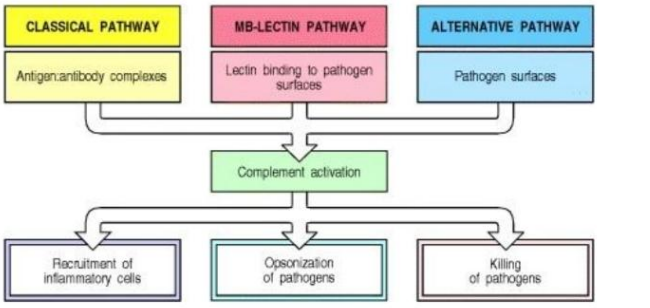
The complement system

• The complement system consists of a number of small proteins found in the blood,generally synthesized by the liver, and normally circulating as inactive precursors (pro-proteins).
• When stimulated by one of several triggers, activation cascade is started and lead to functional effects.
• Over 25 proteins and protein fragments make up the complement system. They account for about 5% of the globulin fraction of blood serum.
• Complement was discovered many years ago as to 'complement' the antibacterial activity of antibody, hence the name.
• Although first discovered as an effector arm of the antibody response (Adaptive), complement can also be activated early in infection in the absence of antibodies (innate) .

Complement functions and activators

• Activation of the complement system leads to:
– Opsonization
– Chemotaxis (Inflammation)
– Direct killing of pathogens (in pathogens)

• The complement system is activated by:
– Antibody-antigen complex
– Mannose residues – mannose binding lectin
– Pathogens and tumor cells



Activation of complement system

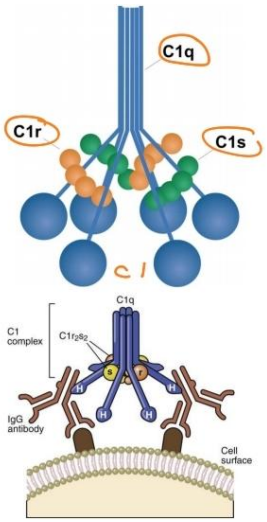
• The precursors of the complement system are widely distributed throughout body fluids and tissues without adverse effects. At sites of infection, however, they are activated locally and trigger a series of potent inflammatory events
• There are three distinct pathways through which complement can be activated on pathogen surfaces. These pathways depend on different molecules for their initiation, but they converge to generate the same set of effector molecules

Activators

• Classical pathway; recognize antibody binding microbe as viruses or bacteria (IGG, IGM)
• Alternative; recognize LPS or endotoxins (part of innate response)
• Lectin pathway. The lectin pathway is homologous to the classical pathway, but with mannose-binding lectin (MBL) instead of C1q. and in the absence of antibody

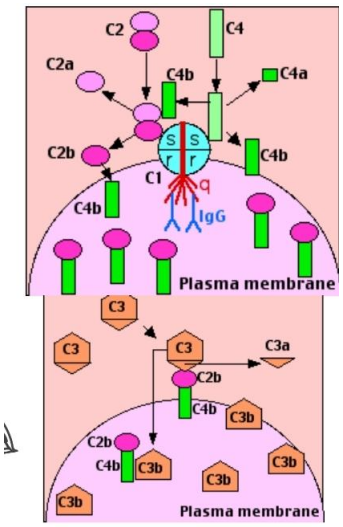
Classical pathway

• The classical pathway (discovered first), one of the major effector mechanisms of the humoral arm of adaptive immune responses.
• Uses C1 which exists in the blood serum as a molecular complex containing:
– C1q - C1r -C1s
• C1q detects antibodies bound to the surface of a microbe or other structure.
• The IGM and IGG that bound by antigen, contain a binding site for C1q. (A single molecule of IgM is enough to initiate the pathway. IgG is far less efficient, requiring many molecules to do so.)
• Once C1q binds to the Fc portion of the antibodies, C1r and C1s (serine proteases), become active and initiate a proteolytic cascade involving other complement proteins (C2, C4) to make C3 convertase



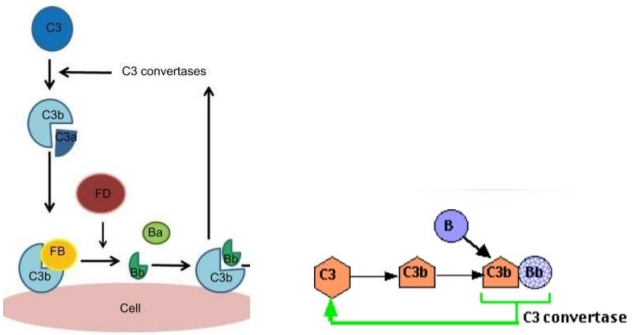
• Binding of C1q activates C1s and C1r.
• Activated C1s (a protease) cleaves two serum proteins:
– C4 is cleaved into
• C4b, a large fragment which binds covalently to surface of antigen (opsonization)
• C4a, smaller, inactive, which diffuses away.
– C2 is cleaved into
• C2b, which binds to a site on C4b

• C2a a smaller, inactive, fragment of which diffuses away.
• The complex of C4b•2b (some books say C4b2a) is called "C3 convertase" because it catalyzes the cleavage of C3.



Alternative pathway

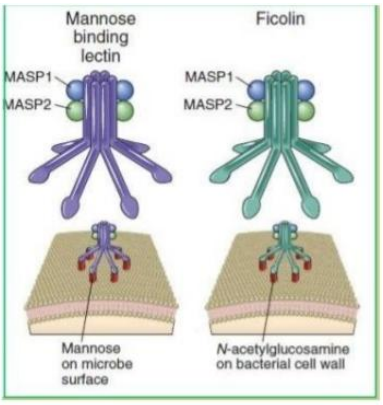
Triggered when a complement protein called C3 is degraded to C3b that recognizes certain microbial surface structures, such as bacterial LPS.
• While C3b undergoes its post-cleavage conformational change, a binding site for a plasma protein called Factor B is also exposed.
• Factor B then binds to the C3b protein that is now covalently tethered to the surface of a microbial or host cell.
• Bound factor B is in turn cleaved by a plasma serine protease called Factor D, releasing a small fragment called Ba and generating a larger fragment called Bb that remains attached to C3b.
• The C3bBb complex is the alternative pathway C3 convertase



Lectin pathway

• Lectin pathway is started by proteins/macromolecules in blood that are highly specific to mannose on pathogen
• The lectin pathway is homologous to the classical pathway, but with mannose-binding lectin (MBL) instead of C1, and in the absence of antibody.
• This pathway is activated by binding of MBL to mannose residues

on the pathogen surface, which can then split C4 into C4a and C4b and C2 into C2a and C2b the rest pathway is similar to classical pathway

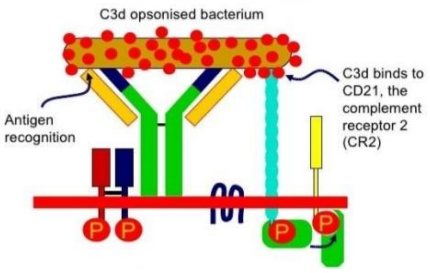


C3

• Recognition of microbes by any of the three complement pathways results in sequential recruitment and assembly of additional complement proteins
• C3 is the most abundant protein of the complement system. Because of its abundance and its ability to activate itself, it greatly magnifies the response.
C3 convertase cuts C3 into two major fragments:
• C3b, which binds covalently to glycoproteins scattered across the microbial cell surface. Macrophages and neutrophils have receptors for C3b and can bind the C3b-coated cell or particle preparatory to phagocytosis. This effect qualifies C3b as an opsonin.
• C3a This small fragment is released into the surrounding fluids. It can bind to receptors on basophils and mast cells triggering them to release their vasoactive contents (e.g., histamine). Because of the role of these materials in anaphylaxis and inflammation, C3a is called an anaphylatoxins.

C3d link innate to humoral immunity

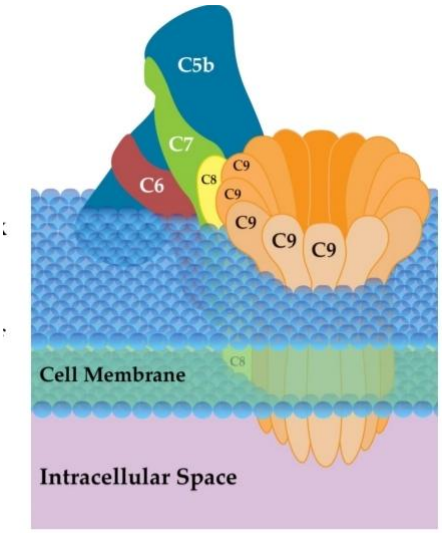
• The complement system of innate immunity is important in regulating humoral immunity largely through the complement receptor CR2, which forms a co-receptor on B cells during antigen induced activation
• antigen gets “tagged” with the appropriate C3d product via the classical or lectin complement pathways.



Membrane attack complex

C3 convertase + C3b = C5 convertase, which cleaves C5
– Cleavage of C5 by (C3bBb3b) and (C4b•2b.3b) produces:
– C5a, which is released into the fluid surroundings where it

• is a potent anaphylatoxin.
• is a chemotactic attractant for neutrophils.
– C5b, which serves as the anchor for the assembly of a complex made of a single molecule of each of: C6, C7, and C8.The Membrane Attack Complex
• The resulting complex C5b•6•7•8 guides the polymerization of 18 molecules of C9 into a tube inserted into the lipid bilayer of the plasma membrane.
• This tube forms a channel allowing the passage of ions and small molecules. Water enters the cell by osmosis and the cell lyses



Summary of complement functions

• Opsonization: C3b, C4b and C5b target foreign particles for phagocytosis.
• Chemotaxis: C5a, C4a and C3a attract phagocytic cells to the site of damage. This is aided by the increased permeability (anaphylatoxins) they cause smooth muscle contraction, vasodilation, histamine release from mast cells, and enhanced vascular permeability mediated by C3a, C5a, C4a.

Done by: Dr.mohammed farhoud

The role of complement in rapid response to a first exposure to a variety of organisms involves which of the following?

a. fixing to immunoglobulin.
b. activation by mannan-binding lectin.
c. participation in immune complex formation.
d. activation of C1.

Renal disease is very common in SLE but occurs in less than 25% of patients with C3 deficiency. A difference between the patient groups would be which of the following?
a. In SLE, the immune complexes in the kidney would contain C3, and in C3 deficiency they would not.
b. In active SLE, serum C3 levels would be normal, and in C3 deficiency they would be low.
c. In inactive SLE, serum C3 levels would be high, and in C3 deficiency they would be low.
d. In active SLE, immune complexes could deposit in joints and skin, and in C3 deficiency they would be only in the kidneys.

Answers:b/a

فكرة سؤال ٢
ال SLE مرض AUTOIMMUNE بتم فيه انتاج AUTO-ANTIBODIES بتهاجم ال Self Antigen
ومنه بتفعل ال complement وبصير activation لل c3 ✅
لكن في حالة ال c3 deficiency ما في complement اصلا يصيرله activation