- **Leukotriene receptor antagonists** block leukotriene receptors and prevent the actions of the leukotrienes. These drugs (e.g., Montelukast) are useful in the treatment of asthma.
- Another approach to manipulating inflammatory responses has been to modify the intake and content of dietary lipids by increasing the consumption of fish oil. The proposed explanation for the effectiveness of this approach is that the polyunsaturated fatty acids in fish oil are poor substrates for conversion to active metabolites by the cyclooxygenase and lipoxygenase pathways but are better substrates for the production of antiinflammatory lipid products.

Cytokines and Chemokines

Cytokines **are proteins produced by many cell types (principally activated lymphocytes, macrophages, and dendritic cells, but also endothelial, epithelial, and connective tissue cells) that mediate and regulate immune and inflammatory reactions.** By convention, growth factors that act on epithelial and mesenchymal cells are not grouped under cytokines. The general properties and functions of cytokines are discussed in Chapter 6. Here the cytokines involved in acute inflammation are reviewed (Table 3-6).

Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1)

TNF and IL-1 serve critical roles in leukocyte recruitment by promoting adhesion of leukocytes to endothelium and their migration through vessels. These cytokines are produced mainly by activated macrophages and dendritic cells; TNF is also produced by T lymphocytes and mast cells, and IL-1 is produced by some epithelial cells as well. The secretion of TNF and IL-1 can be stimulated by microbial products, immune complexes, foreign bodies, physical injury, and a variety of other inflammatory stimuli. The production of TNF is induced by signals through TLRs and other microbial sensors, and the synthesis of IL-1 is stimulated by the same signals but the generation of the biologically active form of this cytokine is dependent on the inflammasome, described earlier.

The actions of TNF and IL-1 contribute to the local and systemic reactions of inflammation (Fig. 3-11). The most important roles of these cytokines in inflammation are the following.

- **Endothelial activation.** Both TNF and IL-1 act on endothelium to induce a spectrum of changes referred to as *endothelial activation*. These changes include increased expression of endothelial adhesion molecules, mostly E- and P-selectins and ligands for leukocyte integrins; increased production of various mediators, including other cytokines and chemokines, growth factors, and eicosanoids; and increased procoagulant activity of the endothelium.
- **Activation of leukocytes and other cells.** TNF augments responses of neutrophils to other stimuli such as bacterial endotoxin and stimulates the microbicidal activity of macrophages, in part by inducing production of NO. IL-1 activates fibroblasts to synthesize collagen and stimulates proliferation of synovial and other mesenchymal cells. IL-1 also stimulates T_H17 responses, which in turn induce acute inflammation.
- **Systemic acute-phase response.** IL-1 and TNF (as well as IL-6) induce the systemic acute-phase responses associated with infection or injury, including *fever* (described later in the chapter). They are also implicated in the syndrome of *sepsis,* resulting from disseminated bacterial infection. TNF regulates energy balance by promoting lipid and protein mobilization and by suppressing appetite. Therefore, sustained production of TNF contributes to *cachexia*, a pathologic state characterized by weight loss and anorexia that accompanies some chronic infections and neoplastic diseases.

TNF antagonists have been remarkably effective in the treatment of chronic inflammatory diseases, particularly rheumatoid arthritis and also psoriasis and some types of inflammatory bowel disease. One of the complications of this therapy is that patients become susceptible to mycobacterial infection, reflecting the reduced ability of macrophages to kill intracellular microbes. Although many of the actions of TNF and IL-1 seem overlapping, IL-1 antagonists are not as effective, for reasons that remain

Table 3-6 Cytokines in Inflammation

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

IFN-γ, Interferon-γ; IL-1, interleukin-1; NK cells, natural killer cells; TNF, tumor necrosis factor.
The most important cytokines involved in inflammatory reactions are listed. Many other cytokines may play lesser roles in inflammation. There is also considerable overlap between the cytokines involved in acute and chronic inflammation. Specifically, all the cytokines listed under acute inflammation may also contribute to chronic inflammatory reactions.