2021-2022

Complement system

Introduction

- A system of soluble enzymes and proteins

- Complement components:
  …C1 to C9, B, $\bar{D}$ and P

- When activated, each component is split into <u>small</u> and <u>large</u> (major) fragments

*A horizontal bar above component or complex = enzymatic activity

Functions of complement system

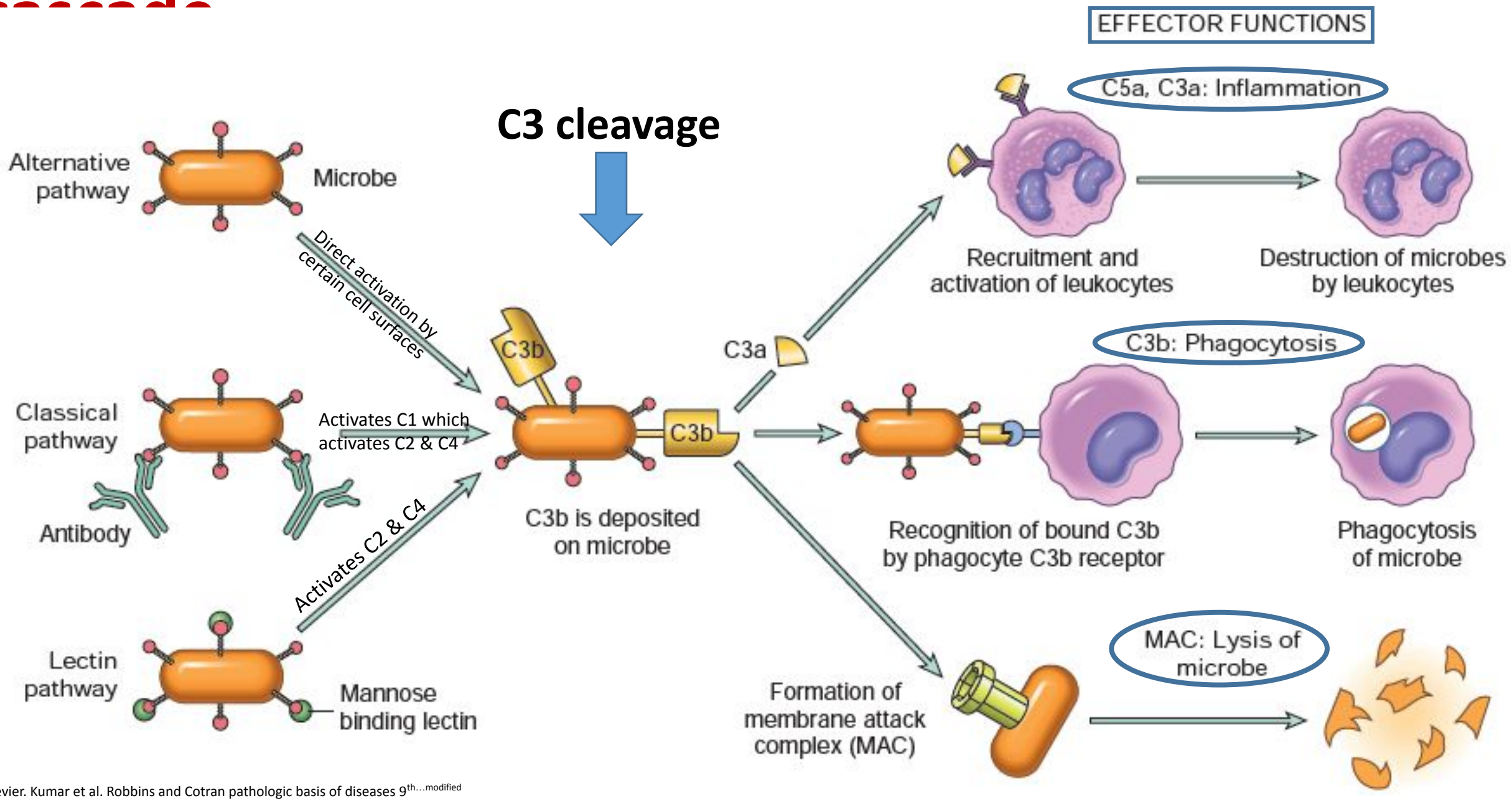
1- Lysis of bacteria, viruses and cells

2- Opsonization

3- Triggering for inflammation

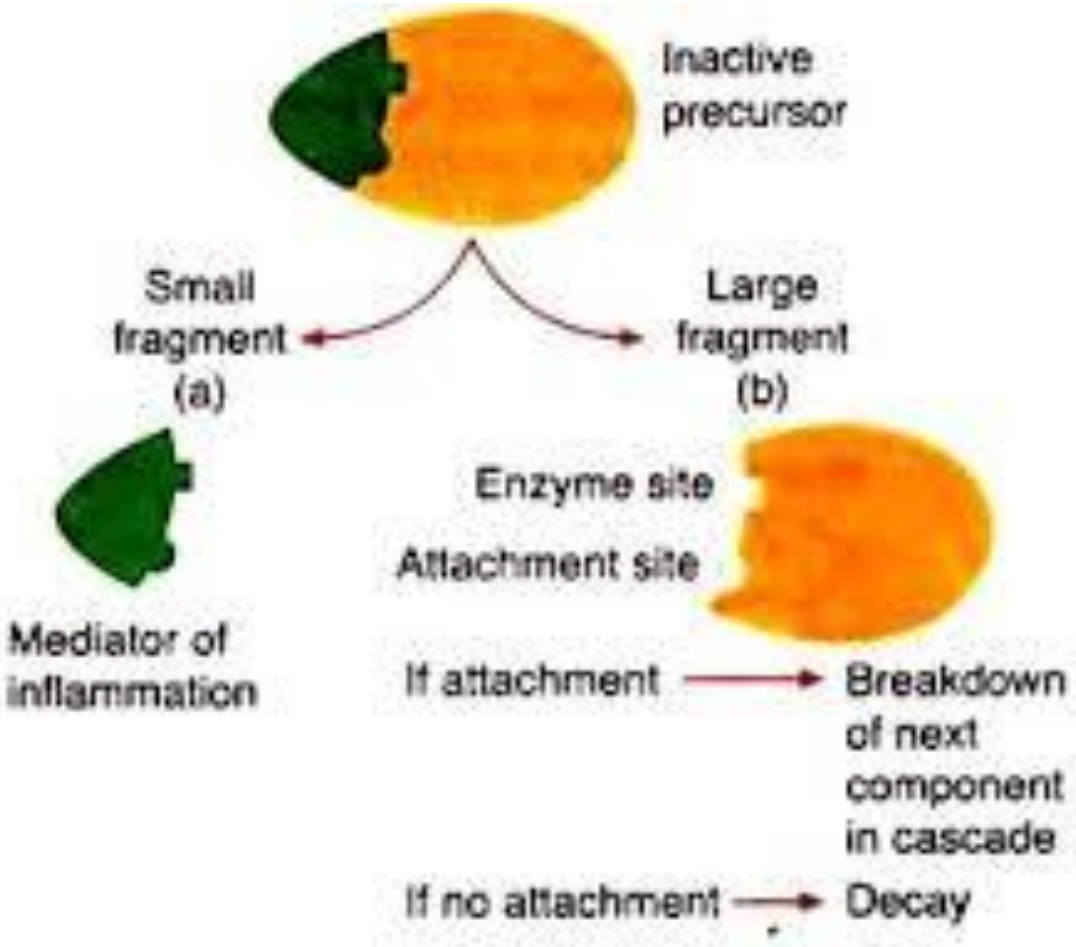
4- Clearance of immune complexes from circulation

An overview of the complement cascade



Elsevier. Kumar et al. Robbins and Cotran pathologic basis of diseases 9th…modified

Cleavage of complement components



Visit http://www.biologydiscussion.com/immunology/complement-system/complement-system-definition-functions-and-components/61928 for references

Lectin pathway

- Mannan-binding lectin (MBL)…a collectin

binds to carbohydrates on bacteria…by its lectin portion

after this binding, the collagen-like domain of MBL activates C2 & C4

C2 & C4 activate **C3**

Lectin pathway, cont'd

- Known to have mannose-containing residues on their surface glycoproteins: *Listeria*, *Salmonella*, *and Candida albicans*…etc.

- MBL is an acute-phase reactant

The classical pathway

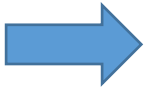
- Discovered first…but the last to evolve
- Triggered by immune complexes (Ag-Ab)
- Fc portion of Ig is recognized by C1q, which then associates with C1r and C1s

*IgM is the best to bind C1 (5 Fc portions)

…after binding to Fc, C1 can activate C2 and C4 which activate **C3**

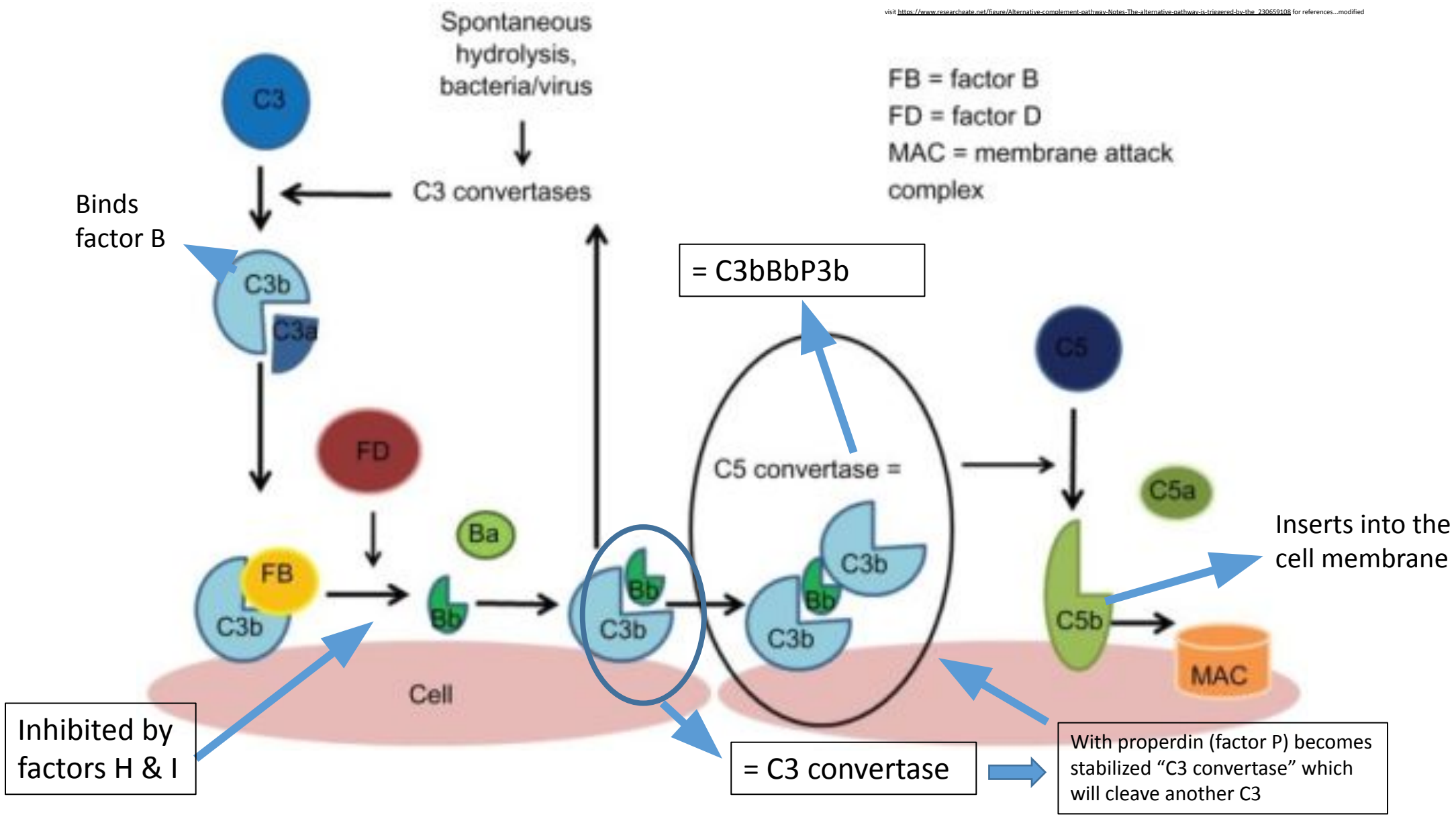
The alternative pathway

- C3 is unstable and always has spontaneous low activity

 this activity is promoted on surfaces

- The normal cells express surface complement inhibitors
- Any cell surface lacking complement inhibitors will be attacked by complement…e.g. surfaces of pathogens
- This pathway is a challenge in xenotransplantation

The alternative pathway, cont'd



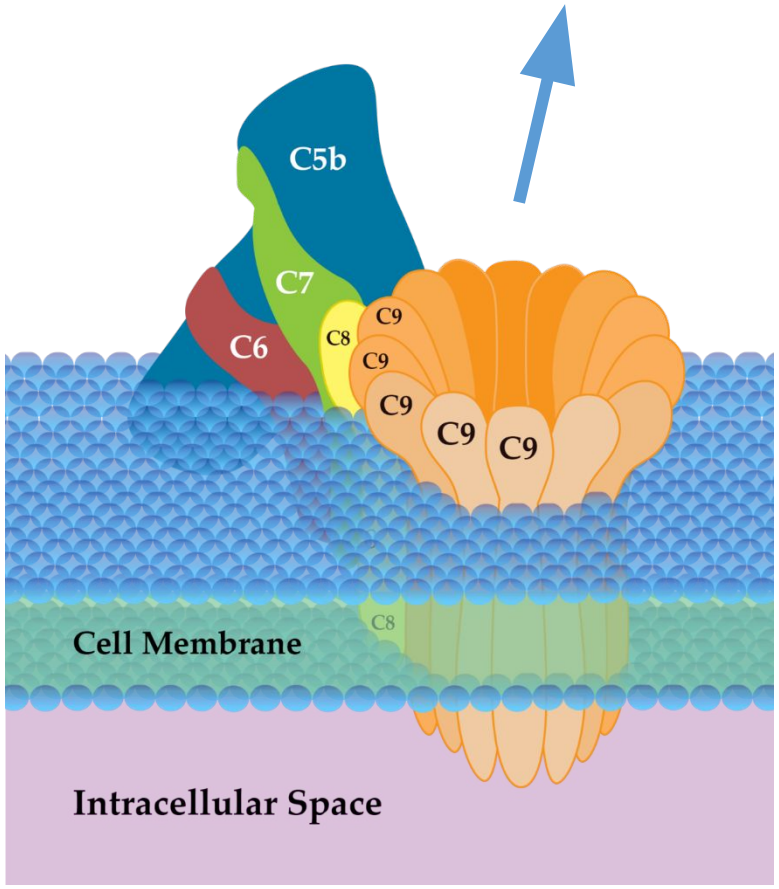
…when MAC is formed:

Terminal (lytic) pathway

- C5b insertion into the bacterial membrane initiates the membrane attack complex

- C5b insertion ➡ addition of C6, C7, and C8 ➡ addition of multiple C9 molecules ➡ pore formation

Especially against *Neisseria*



Visit https://en.wikipedia.org/wiki/Complement_system for references

Anaphylatoxins/Inflammation

*Attractants and activators of WBCs

- C3a
- C4a
- C5a…the strongest

-increased phagocytosis
-phagocyte activation
-mast cell degranulation
-attraction/activation of neutrophils
-activation of vascular endothelium

- C2a is cleaved to produce kinin…vascular permeability (endothelial cell contraction)

Binding to complement receptors

- C3b is the strongest opsonizing complement component, which binds to complement receptors in a variety of phagocytes

*IgG is also an opsonin that binds to Fc receptor

- Phagocytes do not have Fc receptors for IgM…so in primary IgM response, complement-mediated opsonization is important

Binding to complement receptors, cont'd

- When C3 binds to CR2 on B cell, co-stimulation and ⬆⬆antibody production
- EBV makes CR2 busy by binding to it
- Clearance of Ag-Ab complexes, by 2 ways: -high #s of activated C3 interrupt lattice of immune complexes making them soluble

  -C3 & C4 binding to CR1 on RBCs can transport complexes to the liver and spleen, where phagocytes use Fc and complement receptors to destroy these complexes

Additional complement inhibitors

- C1 inhibitor…soluble

…deficiency will cause??

- Membrane-bound inhibitors of C3

- Membrane-bound inhibitors of MAC

Deficiencies

⬇C3 and C4 in lectin and classical pathways…type III hypersensitivity reactions (immune-complex disease), e.g., SLE

⬇ MAC…??

Thank You