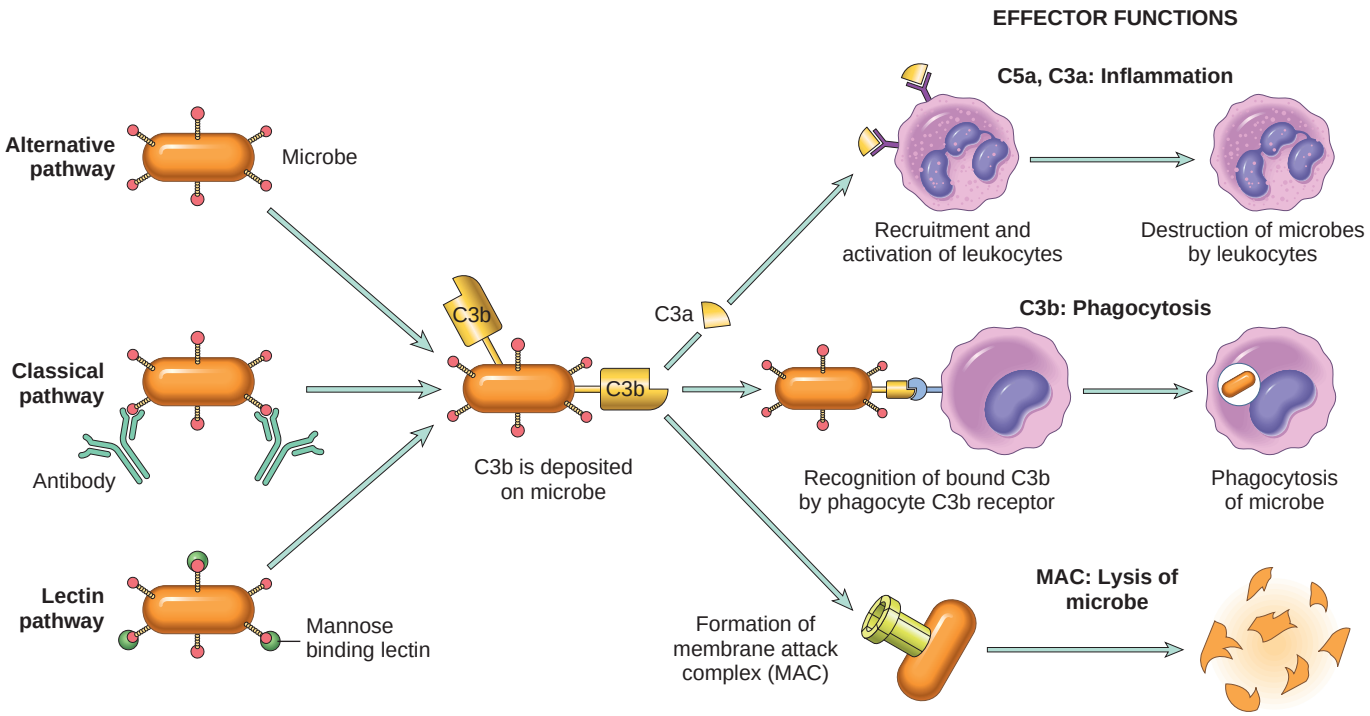

Figure 3-12 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

various cell types in different anatomic regions of the tissues, such as T and B lymphocytes in discrete areas of the spleen and lymph nodes (Chapter 6).

Although the role of chemokines in inflammation is well established, it has proved difficult to develop antagonists that block the activities of these proteins.

Other Cytokines in Acute Inflammation

The list of cytokines implicated in inflammation is huge and constantly growing. In addition to the ones described earlier, two that have received considerable recent interest are IL-6, made by macrophages and other cells, which is involved in local and systemic reactions, and IL-17, produced mainly by T lymphocytes, which promotes neutrophil recruitment. Antagonists against both are approved or have shown impressive efficacy in the treatment of inflammatory diseases. Type I interferons, whose normal function is to inhibit viral replication, contribute to some of the systemic manifestations of inflammation. Cytokines also play key roles in chronic inflammation; these are described later in the chapter.

Complement System

The complement system is a collection of soluble proteins and membrane receptors that function mainly in host defense against microbes and in pathologic inflammatory reactions. The system consists of more than 20 proteins, some of which are numbered C1 through C9. This system functions in both innate and adaptive immunity for defense against microbial pathogens. In the process of complement activation, several cleavage products of complement proteins are elaborated that cause increased vascular permeability, chemotaxis, and opsonization. The activation and functions of complement are outlined in Figure 3-12.

Complement proteins are present in inactive forms in the plasma, and many of them are activated to become proteolytic enzymes that degrade other complement proteins, thus forming an enzymatic cascade capable of tremendous amplification. The critical step in complement activation is the proteolysis of the third (and most abundant) component, C3. **Cleavage of C3 can occur by one of three pathways**:

- The *classical pathway*, which is triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen
- The *alternative pathway*, which can be triggered by microbial surface molecules (e.g., endotoxin, or LPS), complex polysaccharides, cobra venom, and other substances, in the absence of antibody
- The *lectin pathway*, in which plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1.

All three pathways of complement activation lead to the formation of an active enzyme called the *C3 convertase*, which splits C3 into two functionally distinct fragments, C3a and C3b. C3a is released, and C3b becomes covalently attached to the cell or molecule where complement is being activated. More C3b then binds to the previously generated fragments to form *C5 convertase*, which cleaves C5 to release C5a and leave C5b attached to the cell surface. C5b binds the late components (C6-C9), culminating in the formation of the membrane attack complex (MAC, composed of multiple C9 molecules).

The complement system has three main functions (Fig. 3-12):