



Figure 3-11 Major roles of cytokines in acute inflammation. PDGF, Platelet-derived growth factor; PGE, prostaglandin E; PGI, prostaglandin I.

obscure. Also, blocking either cytokine has no effect on the outcome of sepsis, perhaps because other cytokines contribute to this serious systemic inflammatory reaction.

Chemokines

Chemokines are a family of small (8 to 10 kD) proteins that act primarily as chemoattractants for specific types of leukocytes. About 40 different chemokines and 20 different receptors for chemokines have been identified. They are classified into four major groups, according to the arrangement of cysteine (C) residues in the proteins:

- *C-X-C chemokines* have one amino acid residue separating the first two of the four conserved cysteine residues. These chemokines act primarily on neutrophils. IL-8 is typical of this group. It is secreted by activated macrophages, endothelial cells, and other cell types, and causes activation and chemotaxis of neutrophils, with limited activity on monocytes and eosinophils. Its most important inducers are microbial products and other cytokines, mainly IL-1 and TNF.
- *C-C chemokines* have the first two conserved cysteine residues adjacent. The C-C chemokines, which include monocyte chemoattractant protein (MCP-1), eotaxin, macrophage inflammatory protein-1 α (MIP-1 α), and RANTES (regulated and normal T-cell expressed and secreted), generally attract monocytes, eosinophils, basophils and lymphocytes, but are not as potent chemoattractants for neutrophils. Although most of the chemokines in this class have overlapping actions, eotaxin selectively recruits eosinophils.
- *C chemokines* lack the first and third of the four conserved cysteines. The C chemokines (e.g., lymphotactin) are relatively specific for lymphocytes.

- *CX₃C chemokines* contain three amino acids between the two cysteines. The only known member of this class is called *fractalkine*. This chemokine exists in two forms: a cell surface-bound protein induced on endothelial cells by inflammatory cytokines that promotes strong adhesion of monocytes and T cells, and a soluble form, derived by proteolysis of the membrane-bound protein, that has potent chemoattractant activity for the same cells.

Chemokines mediate their activities by binding to seven-transmembrane G protein-coupled receptors. These receptors (called CXCR or CCR, for C-X-C or C-C chemokine receptors) usually exhibit overlapping ligand specificities, and leukocytes generally express more than one receptor type. As discussed in Chapter 6, certain chemokine receptors (CXCR-4, CCR-5) act as coreceptors for a viral envelope glycoprotein of human immunodeficiency virus (HIV), the cause of AIDS, and are thus involved in binding and entry of the virus into cells.

Chemokines may be displayed at high concentrations attached to proteoglycans on the surface of endothelial cells and in the extracellular matrix. They have two main functions:

- **In acute inflammation.** *Inflammatory chemokines* are the ones whose production is induced by microbes and other stimuli. These chemokines stimulate leukocyte attachment to endothelium by acting on leukocytes to increase the affinity of integrins, and they stimulate migration (chemotaxis) of leukocytes in tissues to the site of infection or tissue damage.
- **Maintenance of tissue architecture.** Some chemokines are produced constitutively in tissues and are sometimes called *homeostatic chemokines*. These organize