Complement system

Biological functions of complement proteins

- Lysis of cells, bacteria, and viruses
- Opsonization, which promotes phagocytosis of particulate antigens
- Binding to specific complement receptors on cells of the immune system, triggering specific cell functions, inflammation, and secretion of immunoregulatory molecules
- Immune clearance, which removes immune complexes from the circulation and deposits them in the spleen and liver

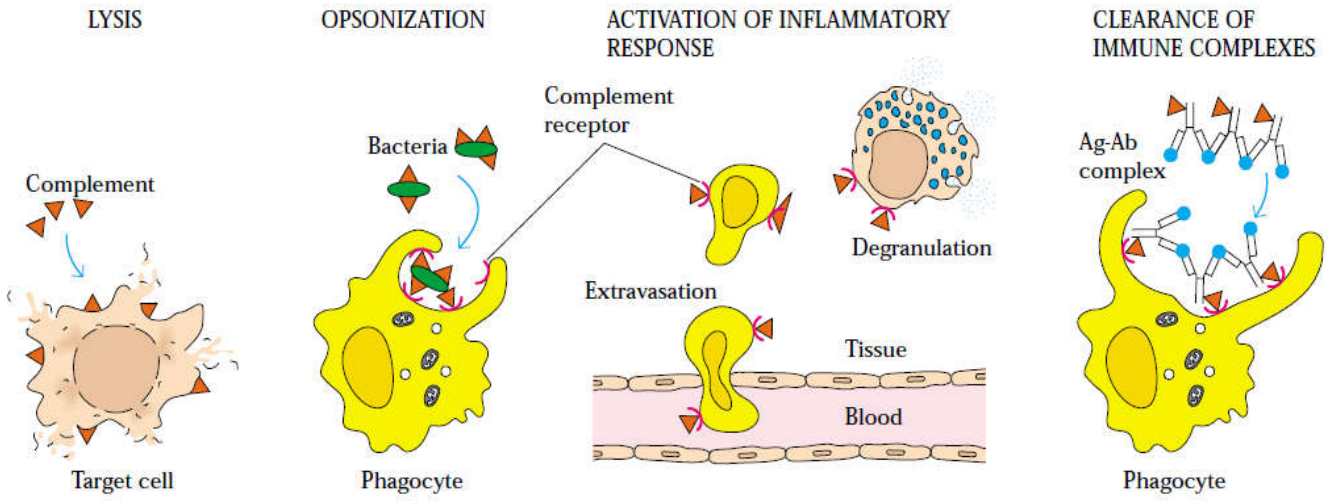

Figure1: The multiple activities of the complement system. Serum complement proteins and membrane-bound complement receptors partake in a number of immune activities: lysis of foreign cells by antibody-dependent or antibody-independent pathways; opsonization or uptake of particulate antigens, including 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.

The Complement Components

The proteins and glycoproteins that compose the complement system are synthesized mainly by liver hepatocytes, although significant amounts are also produced by blood monocytes, tissue macrophages, and epithelial cells of the gastrointestinal and genitourinary

tracts. These components constitute 5% (by weight) of the serum globulin fraction. Complement components are designated by numerals (C1–C9), by letter symbols (e.g., factor D), or by trivial names (e.g., homologous restriction factor). Peptide fragments formed by activation of a component are denoted by small letters. In most cases, the smaller fragment resulting from cleavage of a component is designated “a” and the larger fragment designated “b” (e.g., C3a, C3b; note that C2 is an exception: C2a is the larger cleavage fragment). The larger fragments bind to the target near the site of activation, and the smaller fragments diffuse from the site and can initiate localized inflammatory responses by binding to specific receptors.The complement fragments interact with one another to form functional complexes. Those complexes that have enzymatic activity are designated by a bar over the number or symbol (e.g., C4b2a, C3bBb).

Complement Activation

Figure 2 outlines the pathways of complement activation. The early steps, culminating in formation of C5b, can occur by the **classical pathway,** the **alternative pathway,** or the **lectin pathway.** The final steps that lead to a membrane attack are the same in all pathways.

The Classical Pathway Begins with Antigen-Antibody Binding

Complement activation by the classical pathway commonly begins with the formation of soluble antigen-antibody complexes (immune complexes) or with the binding of antibody to antigen on a suitable target, such as a bacterial cell. IgM and certain subclasses of IgG (human IgG1, IgG2, and IgG3) can activate the classical complement pathway. The initial stage of activation involves C1, C2, C3, and C4, which are present in plasma in functionally inactive forms. Because the components were named in order of their discovery and before their functional roles had been determined, the numbers in their names do not always reflect the order in which they react. The formation of an antigen-antibody complex induces conformational changes in the Fc portion of the IgM molecule that expose a binding site for the C1 component of the complement system. The intermediates in the classical activation pathway are depicted schematically in Figure 2. C1 has two substrates, C4 and C2. The C4 component is a glycoprotein and activated when C1 hydrolyzes it into small fragment (C4a) and the larger fragment (C4b). The C2 proenzyme then attaches to the exposed binding site on C4b, where the C2 is then cleaved by the neighboring C1; the smaller fragment (C2b) diffuses away. The resulting C4b2a complex is called C3 convertase, referring to its role in converting the C3 into

an active form. The smaller fragment from C4 cleavage, C4a, is an anaphylatoxin, or mediator of inflammation, which does not participate directly in the complement cascade. Hydrolysis of C3 component by the C3 convertase generates short fragment (C3a) and C3b. A single C3 convertase molecule can generate over 200 molecules of C3b, resulting in tremendous amplification at this step of the sequence. Some of the C3b binds to C4b2a to form a trimolecular complex C4b2a3b, called C5 convertase. The C3b component of this complex binds C5 and alters its conformation, so that the C4b2a component can cleave C5 into C5a, which diffuses away, and C5b, which attaches to C6 and initiates formation of the membraneattack
Complex in a sequence described later.

The Alternative Pathway Is Antibody-Independent

This major pathway of complement activation involves four serum proteins: C3, factor B, factor D, and properdin. The alternative pathway is initiated in most cases by cell-surface constituents that are foreign to the host For example, both gram-negative and gram-positive bacteria have cell-wall constituents that can activate the alternative pathway. The intermediates in the alternative pathway for generating C5b are shown schematically in Figure 2. In the alternative pathway, serum C3, which contains an unstable thioester bond, is subject to slow spontaneous hydrolysis to yield C3a and C3b. The C3b component can bind to foreign surface antigens (such as those on bacterial cells or viral particles) or even to the host's own cells. The membranes of most mammalian cells have high levels of sialic acid, which contributes to the rapid inactivation of bound C3b molecules on host cells; consequently this binding rarely leads to further reactions on the host cell membrane. Because many foreign antigenic surfaces (e.g., bacterial cell walls, yeast cell walls, and certain viral envelopes) have only low levels of sialic acid, C3b bound to these surfaces remains active for a longer time. The C3b present on the surface of the foreign cells can bind another serum protein called factor B to form a complex stabilized by Mg^{2+}. Binding to C3b exposes a site on factor B that serves as the sub-strate for an enzymatically active serum protein called factor D. Factor D cleaves the C3b-bound factor B, releasing a small fragment (Ba) that diffuses away and generating C3bBb. The C3bBb complex has C3 convertase activity and thus is analogous to the C4b2a complex in the classical pathway. The C3 convertase activity of C3bBb has a half-life of only 5 minutes unless the serum protein properdin binds to it, stabilizing it and extending the half-life of this convertase activity to 30 minutes. The C3bBb generated in the alternative pathway can activate unhydrolyzed C3 to

generate more C3b autocatalytically. As a result, the initial steps are repeated and amplified. The C3 convertase activity of C3bBb generates the C3bBb3b complex, which exhibits C5 convertase activity, analogous to the C4b2a3b complex in the classical pathway. The nonenzymatic C3b component binds C5, and the Bb component subsequently hydrolyzes the bound C5 to generate C5a and C5b, the latter binds to the antigenic surface.

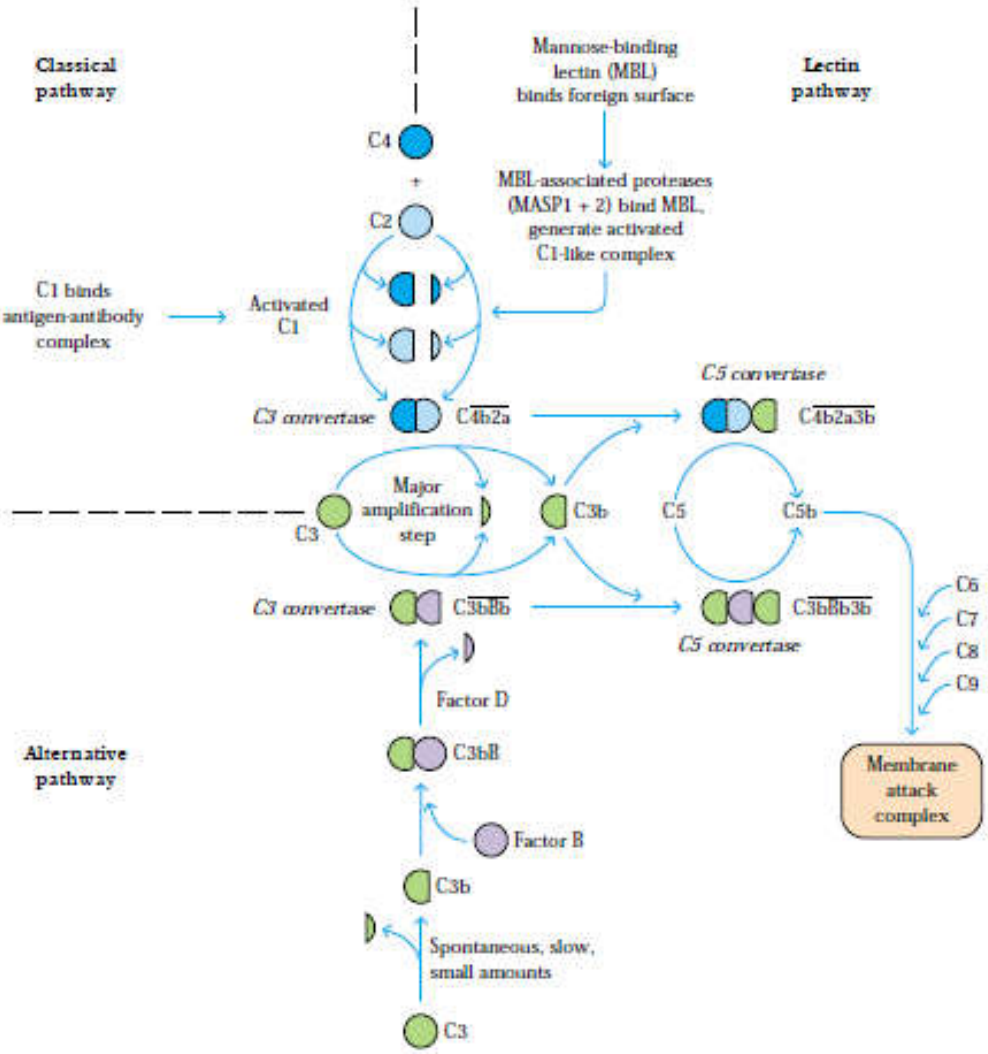

Figure 2: Overview of the complement activation pathways. The classical pathway is initiated when C1 binds to antigen-antibody complexes. The alternative pathway is initiated by binding of spontaneously generated C3b to activating surfaces such as microbial cell walls. The lectin pathway is initiated by binding of the serum protein MBL to the surface of a pathogen. All three pathways generate C3 and C5 convertases and bound C5b, which is converted into a membrane-attack complex (MAC) by a common sequence of terminal reactions. Hydrolysis of C3 is the major amplification step in all pathways, generating large amounts of C3b, which forms part of

C5 convertase. C3b also can diffuse away from the activating surface and bind to immune complexes or foreign cell surfaces, where it functions as an opsonin.

The Lectin Pathway Originates With Host Proteins Binding Microbial Surfaces

Lectins are proteins that recognize and bind to specific carbohydrate targets. (Because the lectin that activates complement binds to mannose residues, some authors designate this the MBL lectin pathway or mannan-binding lectin pathway.) The lectin pathway, like the alternative pathway, does not depend on antibody for its activation. However, the mechanism is more like that of the classical pathway, because after initiation, it proceeds, through the action of C4 and C2, to produce a C5 convertase (see Figure 2). The lectin pathway is activated by the binding of mannose-binding lectin (MBL) to mannose residues on glycoproteinsor carbohydrates on the surface of microorganismsincluding certain *Salmonella, Listeria,* and *Neisseria* strains, as well as *Cryptococcus neoformans* and *Candida albicans.* After MBL binds to the surface of a cell or pathogen, MBL-associated serine proteases,MASP-1 and MASP-2, bind to MBL. The active complex formed by this association causes cleavage and activation of C4 and C2. This means of activating the C2–C4 components to form a C5 convertase without need for specific antibody binding represents an important innate defense mechanism comparable to the alternative pathway, but utilizing the elementsof the classical pathway except for the C1 proteins.

The Three Complement Pathways Converge at the Membrane-Attack Complex

The terminal sequence of complement activation involves C5b, C6, C7, C8, and C9, which interact sequentially to form a macromolecular structure called the **membrane-attack complex (MAC).** This complex forms a large channel through the membrane of the target cell, enabling ions and small molecules to diffuse freely across the membrane.