

COMPLEMENT SYSTEM

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DEFINITION

The term complement refers to a system of factors that occurs in normal serum and is activated characteristically by antigen – antibody interaction and which subsequently mediates a number of biologically significant consequences

HISTORY

- Buchner (1889)
- Bordet (1895) – Immune bacteriolysis & haemolysis require 2 factors
 1. Heat stable antibody
 2. Alexine (Heat labile)
- Ehrlich – Complement
- Bordet & Gengou (1901) – Complement Fixation Test
- 3 systems – Coagulation, Fibrinolytic & Kinin

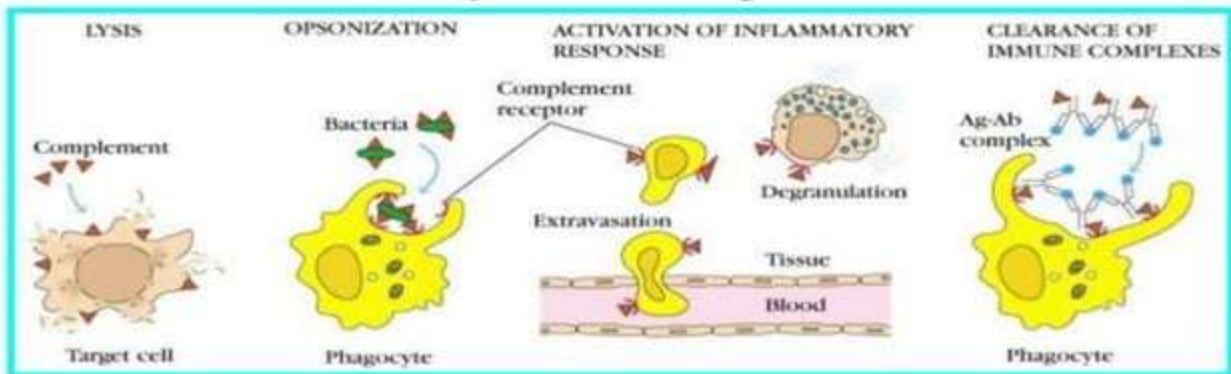
GENERAL PROPERTIES

- Non specific
- 5% normal serum protein
- Destroyed in 30m at 56° C
- Bind only to antibodies that have combined with their antigens
- Only Ig M, Ig G 3,1,2 fix complement
- Binds to Fc portion of Ig
- 30 proteins – C components + Properdin + Control Proteins
- C1 to C9
- Innate & acquired immunity

COMPLEMENT ACTIVATION

- Lysis of cells and bacteria
- Promotes virus neutralisation
- Opsonisation
- Immune clearance
- Amplification of inflammatory process

The Multiple Activities of the Complement System

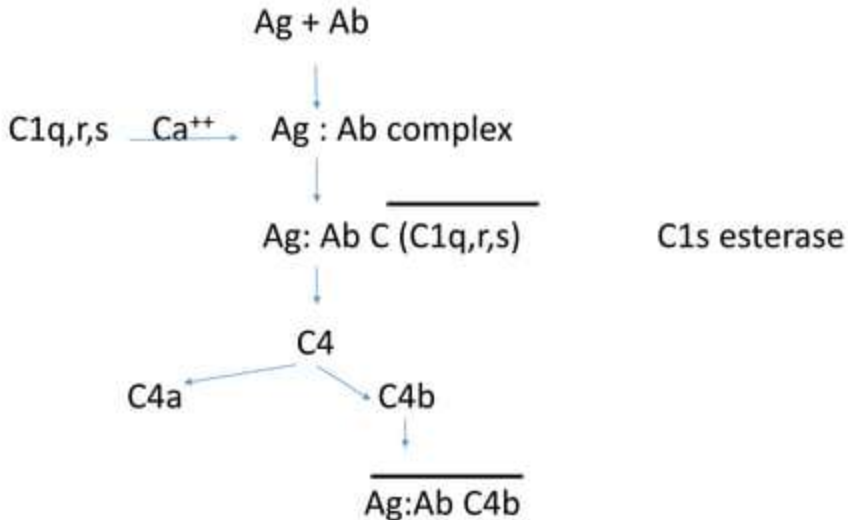


Serum complement proteins and membrane-bound complement receptors partake in a number of immune activities: lysis of foreign cells by antibody-dependent or antibody-independent pathways; opsonization or uptake of particulate antigens including bacteria, by phagocytosis; activation of inflammatory responses; 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 semicircle; no attempt is made to differentiate among individual components of the complement system here.

PATHWAYS

- Classical complement
- Alternative
- Lectin

CLASSIC COMPLEMENT PATHWAY



Ag: Ab C4b (C2 Convertase)

↓ Mg⁺⁺
c2

C2a

C2b

kinin

C4b2a (C3 Convertase)

C3

C3a

C3b

Anaphylotoxic
& Chemotactic

C4b2a3b

C4b2a3b (C5 convertase)



C5

C5a

C5b

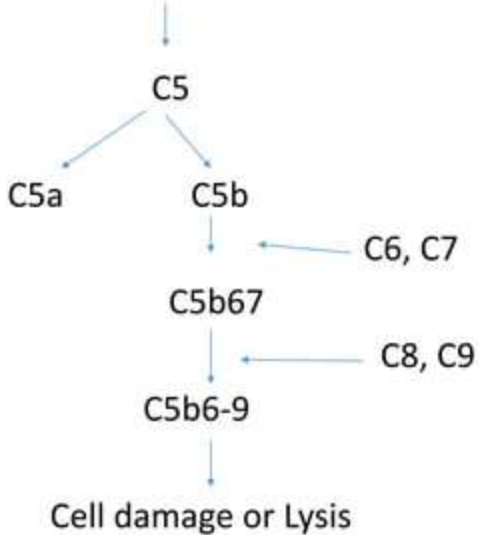
C6, C7

C5b67

C8, C9

C5b6-9

Cell damage or Lysis



ACTIVATION

- Antigen antibody complex
- DNA
- C reactive Protein
- Trypsin like enzymes
- Retroviruses

The Alternative Pathway

Components:

- C3
- Factors B & D (C3 Proactivators)
- P (Properdin factor)
- Factor I (C3b inactivator)
- Factor H (C3b inactivator accelerator)

Activators:

- Endotoxin
- Infectious agents

C3b in circulation

+

Activators (eg. Endotoxin)

Inactivated by Factor H & I

C3b (Bound)

Mg⁺⁺

Factor B

C3bB

Ba

Factor D

C3bBb (C3 convertase)

C3

C3a

C3b

Cascade

Chemotactic & anaphylactic



LECTIN PATHWAY

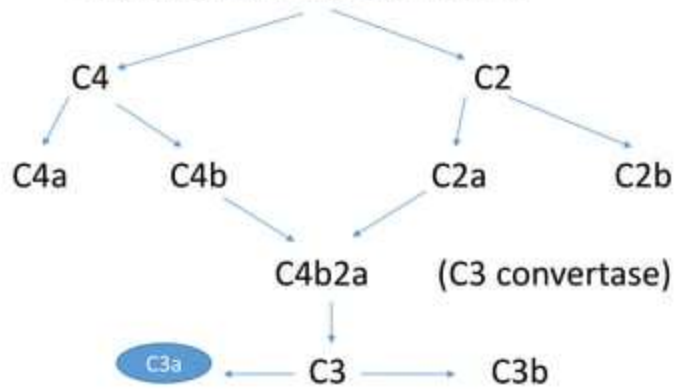
MBL



Mannose on Pathogen surface



Activation of MASP1/ MASP2



REGULATION OF COMPLEMENT ACTIVATION

INHIBITORS

1. C1 esterase Inhibitor
2. S Protein – $\overline{C67}$

INACTIVATORS

- Factor I
- Factor H
- Anaphylatoxin inactivator
- C4 binding protein

BIOLOGICAL EFFECTS OF COMPLEMENT

- Phagocytosis
- Inflammatory response
- Hypersensitivity
- Autoimmune diseases
- Endotoxic shock
- Immune adherence
- Conglutination

PHAGOCYTOSIS

- Opsonisation
- Complement receptors (CR 1,2,3,4)
- B Lymphocytes (CR2) – Epstein Barr virus

INFLAMMATORY RESPONSE

- C fragments – amplify the inflammatory response
- C2b – Kinin
 - amplifies the inflammatory response
- C3a, C5a – anaphylotoxic (Histamine releasing)
 - Chemotactic
- C 567 – Chemotactic
 - Relative lysis

HYPERSENSITIVITY REACTIONS

- Type II (Cytotoxic) – Incompatible transfusion
 - Thrombocytopenia in Sedormid purpura
- Type III (Immune complex) – Serum Sickness
 - Arthus reaction
- Nephrotoxic Nephritis



AUTOIMMUNE DISEASES

- Systemic Lupus Erythematosus
- Rheumatoid Arthritis
- Autoimmune haemolytic anemia

ENDOTOXIC SHOCK

- Endotoxin – Alternative pathway
- Massive C3 fixation
- Thrombocytopenia
- Disseminated Intravascular Coagulation (DIC)
- Gram negative Septicaemia
- Dengue Haemorrhagic fever

IMMUNE ADHERENCE

- Adheres to Erythrocytes & non primate platelets
- Rapidly phagocytosed
- C3, C4

CONGLUTINATION

- Bovine serum – Conglutinin
- Clumping of particles or cells coated with Complement
- Bound C3
- Calcium
- Immunoconglutinin (IK) – Immunisation with complement coated materials

MICROBIAL EVASION OF COMPLEMENT MEDIATED DAMAGE

- LIPOPOLYSACCHARIDE – Prevents insertion of MAC
 - Escherichia coli, Salmonella
- MEMBRANE PROTEINS – Interacts MAC
 - Neisseria gonorrhoea
- Elastases
 - Inactivates anaphylatoxins
- Peptidoglycan
 - Gram positive Bacteria
- Bacterial capsule
 - Physical barrier between C3b & receptors (CR1) on phagocytic cell
- Proteins
 - Mimics complement regulatory proteins
 - Vaccinia virus, Herpes simplex, Epstein Barr, Toxoplasma cruzi, Candida albicans

Assay of Complement/Complement Activity

- Radial Immunodiffusion -> To assay 'C' components
- Complement Activity tests -> Measure the ability of 'C' present in serum to lyse an indicator Ag-Ab system (eg: Sheep RBC-Anti erythrocyte antibodies)

BIOSYNTHESIS OF COMPLEMENT

| | |
|------------|-----------------------|
| C1 | INTESTINAL EPITHELIUM |
| C2, C4 | MACROPHAGES |
| C5, C8 | SPLEEN |
| C3, C6, C9 | LIVER |

| <u>Deficiency</u> | <u>Disease</u> |
|--------------------------------|---|
| C1 Inhibitor | Hereditary Angioneurotic edema |
| C1 , C2, C4 | Systemic Lupus Erythematosus, Collagen Vascular Diseases |
| C3, C3b inactivator | Recurrent Pyogenic Bacterial Infections |
| C5 – C8 | Recurrent Neisserial Infections, Toxoplasmosis |
| C9 | No particular disease |

HEREDITARY ANGIONEUROTIC EDEMA



- C2b
- Kinin
- Fresh Plasma
- Epsilon Aminocaproic acid



THANK U