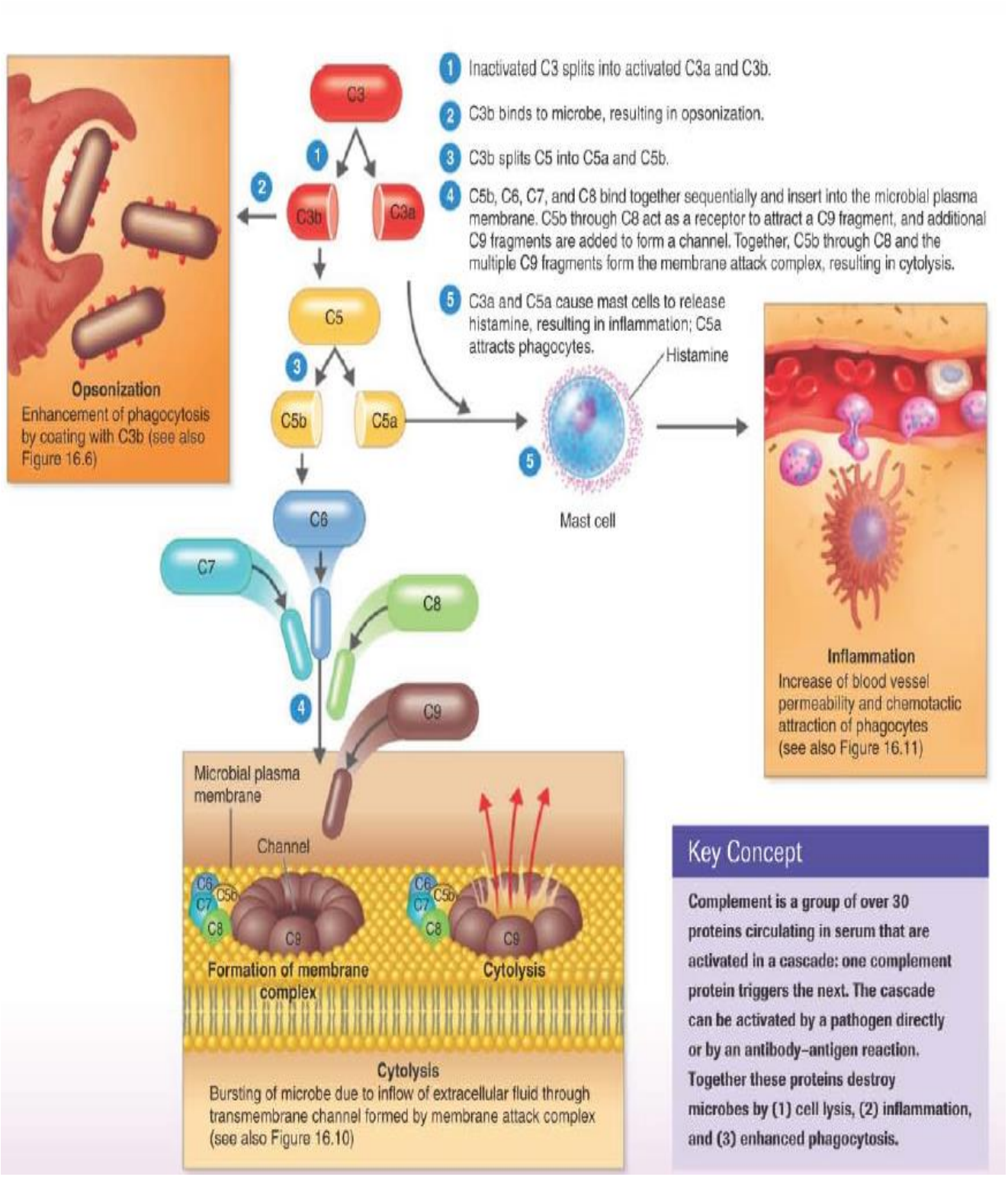
Antimicrobial Substances

Among the most important of these are the proteins of the complement system: interferons, iron-binding proteins, and antimicrobial peptides.

1- The Complement System

The complement system is a defensive system consisting of over 30 proteins produced by the liver and found circulating in blood serum and within tissues throughout the body. The complement system is so-named because it "complements" the cells of the immune system in destroying microbes. The complement system is not adaptable and does not change over the course of a person's lifetime; for these reasons, it belongs to the innate immune system. However, it can be recruited and brought into action by the adaptive immune system. Together, proteins of the complement system destroy microbes by (I) cytolysis, (2) inflammation, and (3) phagocytosis and also prevent excessive damage to host tissues. Complement proteins are usually designated by an uppercase letter C and are inactive until they are split into fragments (products). The proteins are numbered Cl through C9, named for the order in which they were discovered. The fragments are activated proteins and are indicated by the lowercase letters a and b. For example, inactive complement protein C3 is split into two activated fragments, C3a and C3b. The activated fragments carry out the destructive actions of the Cl through C9 complement proteins. Complement proteins act in a cascade; that is, one reaction triggers another, which in turn triggers another, and so on.



Key Concept

Complement is a group of over 30 proteins circulating in serum that are activated in a cascade: one complement protein triggers the next. The cascade can be activated by a pathogen directly or by an antibody–antigen reaction. Together these proteins destroy microbes by (1) cell lysis, (2) inflammation, and (3) enhanced phagocytosis.

Pathways of complement activation

1. Classical pathway.
2. Alternative pathway.
3. Lectin pathway.

The Classical Pathway

The classical pathway is initiated when antibodies bind to antigens (microbes) and occurs as follows:

1- Antibodies attach to antigens (for example, proteins or large polysaccharides on the surface of a bacterium or other cell), forming antigen- antibody complexes. The antigen-antibody complexes bind and activate Cl.

2- Next, activated Cl activates C2 and C4 by splitting them. C2 is split into fragments called C2a and C2b, and C4 is split into fragments called C4a and C4b.

3- C2a and C4b combine and together they activate C3 by splitting it into C3a and C3b. The C3 fragments then initiate cytolysis, inflammation, and opsonization

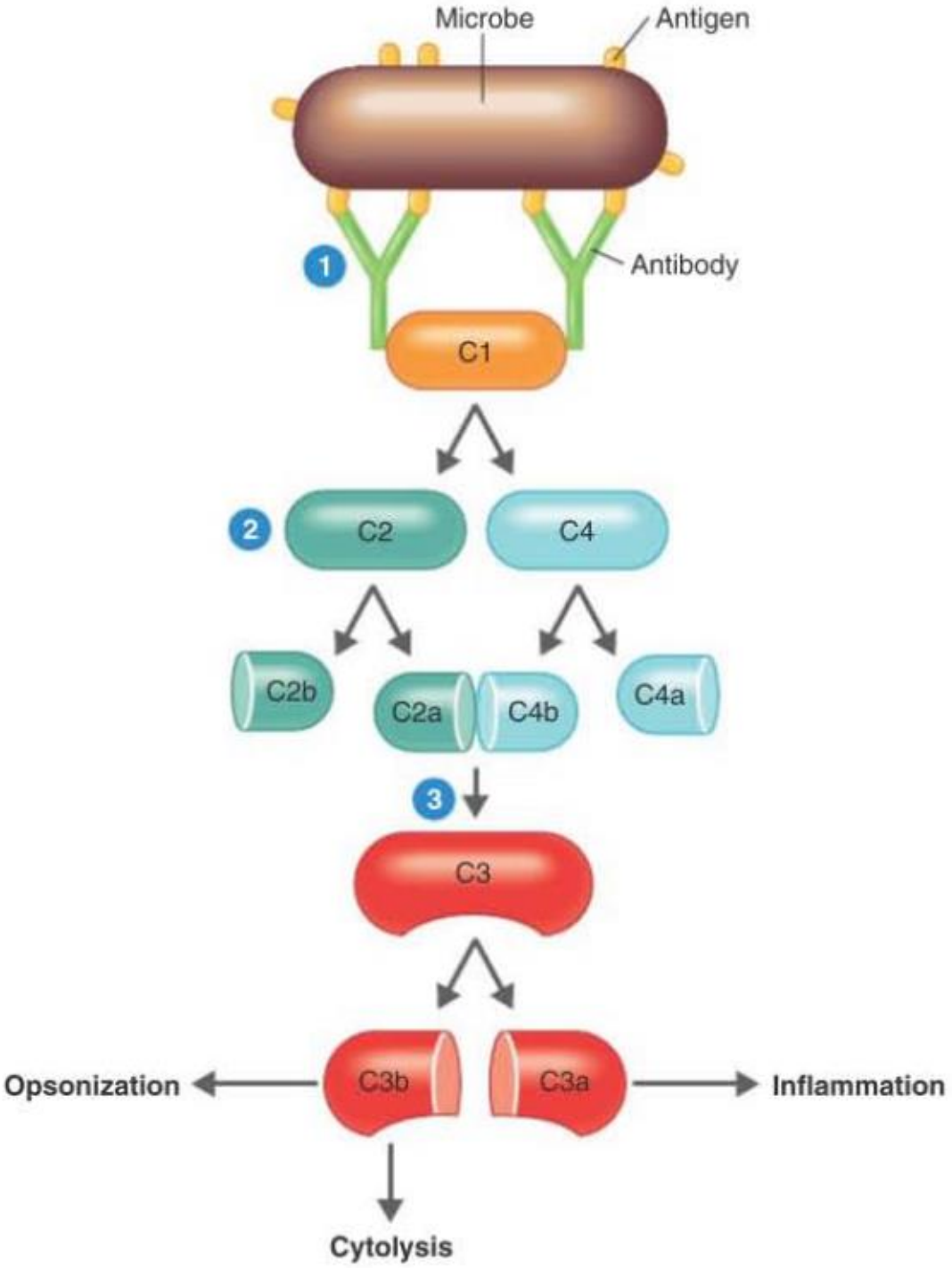
4- C3b binds to the surface of a microbe, and receptors on phagocytes attach to the C3b. Thus C3b enhances phagocytosis by coating a microbe, a process called **opsonization**, or immune adherence. Opsonization promotes attachment of a phagocyte to a microbe.

5- C3b also initiates a series of reactions that result in cytolysis. First, C3b splits C5 into C5b and C5a. Fragments C5b, C6, C7, and C8 bind together sequentially and insert into the plasma membrane of the invading cell. C5b through C8 act as a receptor that attracts a C9 fragment. Additional C9 fragments arc added

to form a transmembrane channel. Together, C5b through C8 and the multiple C9 fragments form the **membrane attack complex (MAC).**

6-The transmembrane channels (holes) of the MAC result in cytolysis, the bursting of the microbial cell due to the inflow of extracellular fluid through the channels.

7- C3a and C5a bind to mast cells and cause them to release histamine and other chemicals that increase blood vessel permeability during inflammations. C5a also functions as a very powerful chemotactic factor that attracts phagocytes to the site of an infection.

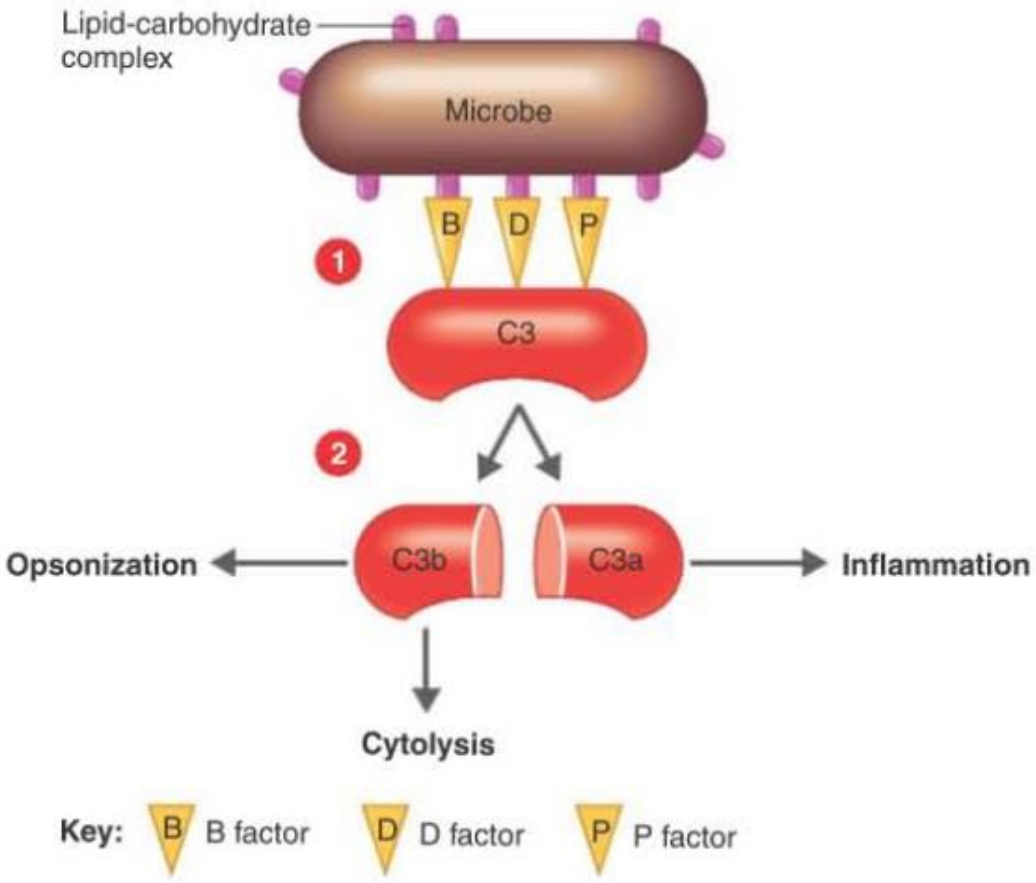


The Alternative Pathway

Unlike the classical pathway, the alternative pathway docs not involve antibodies. The alternative pathway is activated by contact between certain complement proteins and a pathogen.

1- C3 is constantly present in the blood . It combines with complement proteins called factor B, factor D, and factor P (properdin) on the surface of a pathogenic microbe. The complement proteins are attracted to microbial cell surface material (mostly lipid-carbohydrate complexes of certain bacteria and fungi).

2- Once the complement proteins combine and interact, C3 is split into fragments C3a and C3b. As in the classical pathway, C3a participates in inflammation, and C3b functions in cytolysis and opsonization.



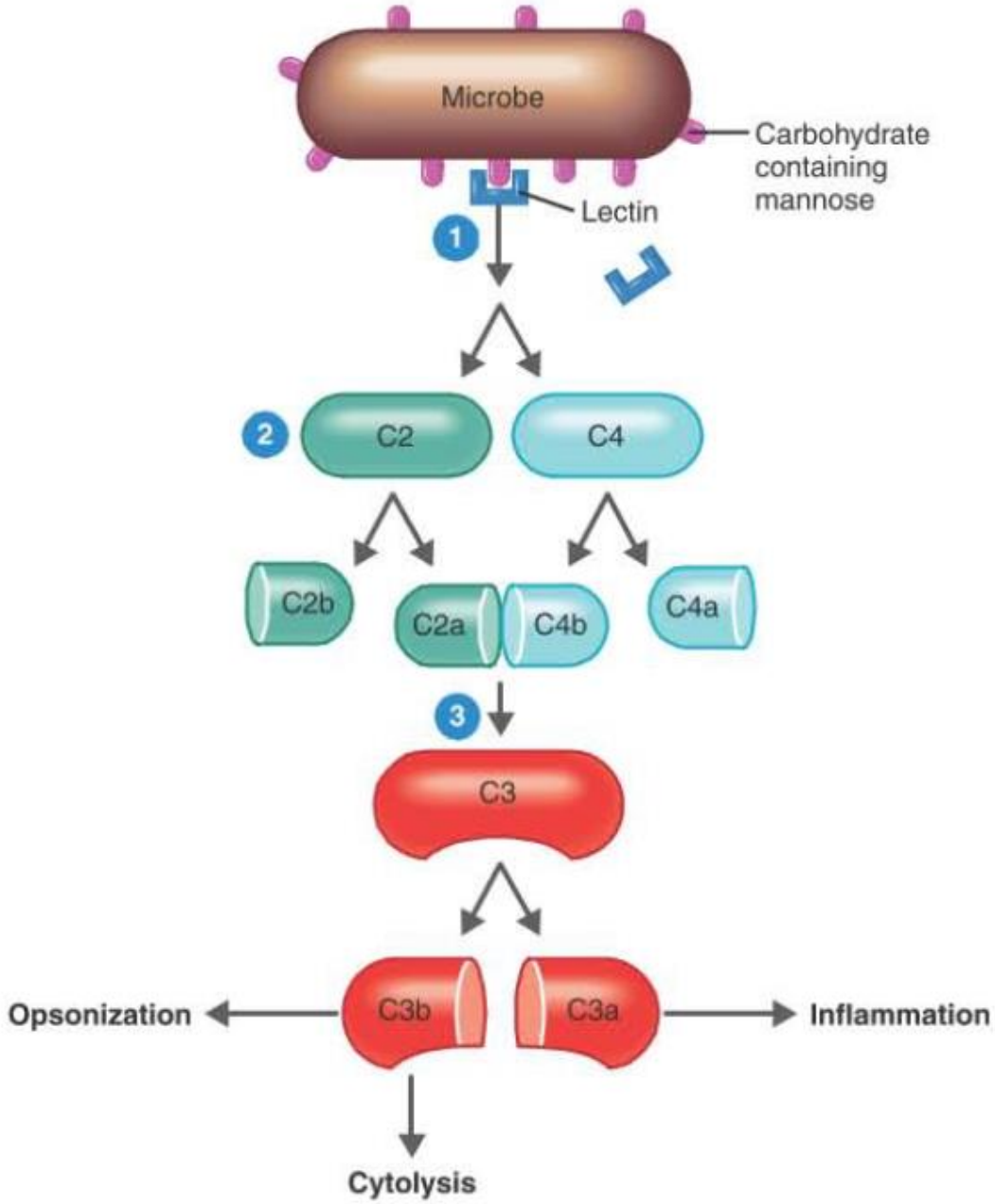
The Lectin Pathway

The lectin pathway is the most recently discovered mechanism for complement activation, When macrophages ingest bacteria, viruses, and other foreign matter by phagocytosis, they release cytokines that stimulate the liver to produce lectins. Proteins that bind to carbohydrates.

1- One such lectin, mannose-binding lectin (MBL), binds to the carbohydrate mannose. MBL binds to many pathogens because the MBL molecules recognize a distinctive pattern of carbohydrates that includes mannose, which is found in bacterial cell walls and on some viruses. As a result of binding, MBL functions as an opsonin to enhance phagocytosis and

2- activates C2 and C4;

3- C2a and C4b activate C3.


Microbe
Carbohydrate containing mannose
Lectin
1
2
C2
C4
C2b
C2a
C4b
C4a
3
C3
Opsonization
C3b
C3a
Inflammation
Cytolysis