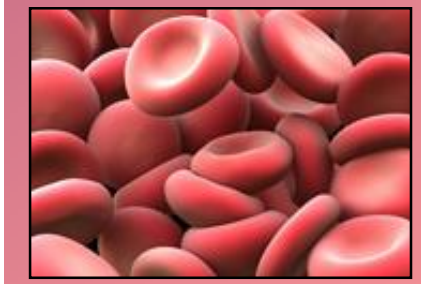
The Complement System



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What's The Complement system?!

Biosynthetic sites

Activation Method

Nomenclature

Biological Effect..

Blood Test..

C4

Complement Deficiencies

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In the late 19th century, serum was found to contain a nonspecific heat-labile complementary principle that have a cytolytic function which primarily lyses bacteria and erythrocytes that were sensitized with antibody.

Ehrlich and Morgan termed this factor .. complement

The complement system as understood today is a multimolecular system composed of : more than 20 proteins and circulate in their inactive form.

When activated, these proteins produce various complexes that play a major role in the innate and adaptive immune defense.

and consisting of serum proteins, serosal proteins,
and cell membrane receptors that bind to complement fragments.
They constitute 10% of the globulin fraction of serum.

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Hepatocytes

Monocyte/Macrophage

Fibroblast

Haematopoietic

Endothelial

Reproductive

Adipocytes

Astrocytes

Neurons

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The complement system functions as an interactive sequence, with one reaction leading to another in the form of a cascade*.

It is initiated by a wide variety of substances and has 2 phases.

In the first phase, a series of specific interactions leads to formation of intrinsic complement proteinase, termed C3 convertase.

Depending on the nature of complement activators, the classic pathway, the alternative pathway, or the newly discovered lectin pathway is activated predominantly to produce C3 convertase.

Each of these pathways uses different proteins.

The second phase for each involves cleavage of C3b, generating multiple biologically important fragments and large, potentially cytolytic complexes.

**Cascade* is a sequence of successive activation reactions involving enzymes (enzyme cascade) or hormones (hormone cascade) characterized by a series of amplifications of an initial stimulus.

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There are 3 pathways to activate the system..

1-The classical pathway

(termed classical because it has been studied for >100 y and was the first pathway to be discovered)

Activated by antigen/antibody complex..

2-The alternate pathway

Activated by microbial cell wall..

3-The mannose-binding lectin (MBL) pathway.

Activated by bacterial lectins..

The end result of this activations always the same .

Only the initial steps differ..

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The ultimate end result of complement activation is the formation of membrane attack Complex (MAC), Formed by Components C5 through C9 ..

In addition , intermediate products such as c3a,,c5a and c3b may play role in upregulating the immune response through chemotaxis or opsonization..

Complement activation via the classical pathway effectively lyses antibody-coated pyogenic bacteria such as Streptococcus pneumoniae and Haemophilus influenzae and cells coated with antibodies (often microbe-infected cells).

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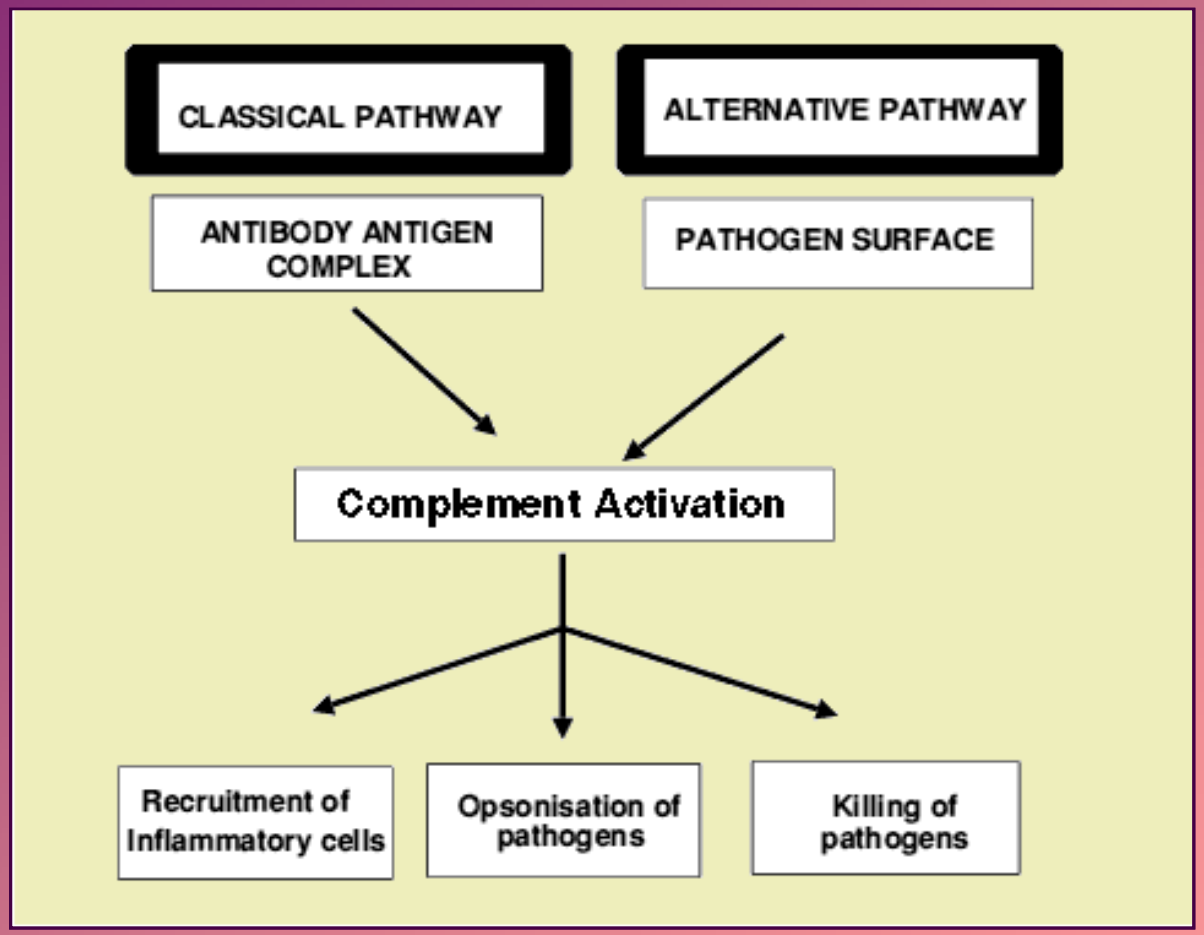

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Nine complement components in the classical pathway are designated by a capital letter C and numbers 1-9.

Two proteins that participate in the alternate pathway are termed factors and are represented by capital letters B and D.

Proteolytically cleaved components of proteins are expressed by lowercase letters (e.g., C2a, C2b).

Inactive components are designated with an " i "

(e.g. inactivated C3b is termed iC3b)..

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The biologic effects of complement include promotion of chemotaxis and anaphylaxis, opsonization and phagocytosis of microorganisms, and removal of immune complexes from the circulation.

Most complement components are acute phase reactants, and their concentration increases in states of infection, trauma, and injury.

Immune complexes formed in the circulation are coated with C3b and bind to erythrocytes, which then transport them to the liver and spleen for removal.

This process maintains the solubility of the immune complexes.

In the early phases of viral infection, when the amount of antibody is limited, the fixation of C3b to the viral antigen-antibody complex increases neutralization.

The terminal components of the complement system result in lysis of virus-infected cells, tumor cells, and most microorganisms.

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The C3b and C4b molecules are opsonins.

That is they coat foreign organisms either by the AP or those already bound by antibody.

Opsonisation of particles greatly enhances their phagocytosis by means of binding to specific complement receptors.

C3b fixes to the antigen-antibody complex and permits its adherence to cells (eg, neutrophils, basophils, eosinophils, monocytes) that have receptors for C3b.

This particular action of opsonization helps in phagocytosis.

C3b-coated particles also bind to B lymphocytes and activate them to enhance the primary antibody response.

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The C5a and the C4a and C3a fragments are important inflammatory activators inducing vascular permeability, recruitment and activation of phagocytes.

Also they are anaphylatoxins and bind to mast cells, triggering the release of histamine and other mediators, leading to vasodilation, erythema, and swelling.

C5a is a major stimulus for influx of neutrophils, basophils, monocytes, and eosinophils.

C5b binds and recruits C6 and C7 to the target surface.

C7 and subsequently C8 change conformation to expose hydrophobic domains which insert in the lipid bilayer.

The C5b678 complex catalyses the polymerisation of the final component C9 which forms a transmembrane pore of ~ 10nm diameter causing lysis of the cell.

This macromolecular assembly is known as the Membrane Attack Complex (MAC).

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Immunochemical methods are used to demonstrate specific complement protein deficiencies by using specific antibodies for each component.

In certain cases, functional properties of complement components are diminished despite the presence of normal amounts of protein component detected by immunochemical measures. Functional assays are required for further evaluation.

C3 and C4 are the most commonly measured complement components..

A complement test may be used to monitor patients with an autoimmune disorder and to see if treatment for their condition is working.

e.g. patients with active **lupus erythematosus*** may have lower-than-normal levels of the complement proteins C3 and C4.

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Complement activity varies throughout the body.

e.g. in patients with rheumatoid arthritis, complement activity in the blood may be normal or higher-than-normal, but much lower-than-normal in the joint fluid..

*lupus

A condition of chronic inflammation caused by an autoimmune disease. Patients with lupus produce abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents.

Lupus can cause disease of the skin, heart, lungs, kidneys, joints, and nervous system. When only the skin is involved, the condition is called discoid lupus.

When internal organs are involved, the condition is called systemic lupus erythematosus. Both discoid and systemic lupus are more common in women than men (about eight times more common).

The disease can affect all ages but most commonly begins from age 20 to 45 years.

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1-Total blood complement level:

41 _ 90 hemolytic units

2- (C1) level:

16 _ 33 mg/dL

3- (C3) levels:

Males: 88 _ 252 mg/dL

Females: 88 _ 206 mg/dL

4- (C4) levels:

Males: 12 _ 72 mg/dL

Females: 13 _ 75 mg/dL

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Deficiencies of the complement components have been reported for most of the constituents. These deficiencies can be inherited or acquired and complete or partial.

Primary complement deficiencies are rare & inherited as autosomal recessive traits.

Except for deficiency of C1 esterase inhibitor, which is autosomal dominant.

Secondary deficiencies may follow complement-fixing (complement-consuming) immunologic reactions, such as drug-induced serum sickness, acute streptococcal glomerulonephritis, and acute active systemic lupus erythematosus.

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Signs and symptoms vary with the specific deficiency as follow..

C2 and C3 deficiencies and C5 familial dysfunction increase susceptibility to bacterial infection (which may involve several body systems simultaneously).

C2 and C4 deficiencies are also associated with collagen vascular disease, such as lupus erythematosus, and with chronic renal failure.

C5 dysfunction, a familial defect in infants, causes failure to thrive, diarrhea, and seborrheic dermatitis.

Defects in latter components of the complement cascade (C5 to C9) may lead to increased susceptibility to infections with *Neisseria.*

C1esterase inhibitor deficiency (hereditary angioedema) may cause periodic swelling in the face, hands, abdomen, or throat, with potentially fatal laryngeal edema.

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C4..

C4

The second component to react in the complement sequence. It is a beta-globulin with a sedimentation coefficient of 18.7, a molecular weight of 240,000 and a serum concentration of 430 micrograms/ml. It is activated by COMPLEMENT 1 and serves as a receptor for C2.

C4a

Smaller fragment formed when C1s splits C4 into C4a and C4b. As an anaphylatoxin, C4a causes symptoms of immediate hypersensitivity but it has weaker activity than C3a or C5a.

C4b

Larger fragment formed when C1s splits C4 into C4a and C4b. C4b combines with C2b to form the activated C4b2b complex which is often called the classical pathway C3 convertase.

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