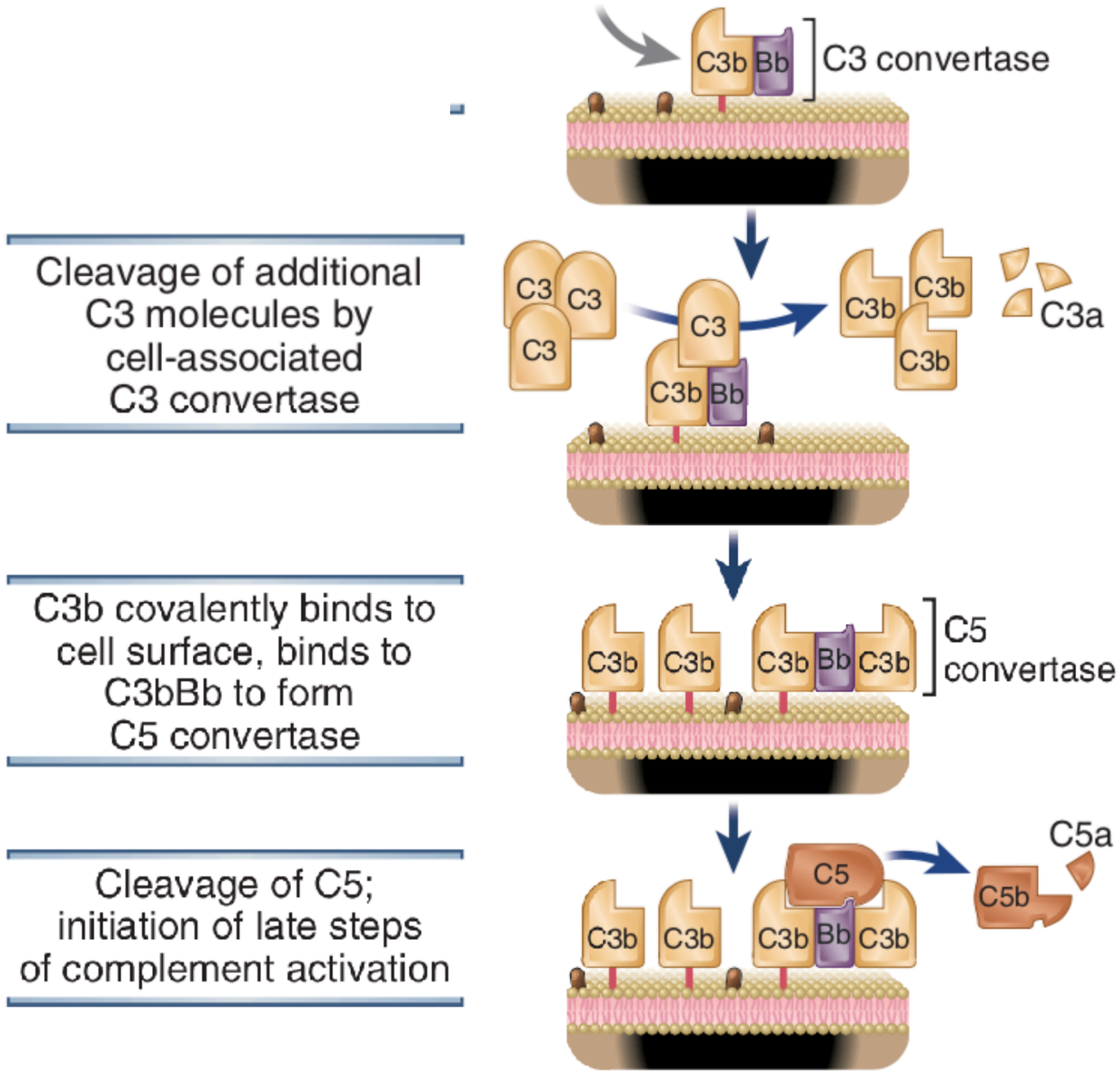
Generation of **C3 convertase!**

Cleavage of additional C3 molecules by cell-associated C3 convertase



The complement system

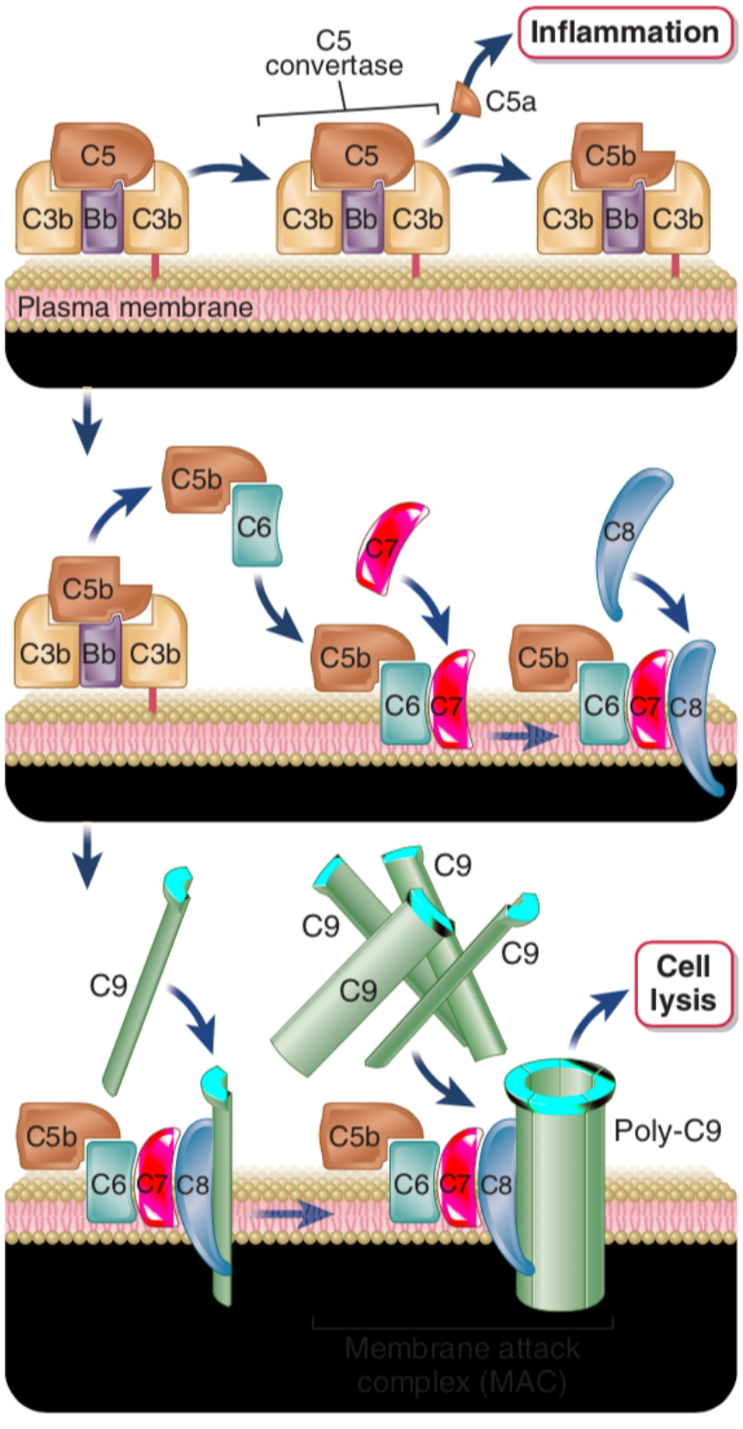
THE ALTERNATIVE PATHWAY



Generation of **C3 convertase!**

Generation of **C5 convertase!**

The complement system
Terminal steps



THE ALTERNATIVE PATHWAY

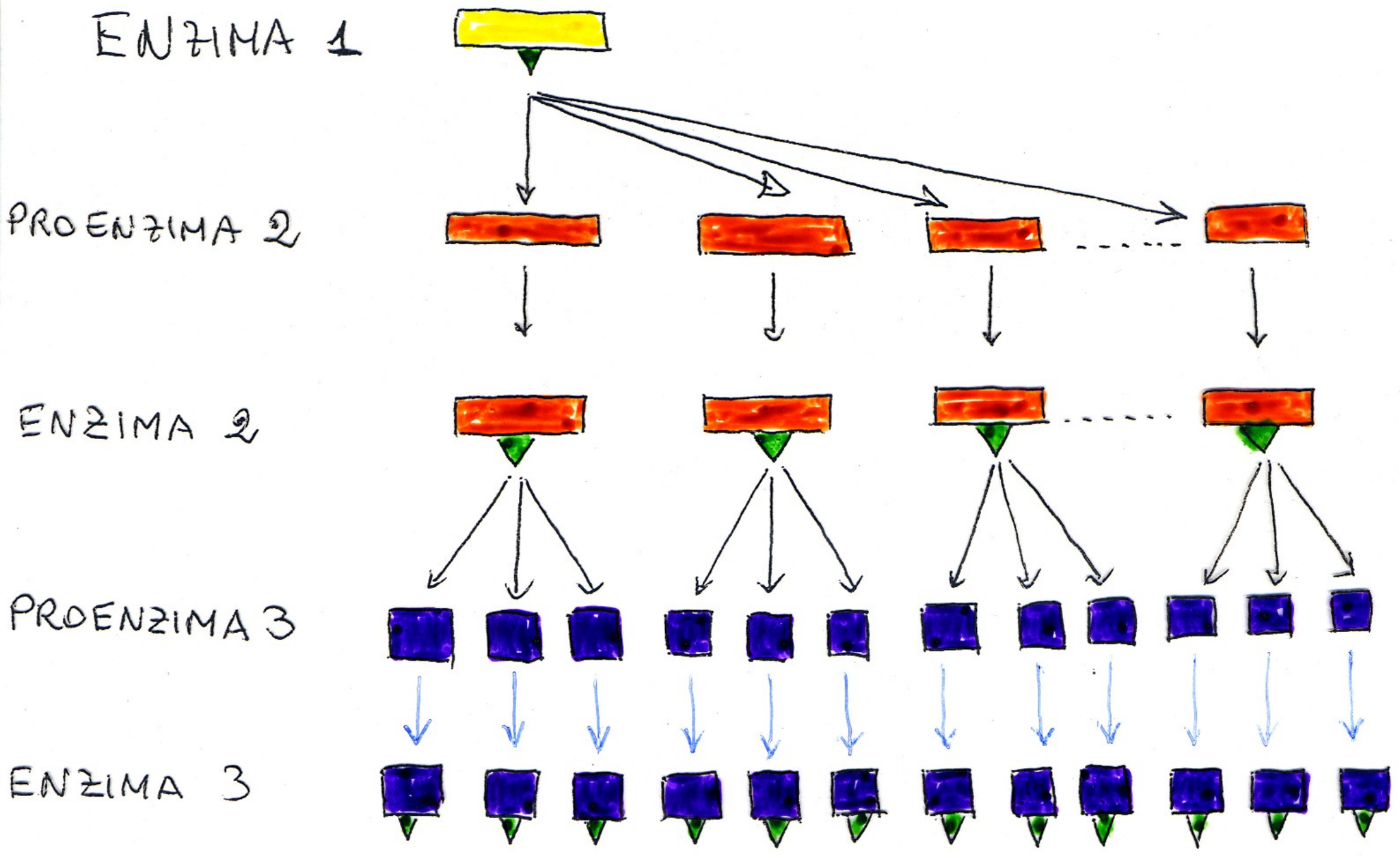
Generation of **C5 convertase!**

Activation of C6-7-8-9

C9 create polymers

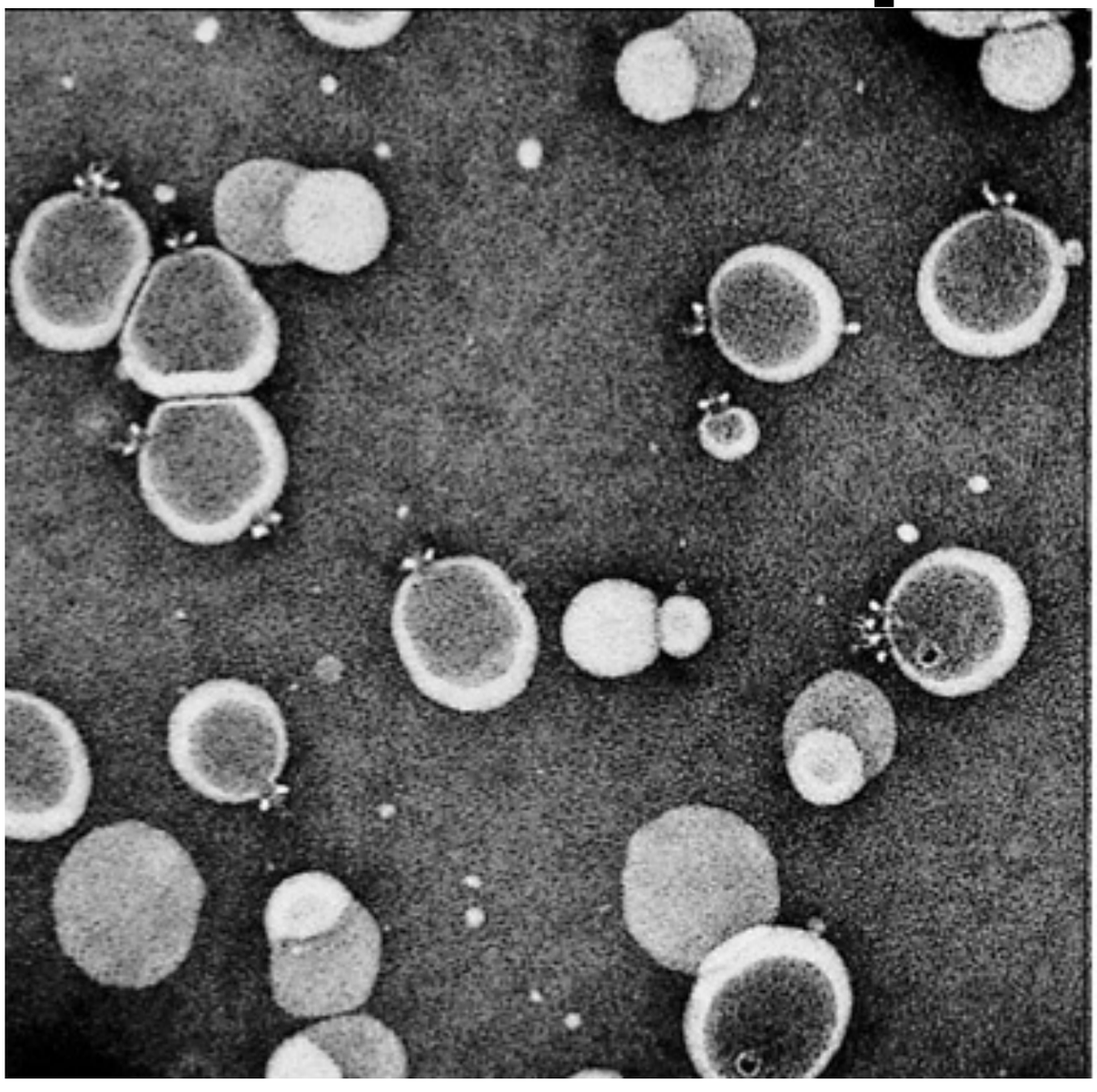
MAC (Membrane Attack Complex)
C5b-C9

Large pores in the attacked cells

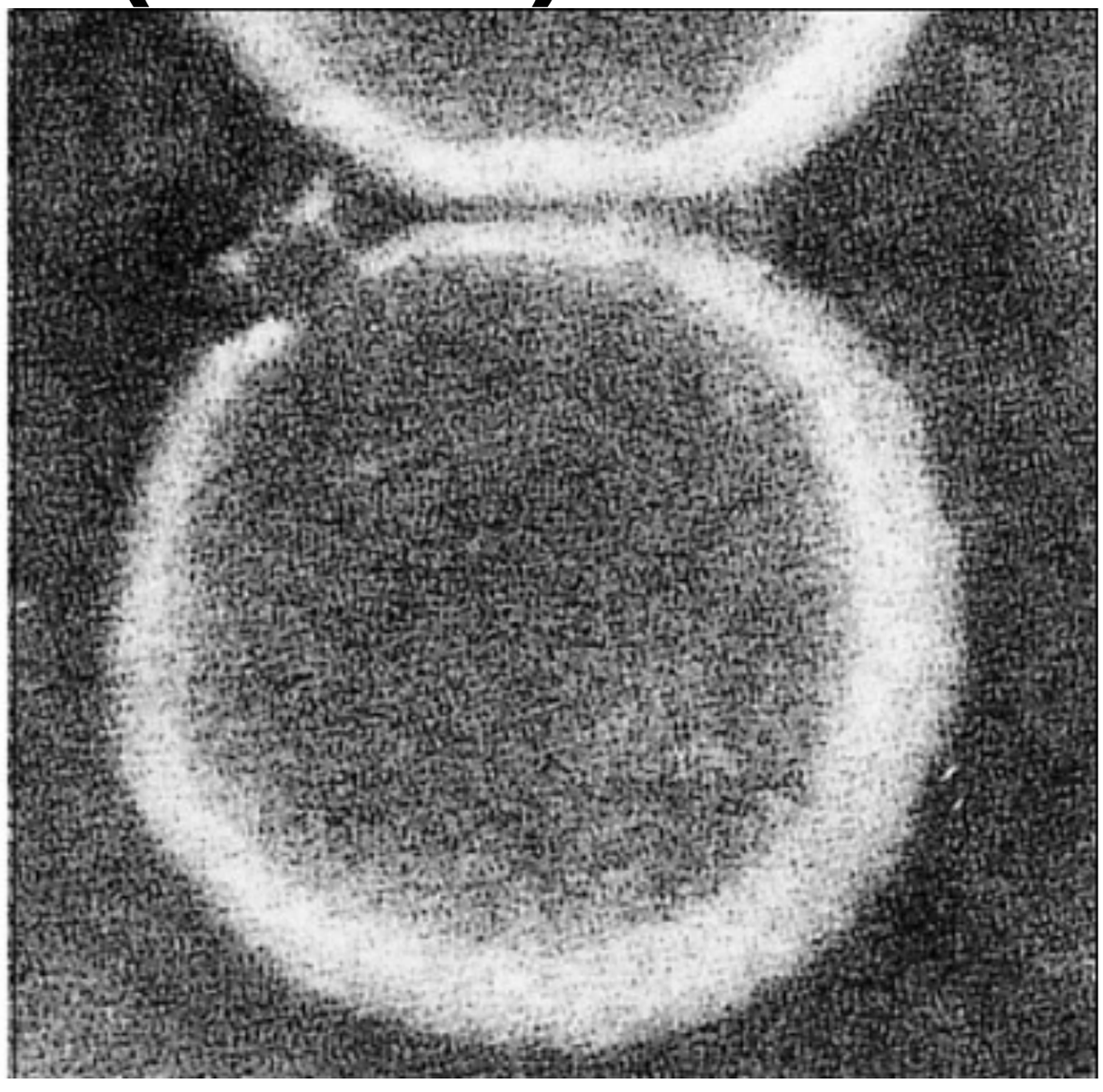


E COSÌ AMPLIFICANDO.....

The membrane attack complex (MAC)

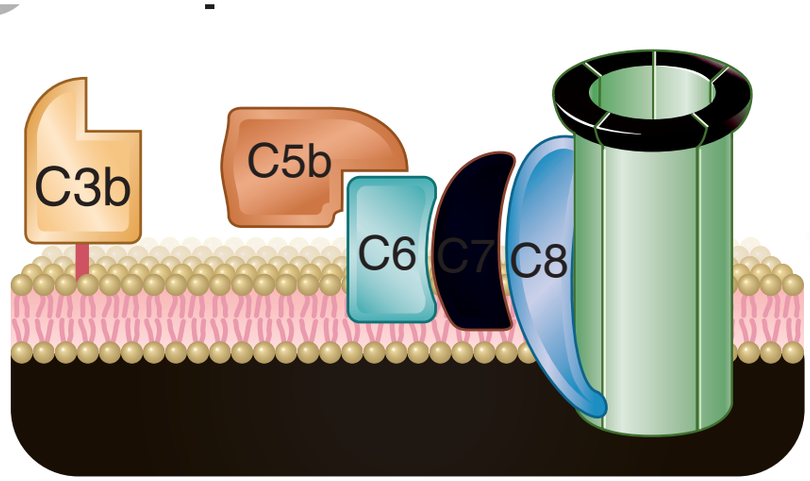


PORES

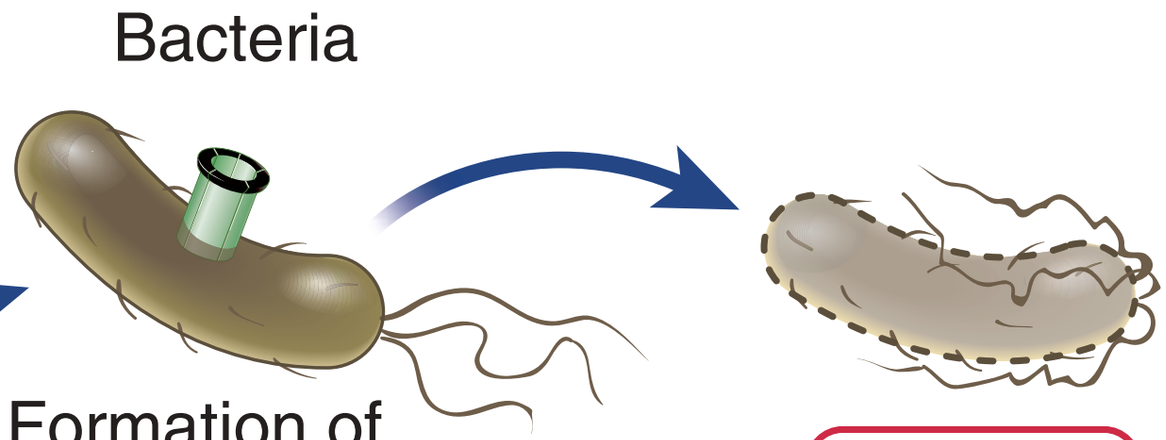


External diameter 20 nm
Internal diameter 10 nm
H 15 nm

Cytolysis mediated by complement



Binding of C3b to bacteria, activation of late components of complement



Formation of the membrane attack complex (MAC)

Osmotic lysis of bacteria

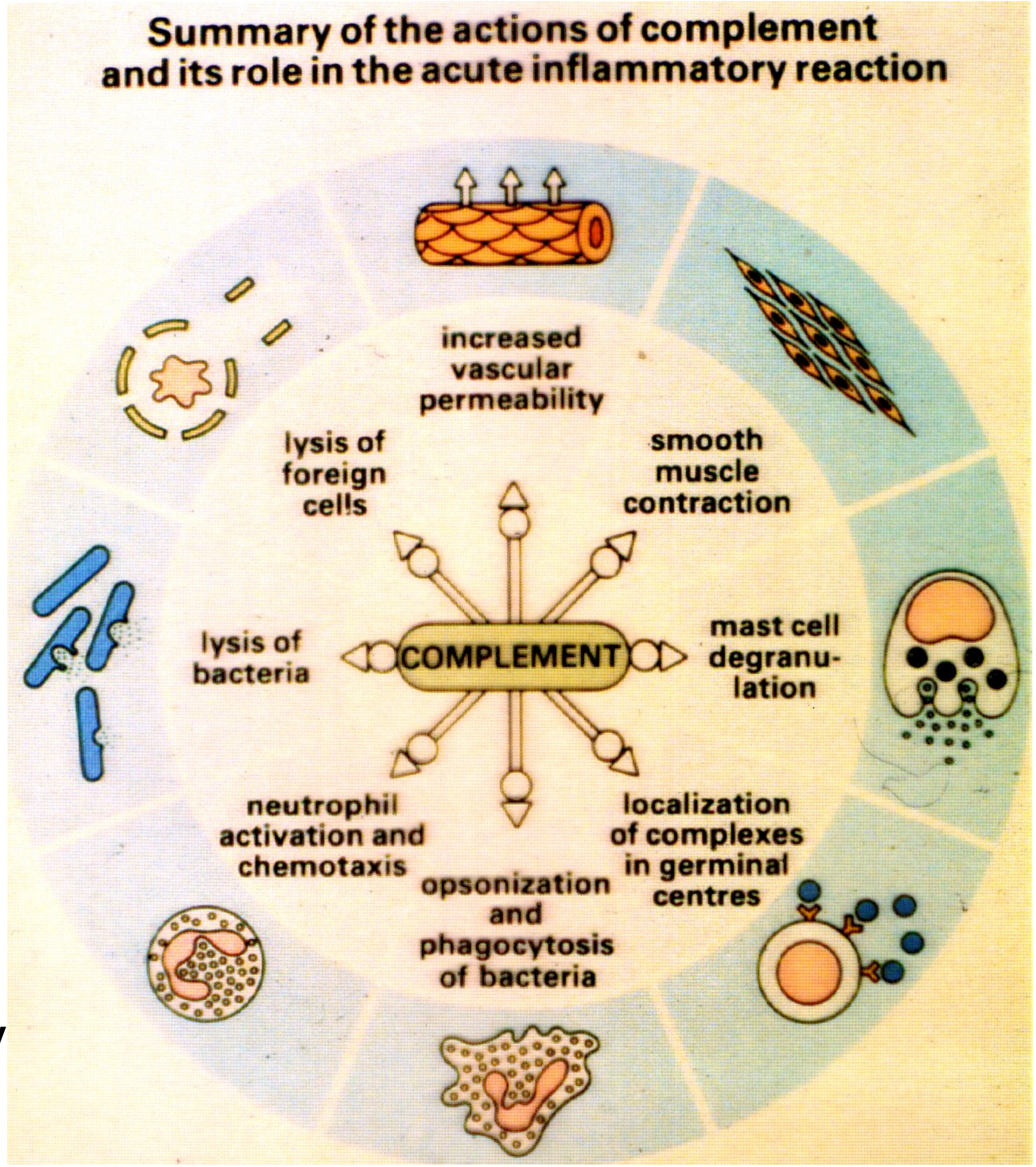
…but the MAC is just the tip of the iceberg

MAC ⟶ Cell lysis

Phagocytosis

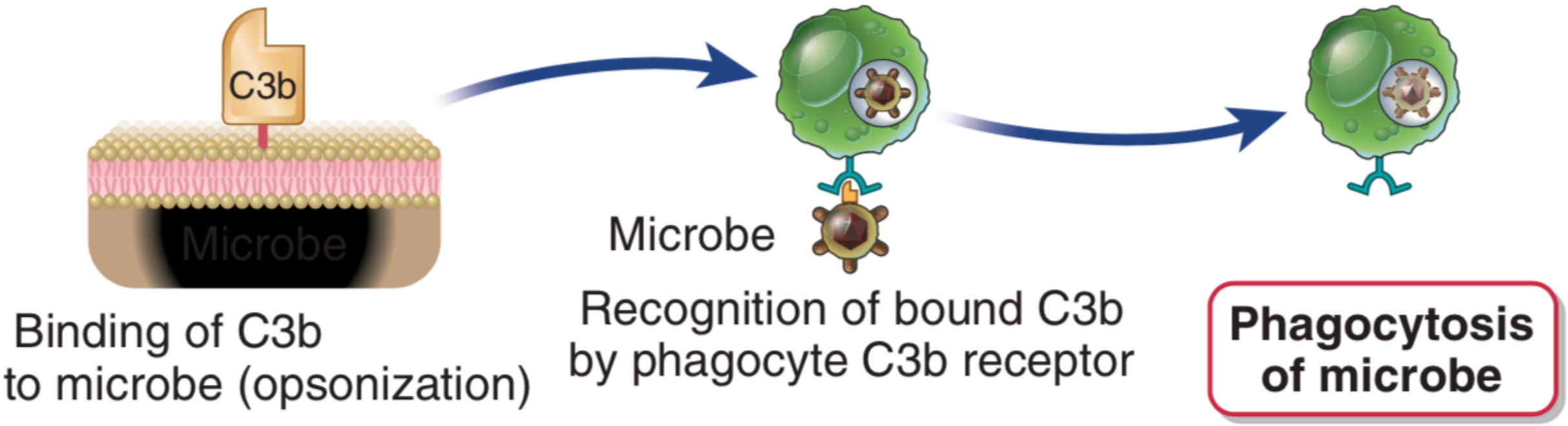
Inflammation

Activation of humoral activity



Phagocytes ligate C3b and uptake opsonized microbes

Macrophages and neutrophils express complement receptors (CR) that ligate complement coated microbes and trigger phagocytosis

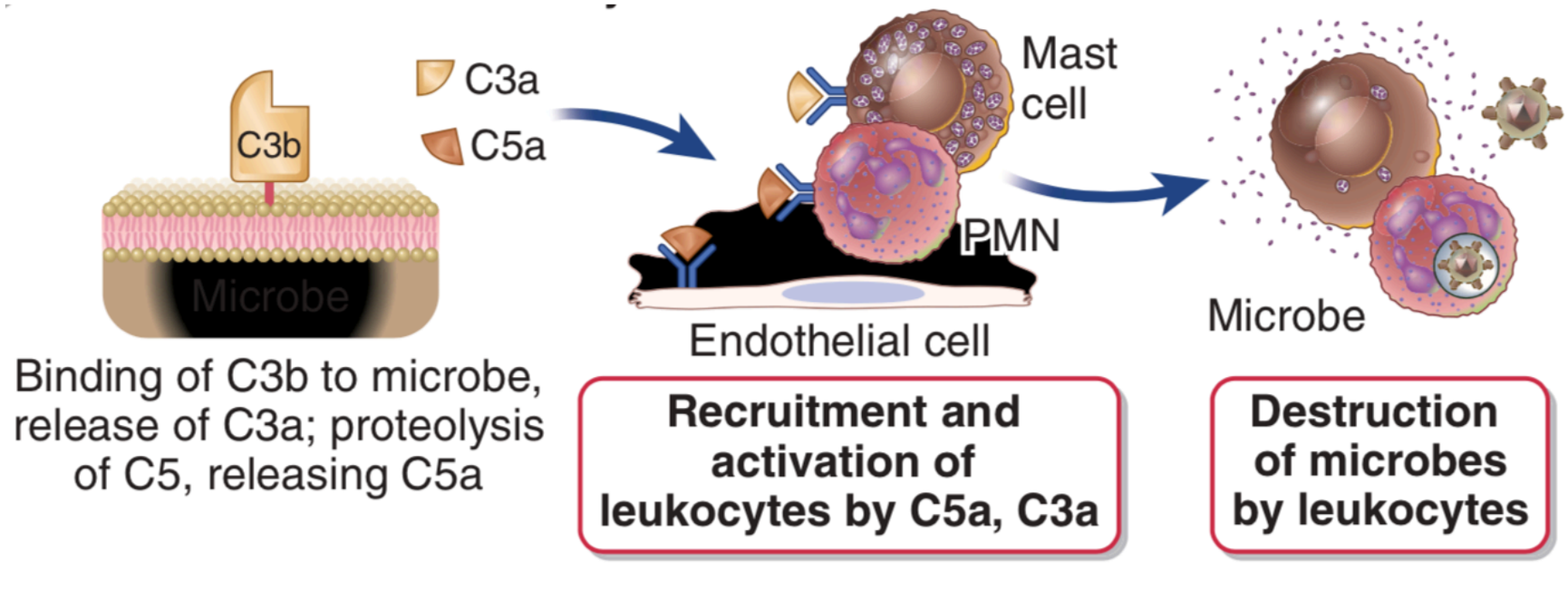


C3a and C5a are soluble mediators of inflammation

C3a and C5a induce **mast cell degranulation** and release of histamine and vasodilatation

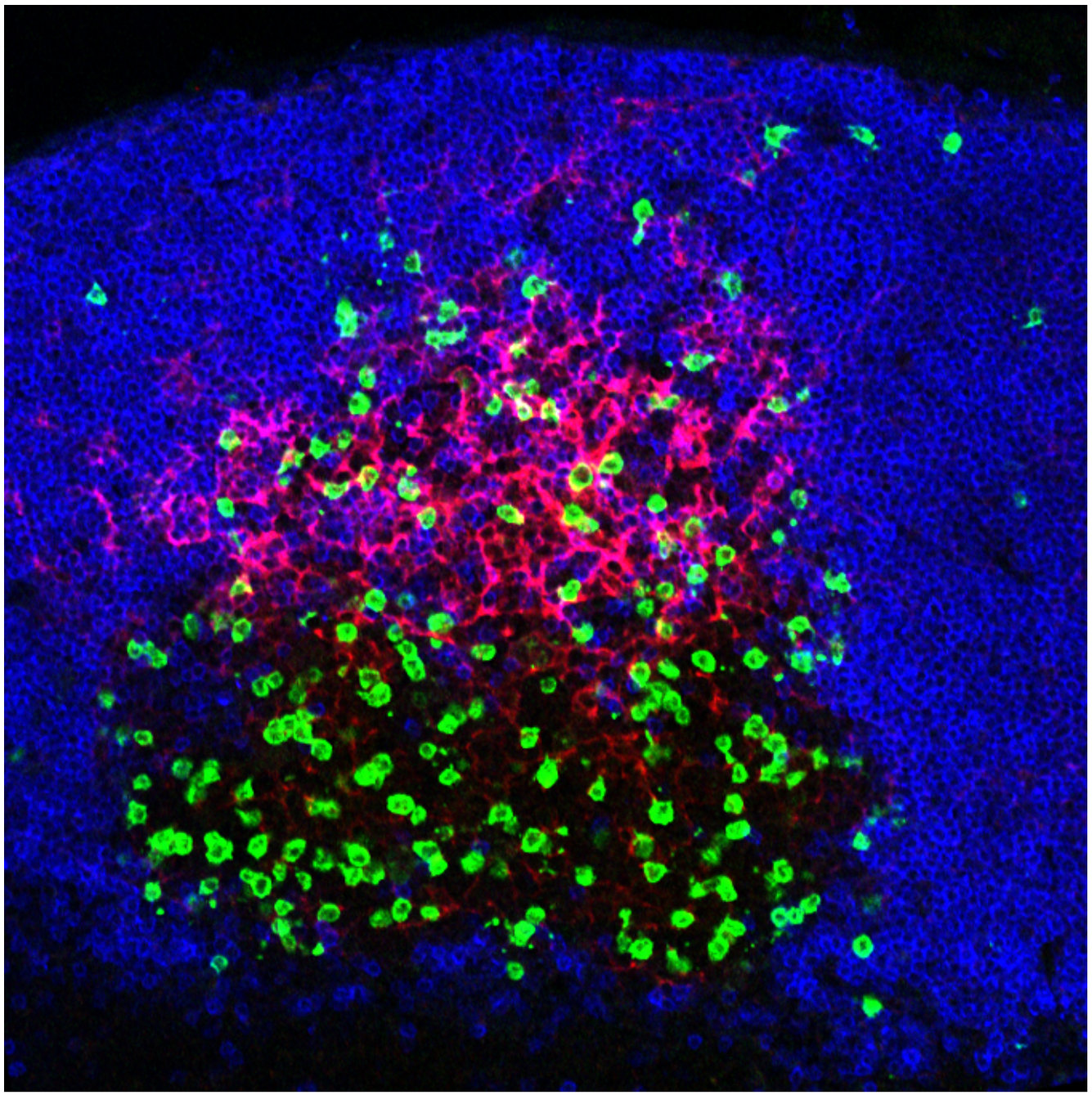
C5a induces **neutrophil activation:** motility adhesion to endothelium and oxidative burst (ROS)

C5a induces expression of **P-selectin** by the vascular endothelium (rolling) and **increased vascular permeability**



RECEPTOR FOR PROTEIN OF COMPLEMENT and activation of humoral response

Follicular dendritic cells express CR2 and capture immune-complexes



The B cell follicle can host germinal centers

Immune complex are covered Of C3 fragments

Antigen is captured in form of immune complexes, and stored by follicular dendritic cells (FDCs) where are

presented to responding B cells

Naive B cells
FDCs
Responding B cells

Summary of the actions of complement and its role in the acute inflammatory reaction