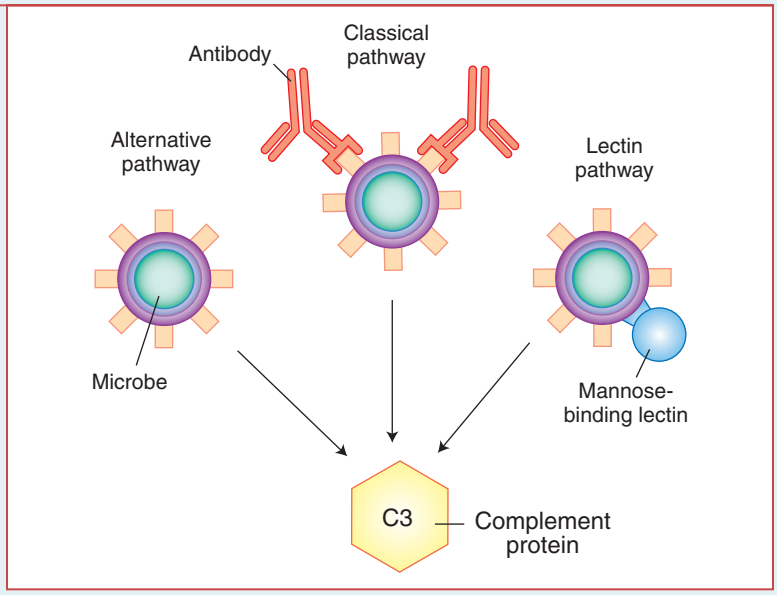
Understanding • The Complement System

The complement system provides one of the major effector mechanisms of both humoral and innate immunity. The system consists of a group of proteins (complement proteins C1 through C9) that are normally present in the plasma in an inactive form. Activation of the complement system is a highly regulated process, involving the sequential breakdown of the complement proteins to generate a cascade of cleavage products capable of proteolytic enzyme activity. This allows for tremendous amplification because each enzyme molecule activated by one step can generate multiple activated enzyme molecules at the next step. Complement activation is inhibited by proteins that are present on normal host cells; thus, its actions are limited to microbes and other antigens that lack these inhibitory proteins.

The reactions of the complement system can be divided into three phases: (1) the initial activation phase, (2) the early-step inflammatory responses, and (3) the late-step membrane attack responses.

1 Initial Activation Phase

There are three pathways for recognizing microbes and activating the complement system: (1) the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody and is a component of innate immunity; (2) the classical pathway, which is activated by certain types of antibodies bound to antigen and is part of humoral immunity; and (3) the lectin pathway, which is activated by a plasma lectin that binds to mannose on microbes and activates the classical system pathway in the absence of antibody.



2 Early-Step Inflammatory Responses

The central component of complement for all three pathways is the activation of the complement protein C3 and its enzymatic cleavage into a larger C3b fragment and a smaller C3a fragment. The smaller 3a fragment stimulates inflammation by acting as a chemoattractant for neutrophils. The larger 3b fragment becomes attached to the microbe and acts as an opsonin for phagocytosis. It also acts as an enzyme to cleave C5 into two components: a C5a fragment, which produces vasodilation and increases vascular permeability; and a C5b fragment, which leads to the late-step membrane attack responses.