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Complement

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Definition : series of heat-labile serum proteins

Site : serum and all tissue fluids except urine and CSF

Synthesis : in liver – appear in fetal circulation during 1st 13 W

Function : Responsible for certain aspects of immune response and inflammatory response

Activation : antigen-antibody complex or endotoxin, capsule series of proteins activated sequentially

Inactivation: inhibitors in plasma (short lived)

Biological effects: either beneficial or harmful to host

Complement pathway

A) Classical pathway:

- Complement is activated by antigen –antibody complex (IgM or IgG)

- Fc portion of the antibody form a binding site for C1q

- The numerical sequence of the complement factors in the classic pathway is:

  C1q,r,s , C4, C2, C3, C5, C6, C7, C8, C9

A) Classical Pathway

The reaction sequence divided into three stages:

1) Recognition stage:

- C_{1q} act as the recognition element
- It binds to Fc portion of IgM or IgG
- The activated C_1 molecule can cleave many C_4 molec.

2) Activation stage:

The complement components C_4, C_2, C_3, C_5, C_6, C_7, C_8, C_9 participate in that order

3) Membrane attack stage:

Complement components C_5, C_6, C_7, C_8, C_9 participate where cell membrane damage and cell lysis occur

B) Alternative pathway

This pathway is initiated by:

* Bacterial endotoxin, polysaccharide capsule, aggregates of IgE and properdin

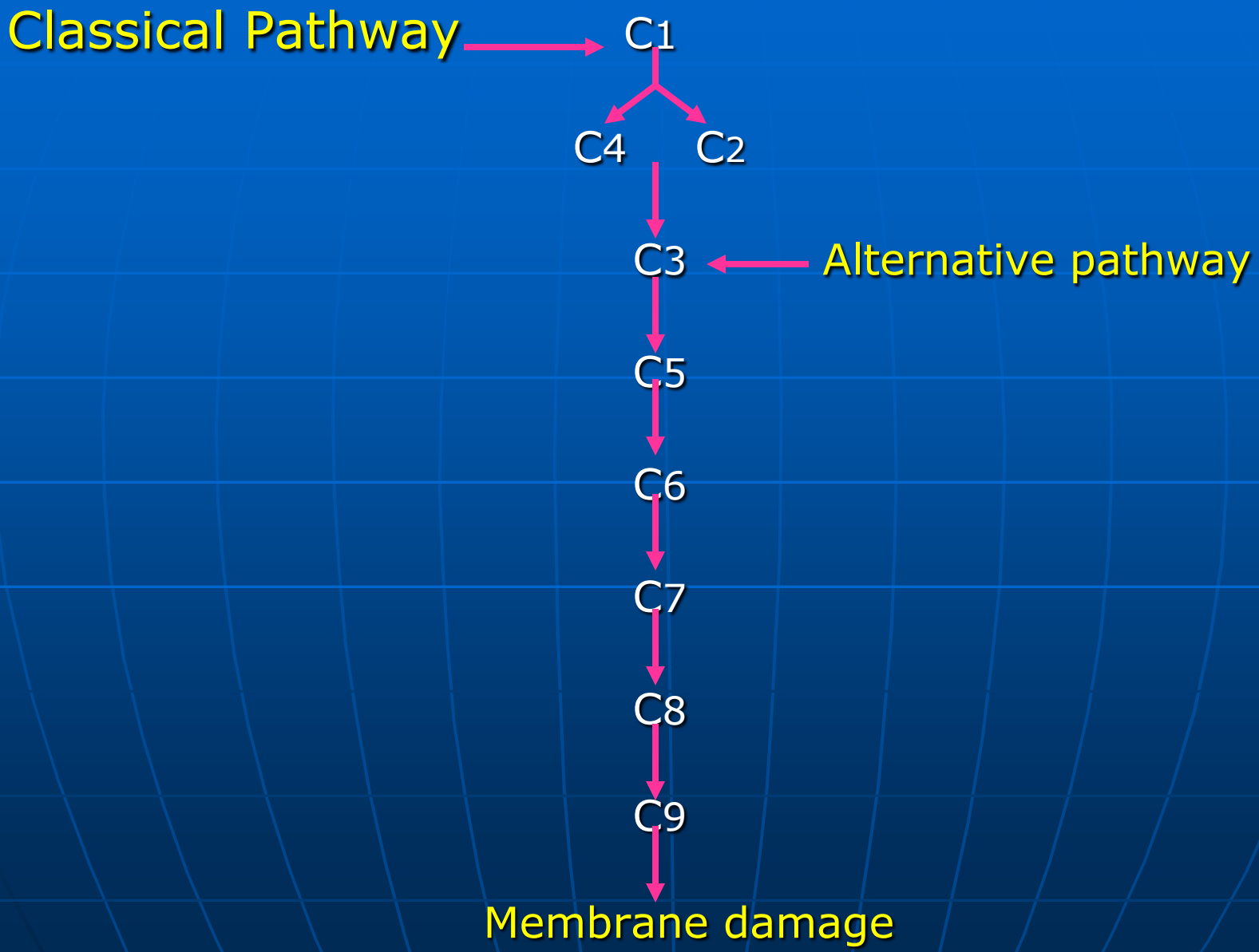
* It starts at C3 then C5, C6, C7, C8, C9

* The complement compon. C1, C4, C2 are by-passed

* Antibodies are not required to initiate activation of this pathway

* This pathway provides a means of non-specific resistance

Complement Activation



Classic And Alterenative pathways

Classic Pathway	Alternative pathway
* Specific acquired immunity	* Non-specific innate immunity
* Initiated by antibody	* Bacterial endotoxin, capsule
* Interaction of all components	* C1, C4, C2 are by-passed
* Properdin system not involved	* Properdin system is involved

C-Mannose-Binding Protein Pathway

- A third way of activating the complement system involves mannose-binding protein. This ,is like the alternative complement pathway, is a part of innate immune system. When macrophages ingest bactria or other foreign material they are stimulated to secrete IL-1, IL-6 and TNF-α (Tumor Necroting Facter). These three cytokines act on hepatocytes, stimulating them to secrecte acute-phase proteins, among which is mannose-binding protein. Mannose is a major component of bacterial and fungal cell walls. It has strucyural similarities to C1q and forms a multimolecular complex with two serum proteases designated MASP-1 and MASP-2. This complex cleaves C2 and C4 so activates the classical pathway.
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Biological Effects of Complement

Beneficial effects:

1) Cytolysis:

- activated complement proteins polymerize on cell surfaces of bacteria or erythrocyte to form pores in its membrane (killing by osmotic lysis)

Biological Effects of Complement

2) Opsonization:

- binding of complement proteins opsonin (C3b) to surfaces of foreign organisms or particles

- Phagocytic cells express specific receptors for opsonins, so promote phagocytosis

Biological Effects of Complement

3) Inflammatory response :

Small fragments released during complement activation have several inflammatory actions:

a) C5a is chemotactic and attract neutrophiles and macrophages

b) C5a activate phagocytes and neutrophils

C) C3,C4 and C5 are anaphylatoxins
Cause degranulation of mast cells and release of histamine and other inflammatory mediators

Biological Effects of Complement

4) Immune complex clearance:

- C3b facilitate binding of immune complex to several surfaces (erythrocytes) and enhance removal by liver and spleen

- binds erythrocytes to blood vessels , make them as easy prey for phagocytosis

- C3 deficiency associated with Immunocomplex disease and susceptibility to recurrent infections

Biological Effects of Complement

5-Enhancement of antibody production:

- Binding of C3b to its receptors on activated B cells (CR2) greatly enhances antibody production

- Patient who are deficient in C3b produce much less antibody than normal individuals and more susceptible to pyogenic infection

Biological Effects of Complement

Harmful effects:

- If complement activate systematically on a large scale (Cm –ve bacilli)

- If activated by an autoimmune response to host cells

Thanks