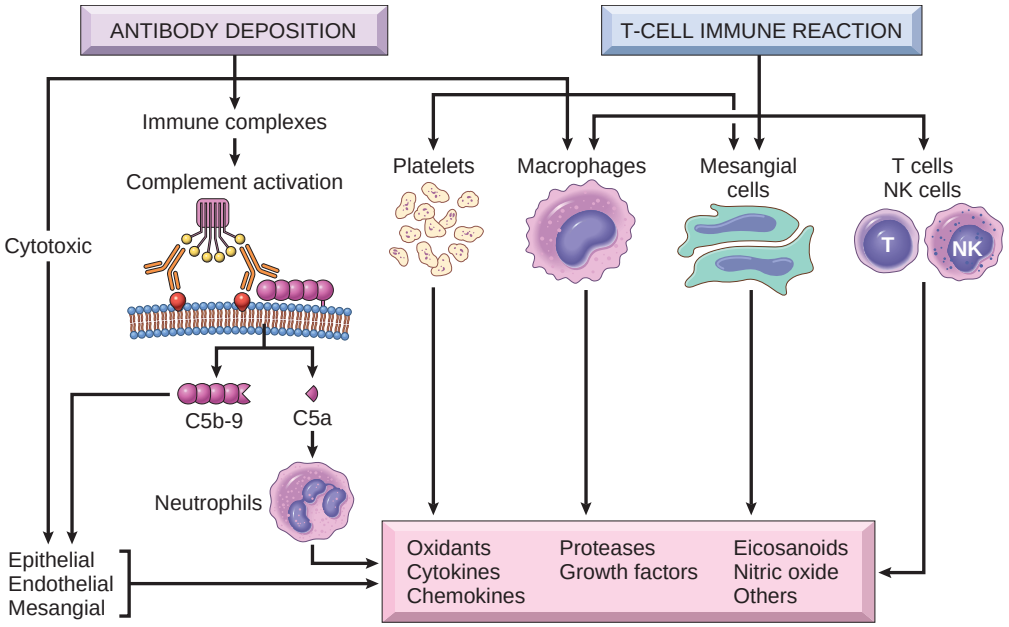

Figure 20-6 Mediators of immune glomerular injury.

phritis (MPGN type II), and in an emerging diagnostic category of diseases broadly termed *C3 glomerulopathies.* This is discussed later in the sections describing these diseases.

Mediators of Glomerular Injury

Once immune reactants or sensitized T cells have localized in the glomerulus, how does the glomerular damage ensue? The mediators—both cells and molecules—are the usual suspects involved in acute and chronic inflammation, described in Chapter 3, and only a few are highlighted here (Fig. 20-6).

Cells

- *Neutrophils* and *monocytes* infiltrate the glomerulus in certain types of glomerulonephritis, largely as a result of activation of complement, resulting in generation of chemotactic agents (mainly C5a), but also by Fc-mediated adherence and activation. Neutrophils release proteases, which cause GBM degradation; oxygen-derived free radicals, which cause cell damage; and arachidonic acid metabolites, which contribute to the reductions in GFR.
- *Macrophages and T lymphocytes,* which infiltrate the glomerulus in antibody- and cell-mediated reactions, when activated, release a vast number of biologically active molecules.
- *Platelets* may aggregate in the glomerulus during immune-mediated injury. Their release of eicosanoids, growth factors and other mediators may contribute to vascular injury and proliferation of glomerular cells. Antiplatelet agents have beneficial effects in both human and experimental glomerulonephritis.
- *Resident glomerular cells,* particularly mesangial cells, can be stimulated to produce several inflammatory mediators, including reactive oxygen species (ROS), cytokines, chemokines, growth factors, eicosanoids, nitric oxide, and endothelin. They may initiate inflammatory responses in the glomerulus even in the absence of leukocytic infiltration.

Soluble Mediators

Virtually all the known inflammatory chemical mediators (Chapter 3) have been implicated in glomerular injury.

- *Complement activation* leads to the generation of chemotactic products that induce leukocyte influx (complement-neutrophil–dependent injury) and the formation of C5b-C9, the membrane attack complex. C5b-C9 causes cell lysis but, in addition, stimulates mesangial cells to produce oxidants, proteases, and other mediators. Thus, even in the absence of neutrophils, C5b-C9 can cause proteinuria, as has been demonstrated in experimental membranous glomerulopathy.
- *Eicosanoids*, *nitric oxide*, *angiotensin*, and *endothelin* are involved in the hemodynamic changes.
- *Cytokines*, particularly IL-1 and TNF, which may be produced by infiltrating leukocytes and resident glomerular cells, induce leukocyte adhesion and a variety of other effects.
- *Chemokines* such as monocyte chemoattractant protein 1 promote monocyte and lymphocyte influx. *Growth factors* such as platelet-derived growth factor (PDGF) are involved in mesangial cell proliferation. TGF-β, connective tissue growth factor, and fibroblast growth factor seem to be critical in the ECM deposition and hyalinization leading to glomerulosclerosis in chronic injury. Vascular endothelial growth factor (VEGF) seems to maintain endothelial integrity and may help regulate capillary permeability.
- The *coagulation system* is also a mediator of glomerular damage. Fibrin is frequently present in the glomeruli and Bowman space in glomerulonephritis, indicative of coagulation cascade activation, and activated