Complement

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Complement

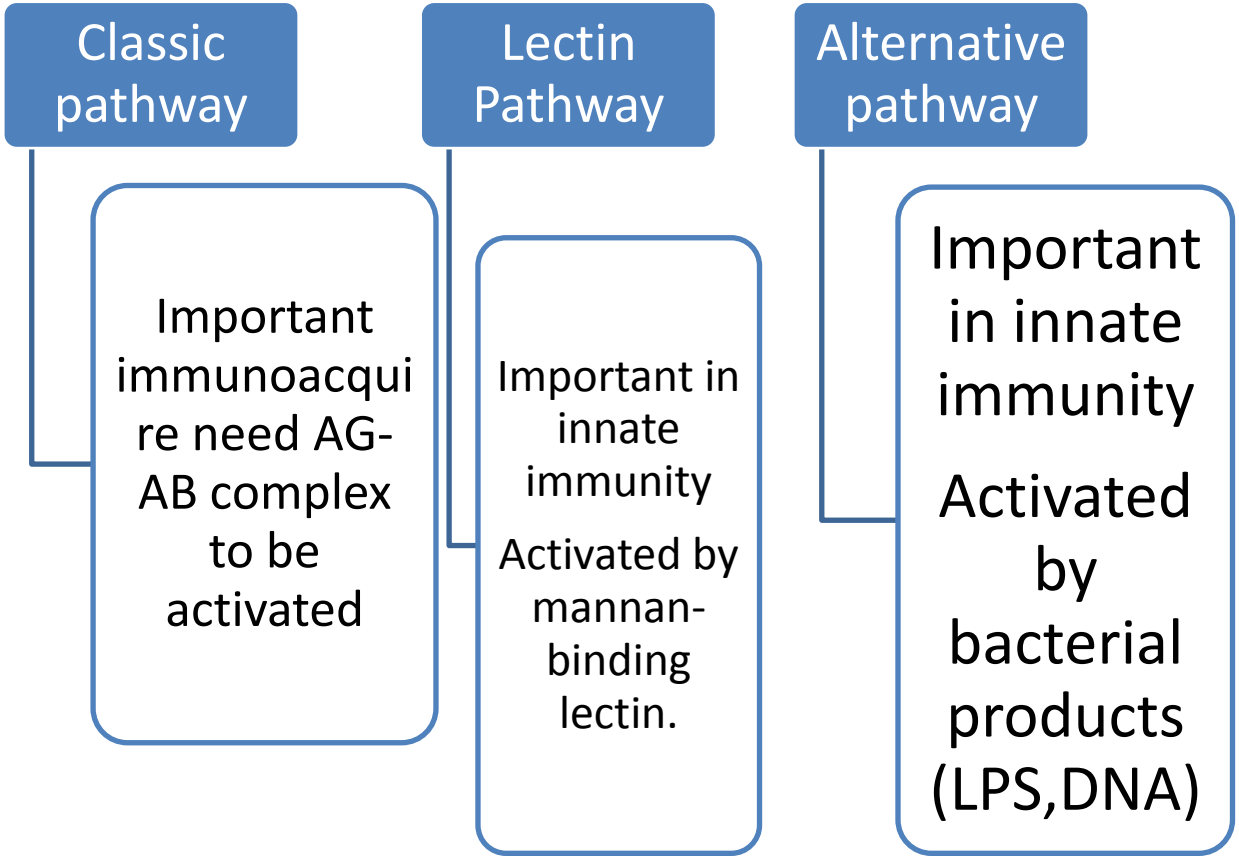
- The Complement System Consists of :
- Approximately 30 soluble and cell-bound proteins that are present in normal human serum
- Complement protein are synthesized mainly in **liver, also blood monocytes and tissue macrophage.**
- Complement is heat labile (i.e- Inactivated by heat) 56 degree centigrade for 30 minutes
- Complements have biological role in both INNATE and ACQUIRED IMMUNITY.

The basic functions of complement

1. Lyses of cells such as bacteria, viruses,allografts and tumor cells .
2. Generation of mediators which activate and trigger specific cells for inflammation and secretion of immunoregulatory molecules.
3. Opsonization , which promote phagocytosis of particulate ANTIGENS.
4. Immune clearance, which removes immune complexes from circulation and deposits them in the ***spleen*** and ***liver***.

Activation of Complement

- Activation of complement components occurs via one of the three pathways



complement

- All three pathways leads to the production of C3b the central molecule of the complement decade.

1. It combines with other complement component to generate C5 (convertase enzyme) which lead to production of **membrane attact complex**

Biological affect of complement

1. CELL LYSIS
2. ANTIGEN OPSONIZATION
3. VIRAL NEUTROLIZATION
4. INFLAMATORY RESPONSE
5. SOLUBILIZATION OF IMMUNE COMPLEX

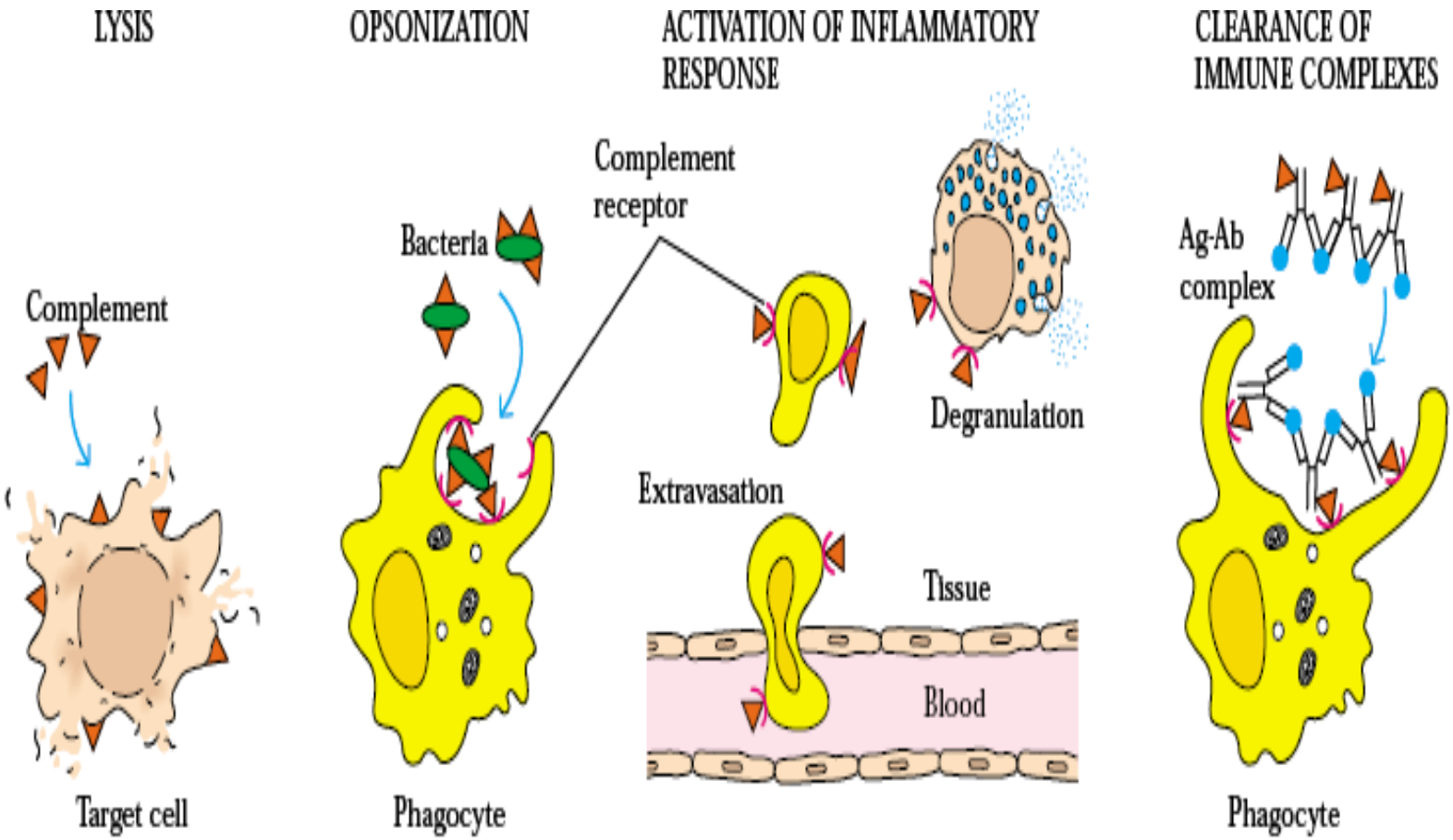


FIGURE 13-1 The multiple activities of the complement system. Serum complement proteins and membrane-bound complement receptors partake in a number of immune activities: lysis of foreign cells by antibody-dependent or antibody-independent pathways; opsonization or uptake of particulate antigens, including bacteria, by phagocytes; activation of inflammatory responses; and clearance of circulating immune complexes by cells in the liver and spleen. Soluble complement proteins are schematically indicated by a triangle and receptors by a semi-circle; no attempt is made to differentiate among individual components of the complement system here.

1. Cell Lysis

Cells susceptible to complement mediated - lysis are :

1. Viruses

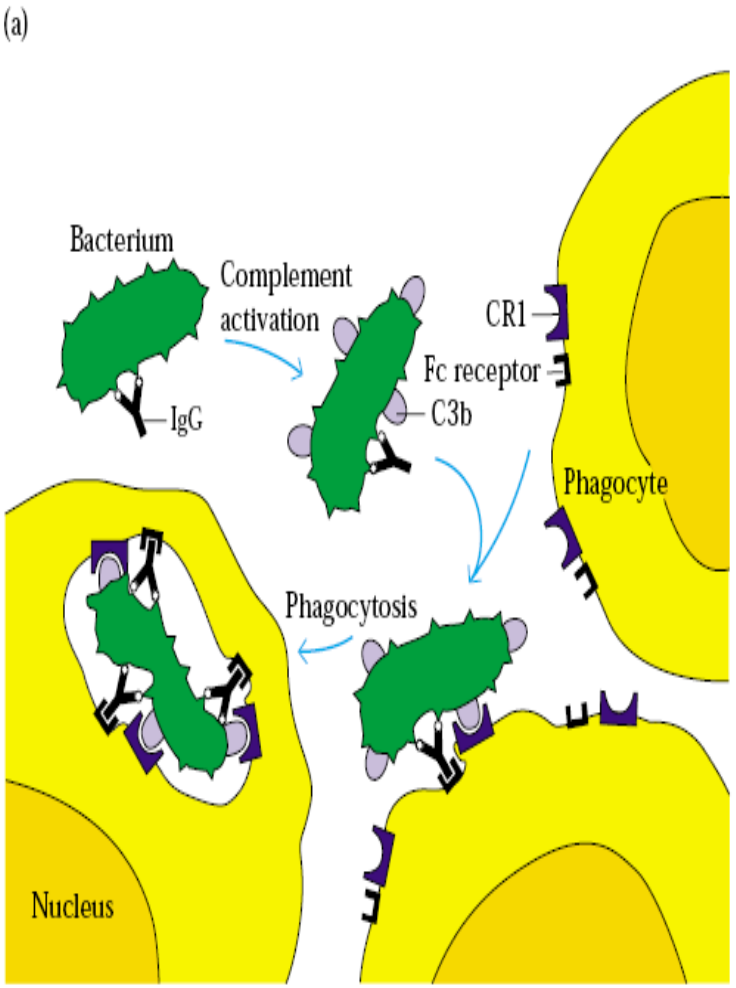
2. Gram negative bacteria not all

some gram negative bacteria and most of gram positive bacteria are generally *resistant* to complement mediated - lysis

2. Antigen Opsonization

C3b is the major & potent opsonin comlement

Phagocytic cells (*Neutrophils* , *monocytes & macrophages*) express complement receptors can bind C3b that will enhance phagocytosis



3. Viral Neutralization

Mechanisms of Viral neutralization :

1. For most viruses the binding of serum ANTIBODY to the viral structural protiens create CLASICAL viruses can activate the alternative pathway. PATHWAY of complement also some other

2. Binding of Ab & complement to the viral particles forms a thick protein coat which neutralizes viral infectivity.

3. Complement is effective in Lysing most enveloped viruses that leads to fragmentation of the envelope & disruption of the nucleocapsid

4. Inflammatory Response

- Smaller fragments resulting from complement cleavage , **C3a, C4a & C5a** called **ANAPHYLATOXINS** which can bind to receptors on basophiles & mast cells → degranulations with release of pharmacologically active mediators :

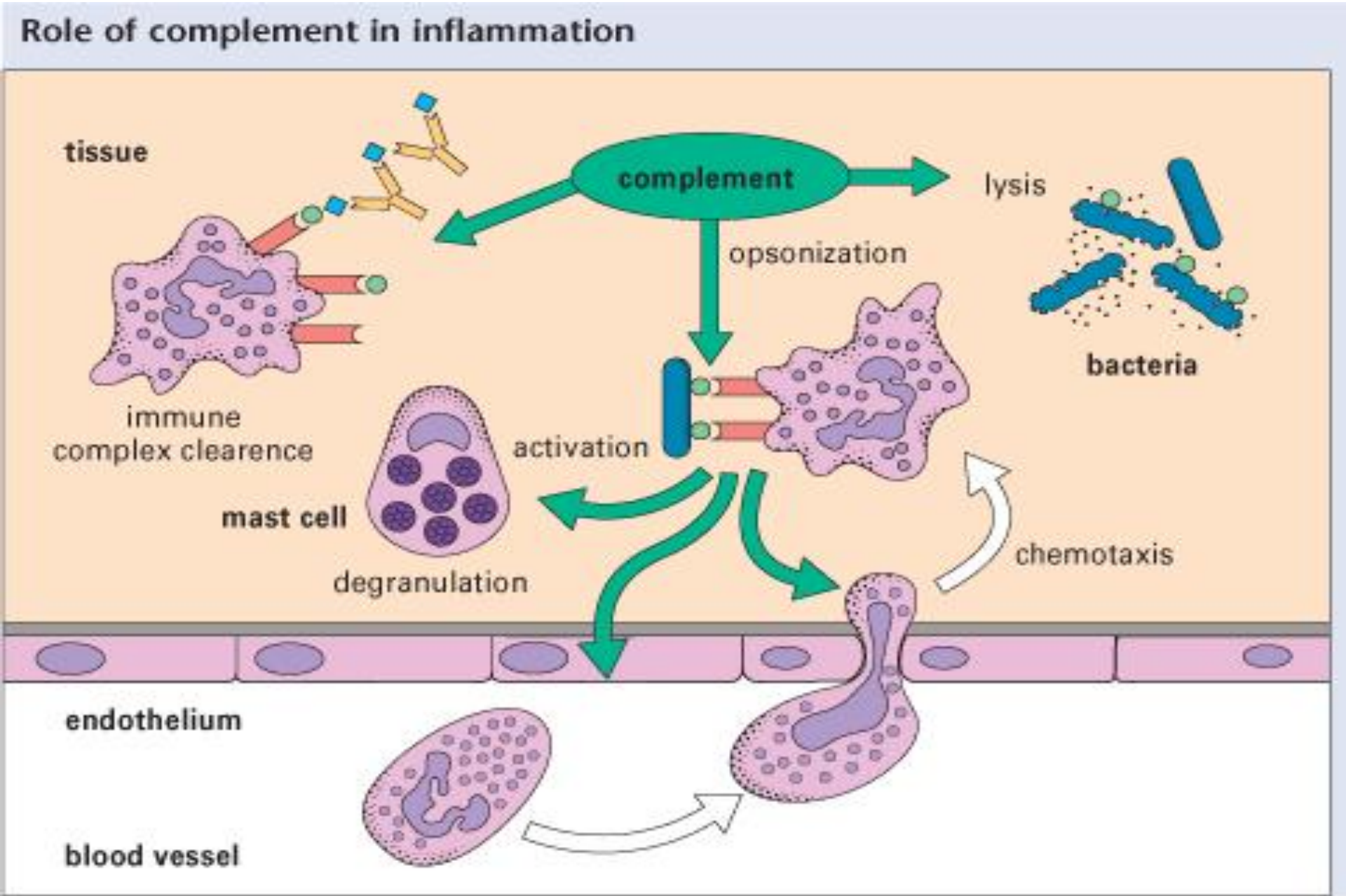
↓

1. Smooth muscle contraction
2. Increased vascular permeability

- So complement activation → influx of fluids that carries antibody & phagocytic cells to the site of antigen entry

- C3a, C5a & C5b67 are the most important chemotactic factors with C5a is the most potent in mediating this process

Complement has a central role in inflammation causing chemotaxis of phagocytes, activation of mast cells and phagocytes, opsonization and lysis of pathogens, and clearance of immune complexes.



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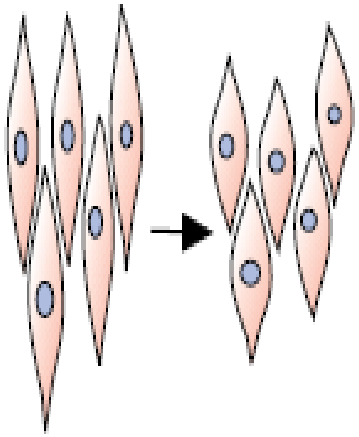
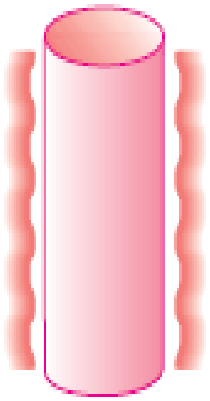
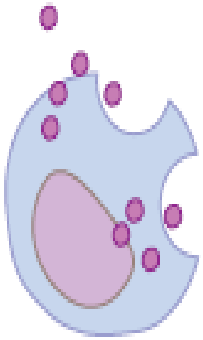


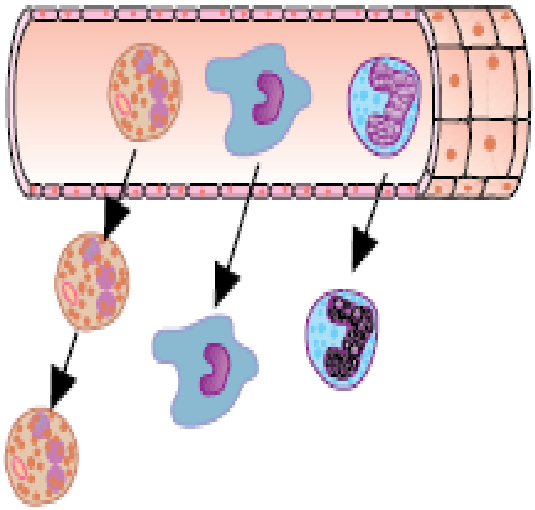
1. Contraction of smooth muscles



2. Increased permeability of blood vessles



3. Degranulation of basophils



4. Chemotaxis, release of O_2-radicals and lysosomal enzymes

Anaphylatoxins

C3a	+	+	+	-
C4a	(+)	(+)	(+)	-
C5a	++++	++++	+	++++

5. Solubilization of Immune Complexes

- This function is evident in patients with SLE

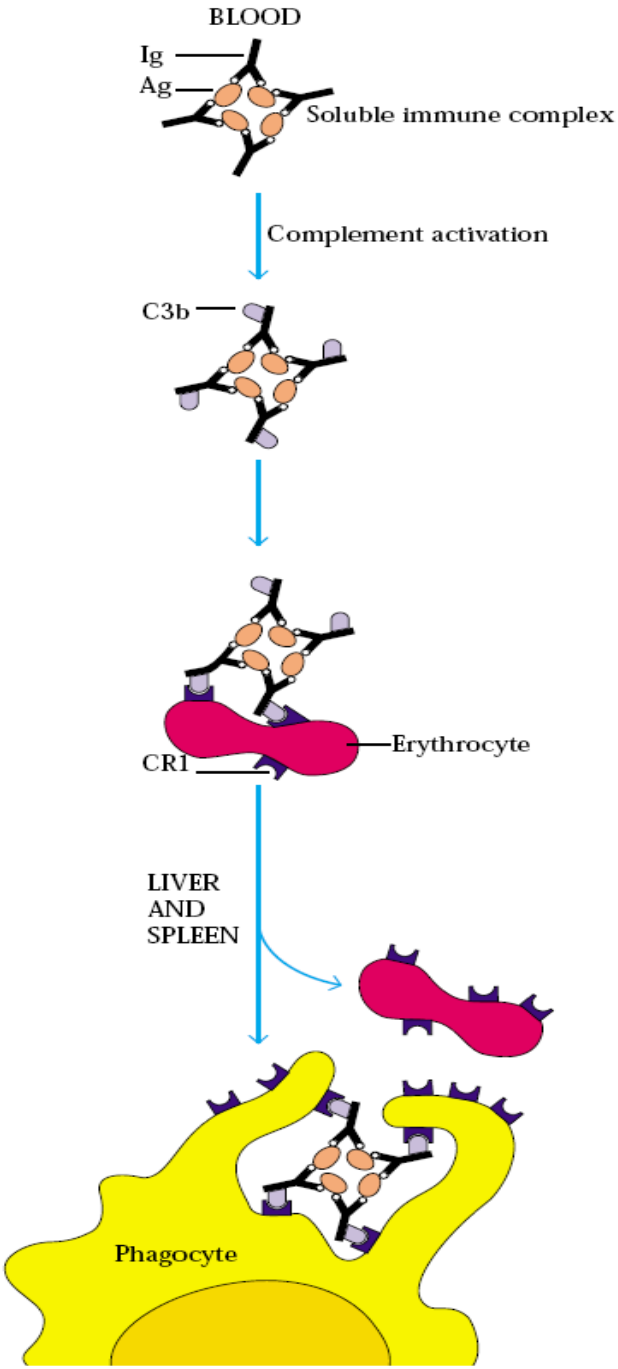
- Complement deficiency **(C4)** leads to SLE as it interfere with effective solubilization & clearance of immune complexes which in turn leads to their persistence

TISSUE DAMAGE

(Type II or III hypersensitivity reaction)

- RBCs express CR1. Coating the immune complexes with C3b helps in binding to CR1 on RBCs.

- These immune complexes are carried to liver & spleen where they are separated from RBCs to be phagocytosed & prevented from their deposition in tissues



Regulation of the Complement System

- Complement can be activated spontaneously through the alternative pathway

- It must be controlled by regulatory proteins to prevent complement mediated damage of healthy autologous cells

Several serum proteins regulate the complement system :

1. C1 inhibitor regulate classic pathways
2. Alternattive pathway regulator
3. Decay accelerator factor in glycoprotien located on surface of human cell prevent formation of membrane attack complex

Regulation of the complement system

- In classic pathways only IgG and IgM fix complement antigen antibody complex activate C1
- The complement binding site of the heavy chain of IgM&IgG is not available to the C1 if antigen is not bound to antibodies
- This means that complement is not activated by IgM&IgG presented in blood if not attached with antigen.

Regulatory Mechanisms

1. Serum proteins enzymatically attack complement components so inactivate them

2. Serum proteins bind to & inhibit complement component

3. Regulatory proteins in cell membranes

Complement Deficiency

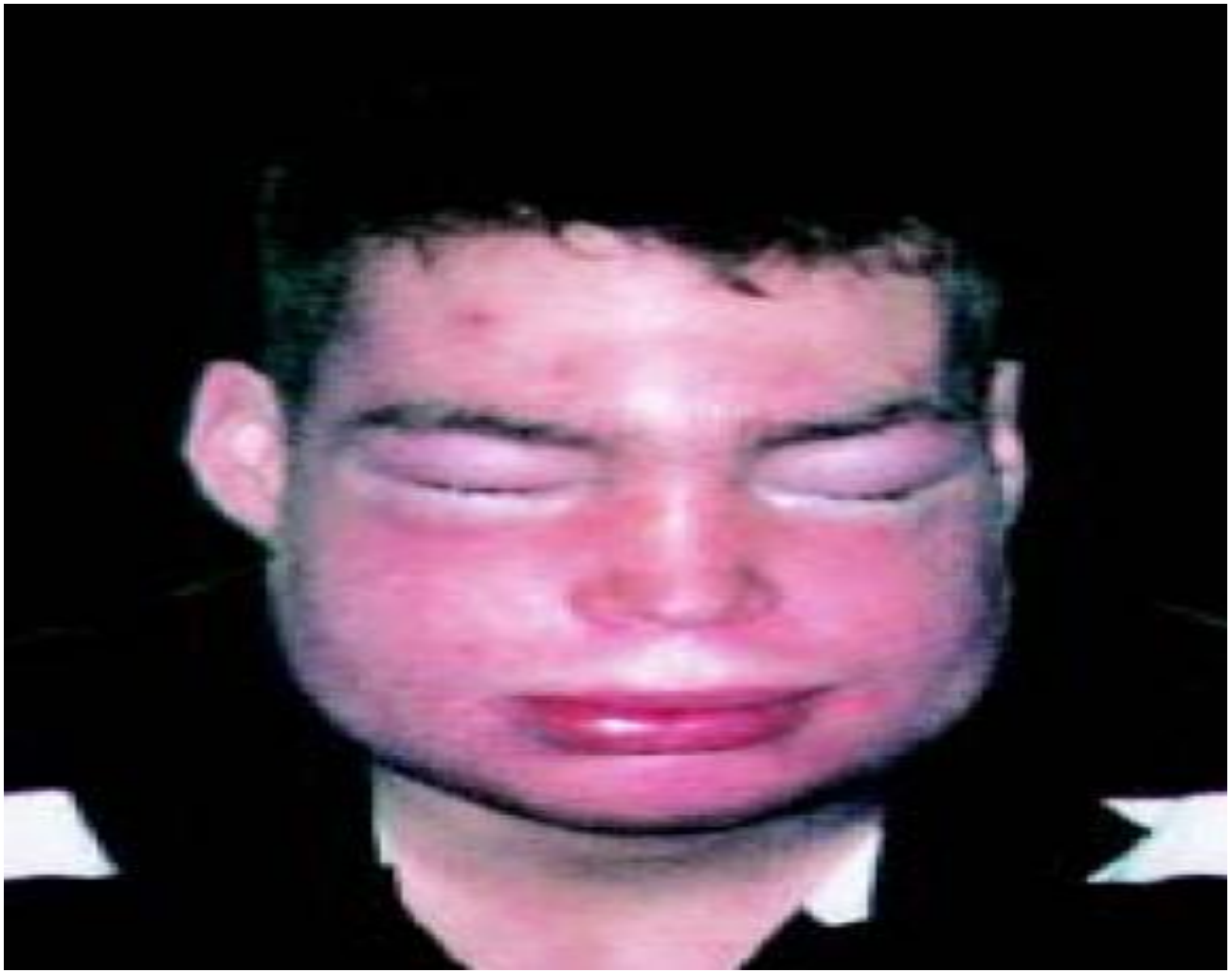
- Deficiency of one of the regulatory components can lead to a significant disease

- *Example :*

Deficiency of C1 inhibitor (C1Inh) → Hereditary Angioedema

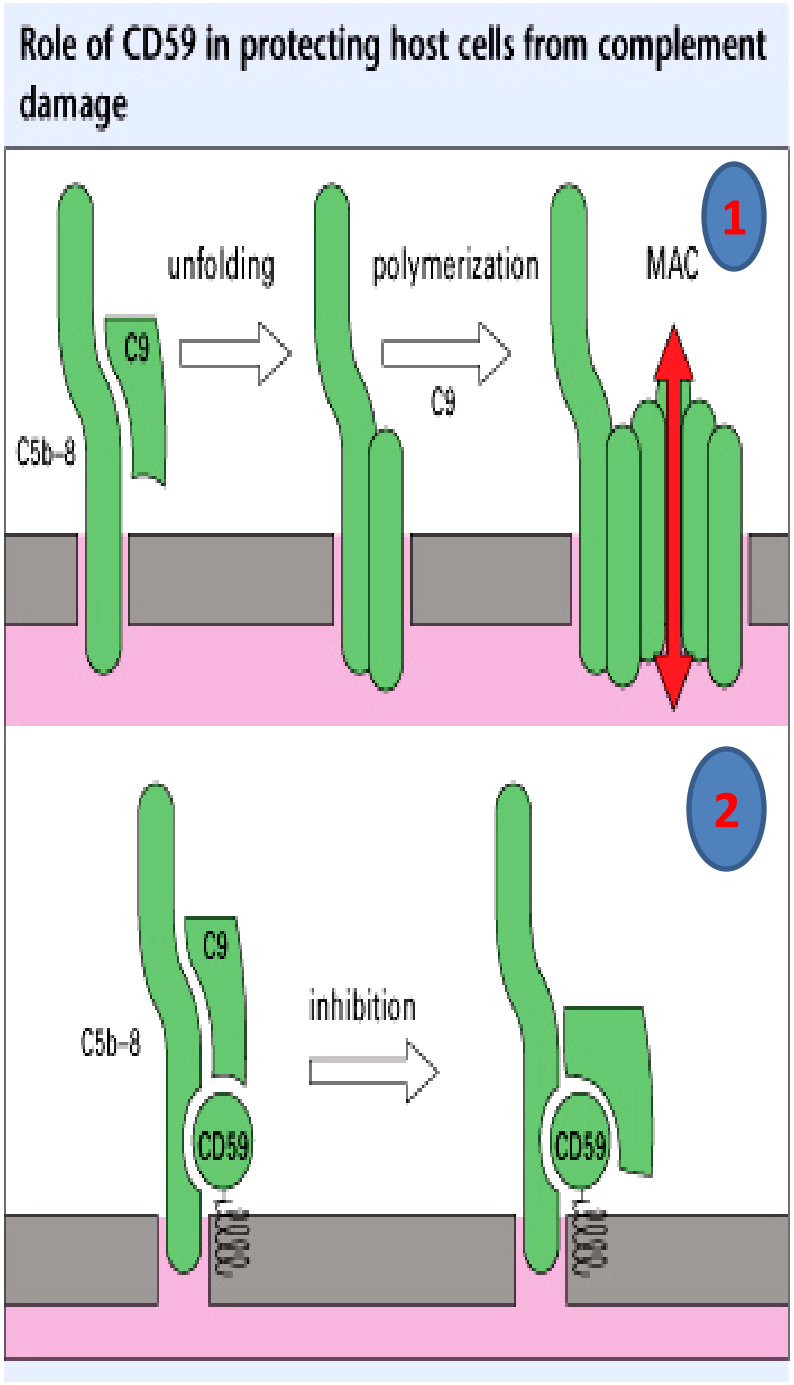
There is activation of Classical Pathway

It may be fatal if not treated & controlled ; as if it occurs in Larynx that end with fatal swelling & oedema which can obstruct the airway



Deficiency or dysfunction of CD59 can leads to → Increased susceptibility of erythrocytes (RBCs) to lysis ***(Low levels of autologous complement that is much lower than normally required)*** **in a diseases called → Paroxysmal Nocturnal Haemoglobinuria (PNH)**

- The upper diagram (1) : Assembly of MAC in absence of the regulator CD59. C9 binds C5b-8, with further recruitment of C9 molecules, which in turn forms MAC
- In the lower diagram (2) : CD59 binds the C5b-8 complex and prevents insertion of C9, which is essential for the initiation of MAC pore formation.



Clinical Aspects of complement

- Inheritance or acquired deficiency of some compliment component can greatly enhance susceptibility to infection with *NEISSERIA*
- Deficiency of C1 estrase inhibitor → anaphylatoxin which cause capillary permeability →oedema (angioedema)
- In blood transfusion mistake classic pathway complex well activated → red cell heamolysis
- Immune complex bind complement e.g (acute glomerulonephritis and systemic lupus erythmatosus → attracts polymorphonuclear leukocytes which release enzymes that damage tissues
- Patients with severe liver disease e.g alcoholic cirrhosis or chronic hepatitis B will have significant ⇓ complement → ⇑ pyogenic bacterial infection

Measurement of Complement Components

Measurement of Complement components especially : C3 & C4

- ELISA
- Single radioimmuno diffusion
- Nephlerometry

Mainly in Immunodeficiency diseases & autoimmune disorders (SLE)

Complement Haemolytic Assay (CH50)

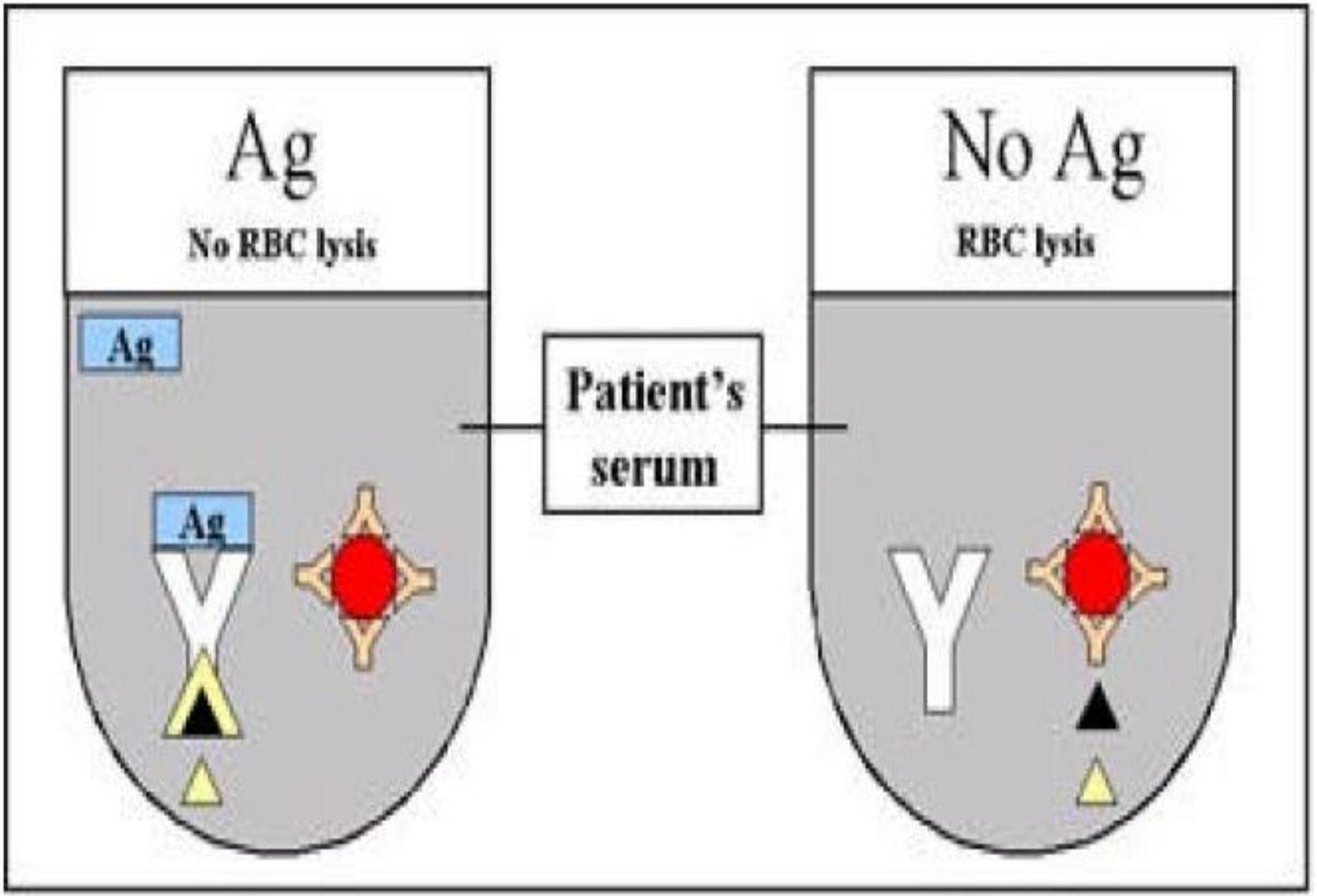
- Functional evaluation of Classical pathway with assessment of MAC
- CH50 measures complement required to obtain 50% haemolysis of sheep RBCs under standard conditions
- Haemolysis is measured by amount of haemoglobin released from lysed RBCs

Measurement of Complement Activity

- Complement Fixation Test **(CFT)** depends on formation of Ag/Ab complex that based on consumption of complement

- CFT can be used to identify one of them if the other is known (Usually AB)

- Mainly used in viral infections


Ag
No RBC lysis
Ag
Ag
Patient's serum
No Ag
RBC lysis

ANY QUESTIONS ?

Thank you

Opsonization

- Microbes such as bacteria and virus are phagocytosed much better in presence of C3b because C3b receptor on surface of many phagocytes

Chemotaxis

- C5a and C5,6,7 complex attract neutrophils
- Also enhance the adhesion of neutrophil to the endothelium (inflammation)

Anaphylatoxin

- C3a,C4a C5a cause degranutlation of ***mast*** cells with release of mediators
- E.g histamine → vascular permeability and smooth muscle contraction (bronchospasm)

Cytolysis

- Insertion of C5b,6,7,8,9 complex into the cell membrane leads to killing or lysis of many cells including erythrocytes ,bacteria and tumor cells

Enhancement of antibody production

- B cell have receptors of C3b so binding C3b with its receptor on B cell will activate production of antibodies so people with C3B deficiency the production with antibody is much less

ANY QUESTIONS ?

Thank you