The Complement System

Part 2

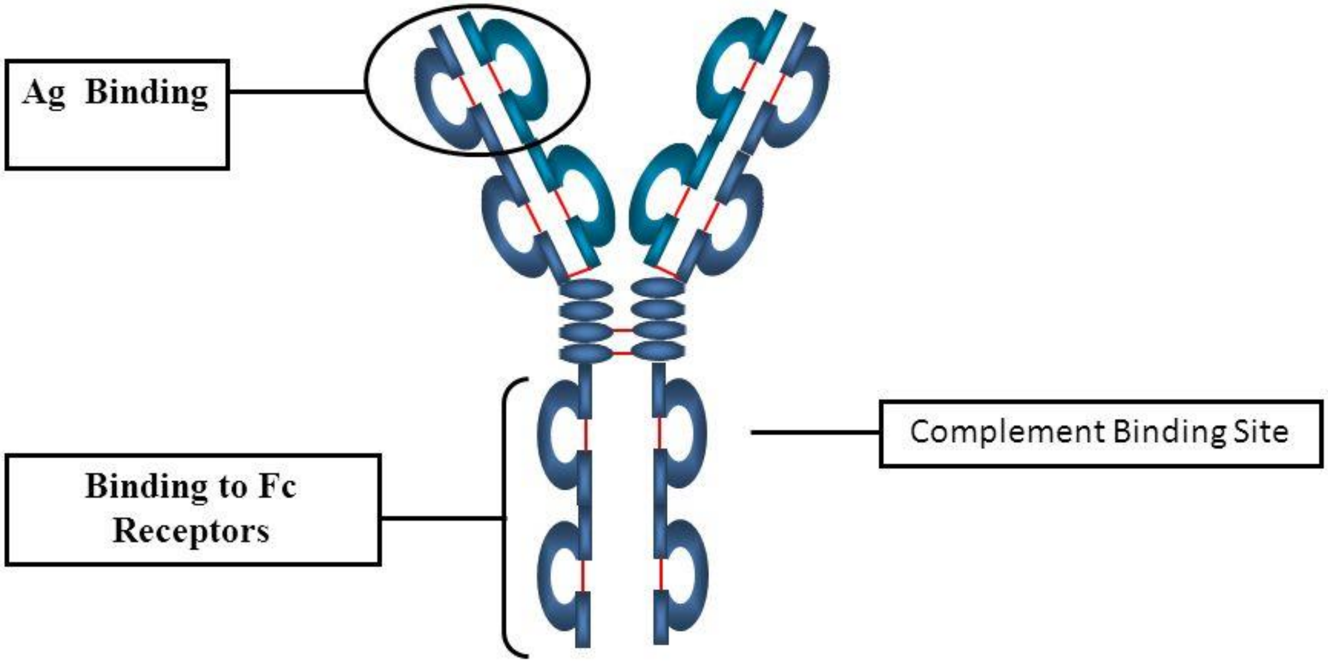
Regulation of complement system

-- The **first regulatory step** in classic pathway is at the **level of the antibody** itself.

-- The **complement binding site** on the heavy chain of IgM and IgG is **unavailable** to **C1** of complement if antigen is **not bound** to these antibodies.

-- It means that complement is **not activated** by antibodies **without** the presence of antigen.

Antibody Functions



Additionally, several proteins regulate complement system at different stages:

-- **C1 inhibitor** is an important regulator of **classic pathway**. It inactivates protease activity of **C1**.

-- Regulation of **alternative pathway** is mediated by the **binding of factor H to C3b** and cleavage of this complex by **factor 1**, a protease.

-- Protection of human cells from lysis by **membrane attack complex (MAC)** of complement is mediated by **decay- accelerating factor**, a glycoprotein located on the surface of human cells.

Decay-accelerating factor is a 70 kDa membrane protein that **protects cells** from activation of complement components on their surfaces.

It acts to **accelerate the decay** of the classical and alternative C3 and C5 convertases, the central amplification enzymes of the cascade.

Biological effects of complement

1. Complement cleavage products mediate inflammation.
2. C3a, C4a, C5a are anaphylatoxins.
3. Complement products facilitate opsonization
4. Complement proteins neutralize viruses
5. Complement clears immune complexes from circulation
6. Complement products stimulate Chemotaxis
7. Complement products cause Cytolysis
8. Complement products cause enhancement of antibody production

1. Complement cleavage products mediate inflammation.

These products **induce**:

- **degranulation**
- release of **histamines** and **inflammatory mediators**
- **smooth muscle contraction**
- **increase in vascular permeability**

C3a, C5a, C5b induce **monocytes** and **neutrophils** to migrate to the site of complement activation.

2. C3a, C4a, C5a are anaphylatoxins.

-- They are **regulated** by serum protease **carboxypeptidase N**.

-- They bind to receptors on **mast cells** and **blood basophils.**

-- These **mediators** increase **vascular permeability** and **smooth cell contraction**, esp. that of bronchioles leading to **bronchospasm**.

-- They also **activate macrophages**.

-- **C5a** is by far the **most potent**.

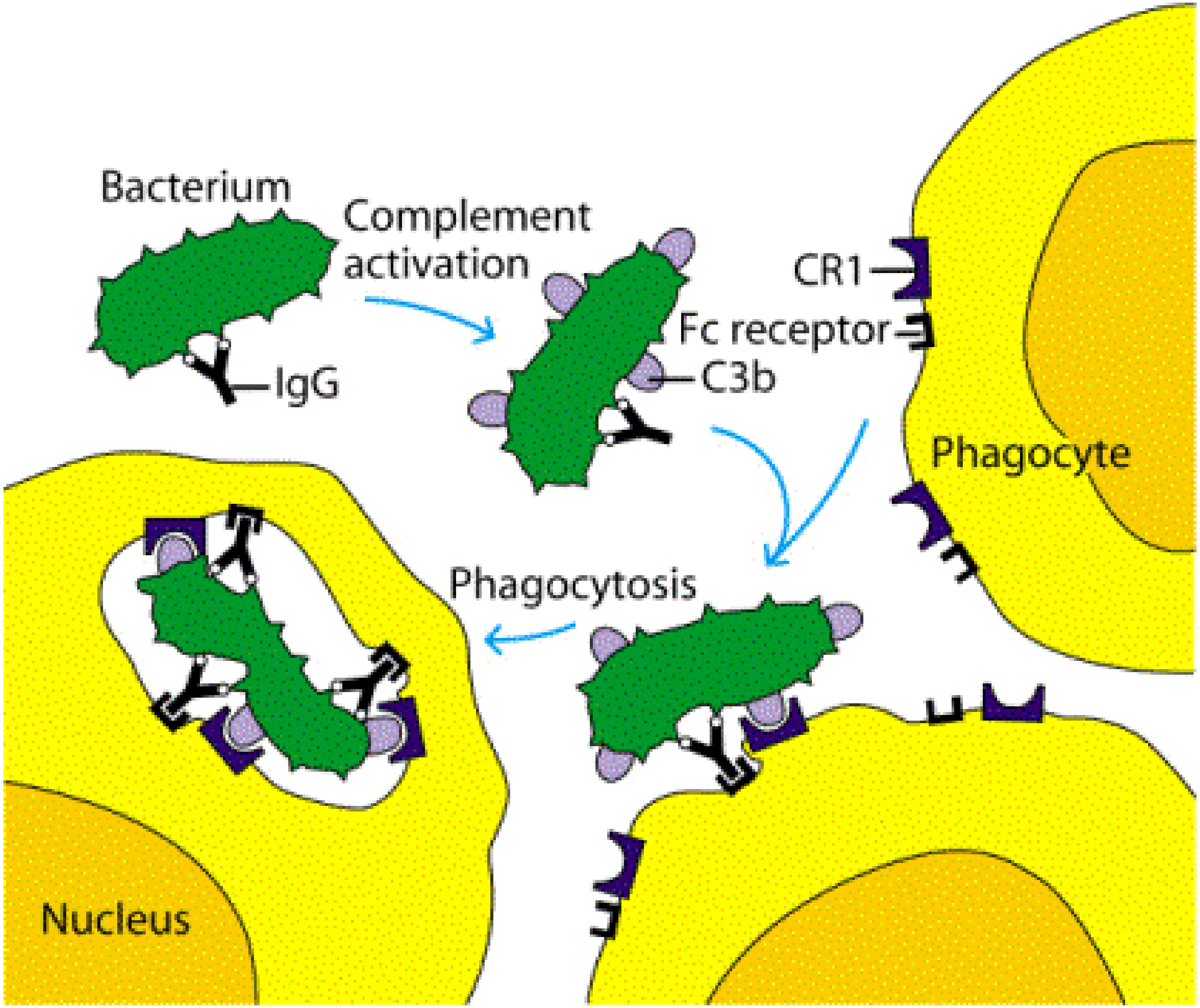
3. Complement products facilitate opsonization

-- **C3b** is the primary **opsonin**; **C4b** and **C5b** are also opsonins.

-- **C3b** coats immune complexes or antigens.

-- It is bound by complement receptors **(CR1, CR3, CR4)** on phagocytes.

-- Receptors expression is upregulated by **C5a anaphylatoxin.**


Bacterium
Complement
activation
IgG
CR1
Fc receptor
C3b
Phagocyte
Phagocytosis
Nucleus

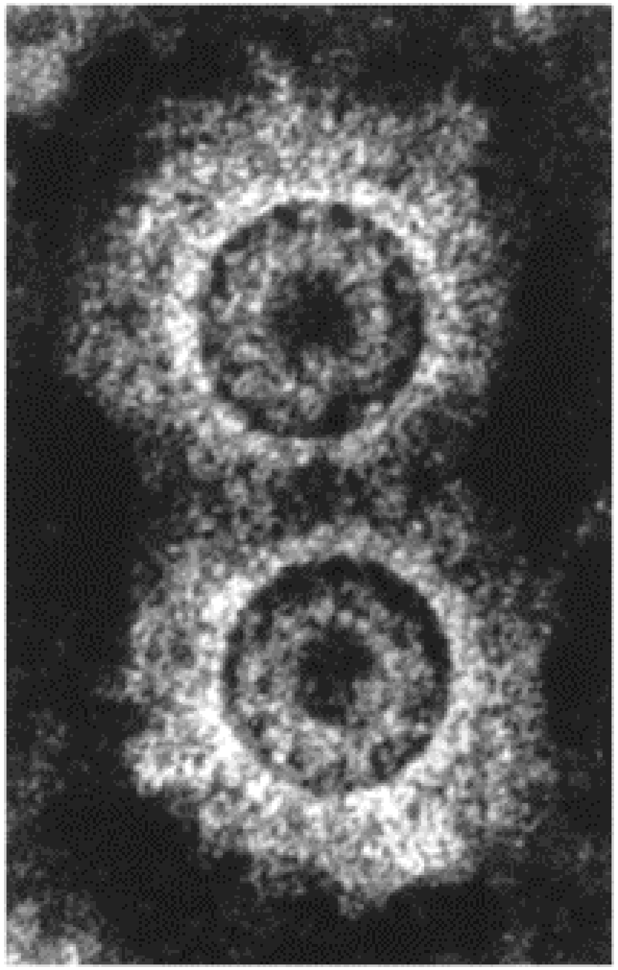
4. Complement proteins neutralize viruses

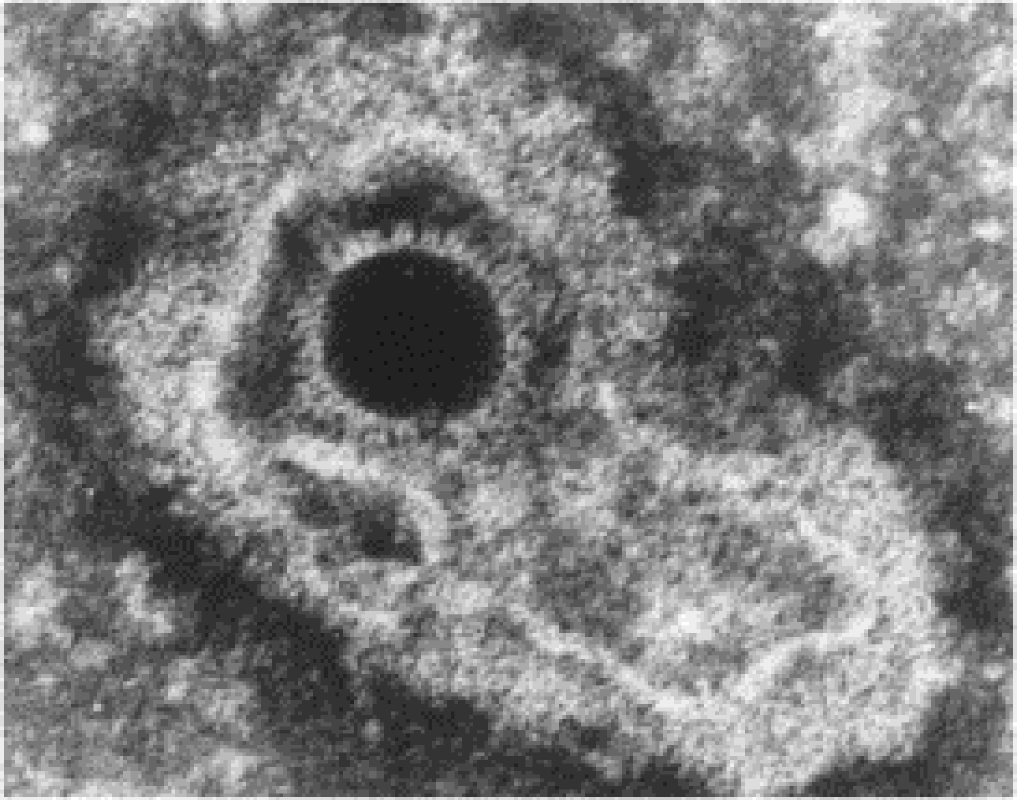
There are **three** phenomena:

-- They form large **viral aggregates** by **coating** of virus with antibody and /or complement.

-- They also increase **binding** of viral particle to **Fc** or **type I** complement receptors of immune cells.

-- They cause **direct lysis** of enveloped virus.

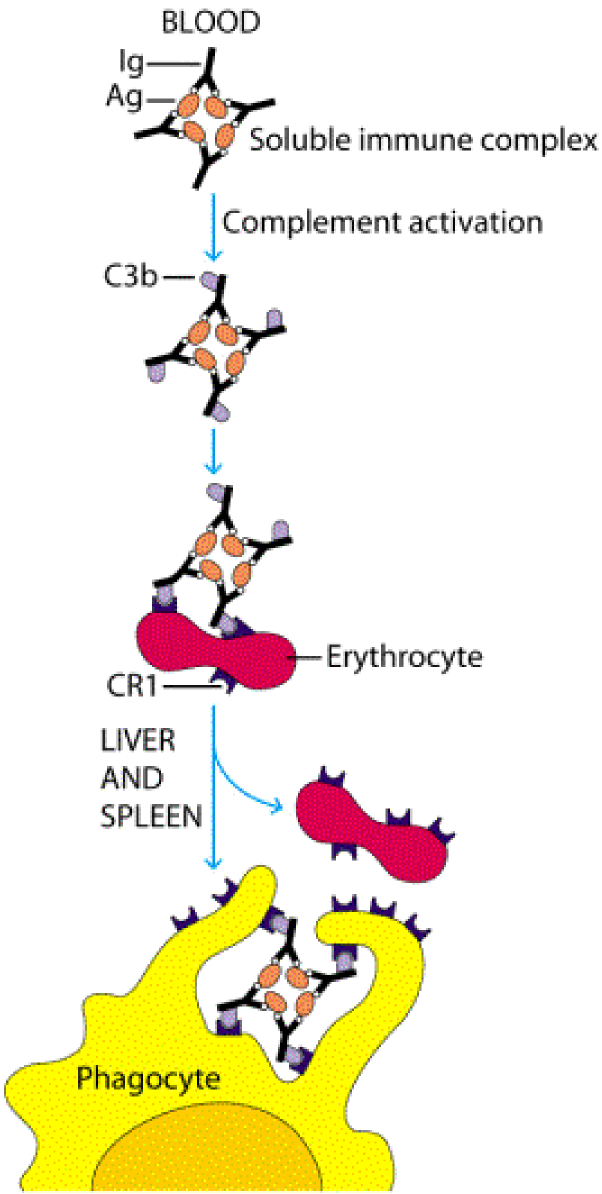




5. Complement clears immune complexes from circulation

-- **C3b** coats the immune complexes and **CR1** on erythrocytes binds to **C3b**.

-- **Erythrocytes** carry this complex to the **liver** and **spleen** where it is **phagocytosed**.


BLOOD
Ig
Ag
Soluble immune complex
Complement activation
C3b
Erythrocyte
CR1
LIVER
AND
SPLEEN
Phagocyte

6. Complement products stimulate Chemotaxis

-- **C5a** and the **C5, C6, C7** complex attract **neutrophils.**

-- **C5a** also enhances **adhesiveness** of neutrophils to endothelium.

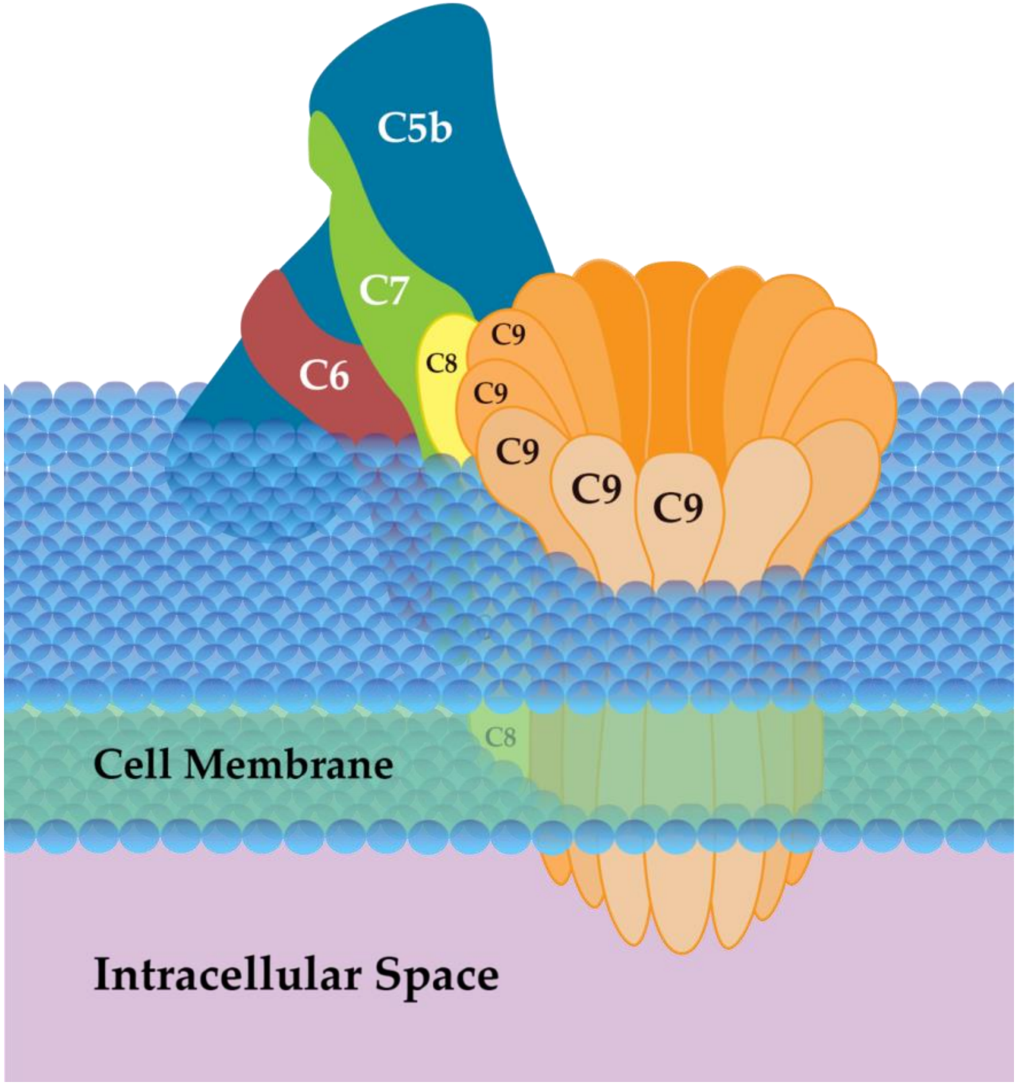
* The endothelium is a thin membrane that lines the inside of the heart and blood vessels.

7. Complement products cause Cytolysis

-- **Insertion** of the **C5b, C6, C7, C8, C9 membrane attack complex (MAC)** into the cell membrane forms a **“pore”.**

-- This results in **lysi**s of many types of cells including RBCs, bacteria and tumor cells.

-- **Gram negative** bacteria, esp., *Neisseria* spp. are very susceptible.


C5b
C7
C6
C8
C9
C9
C9
C9
C9
C8
Cell Membrane
Intracellular Space

8. Complement products cause enhancement of antibody production

-- **Binding of C3b** to its receptors on the surface of activated B cells greatly **enhance** antibody production as compared with cells activated only by antigen.

-- Low concentration of antibody and C3b significantly **impairs** host defenses resulting in multiple, severe, **pyogenic** infections.

Clinical aspects of complement

-- **Inherited** or **acquired deficiency** of some serum components esp. C5-C8 greatly **enhances susceptibility** to *Neisseria* bacteremia and other infections.

-- **Deficiency of C3** leads to severe, **recurrent pyogenic** sinus and respiratory infections.

-- Inherited deficiency of **C1 esterase inhibitor** results in **angioedema** (swelling underneath the skin).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