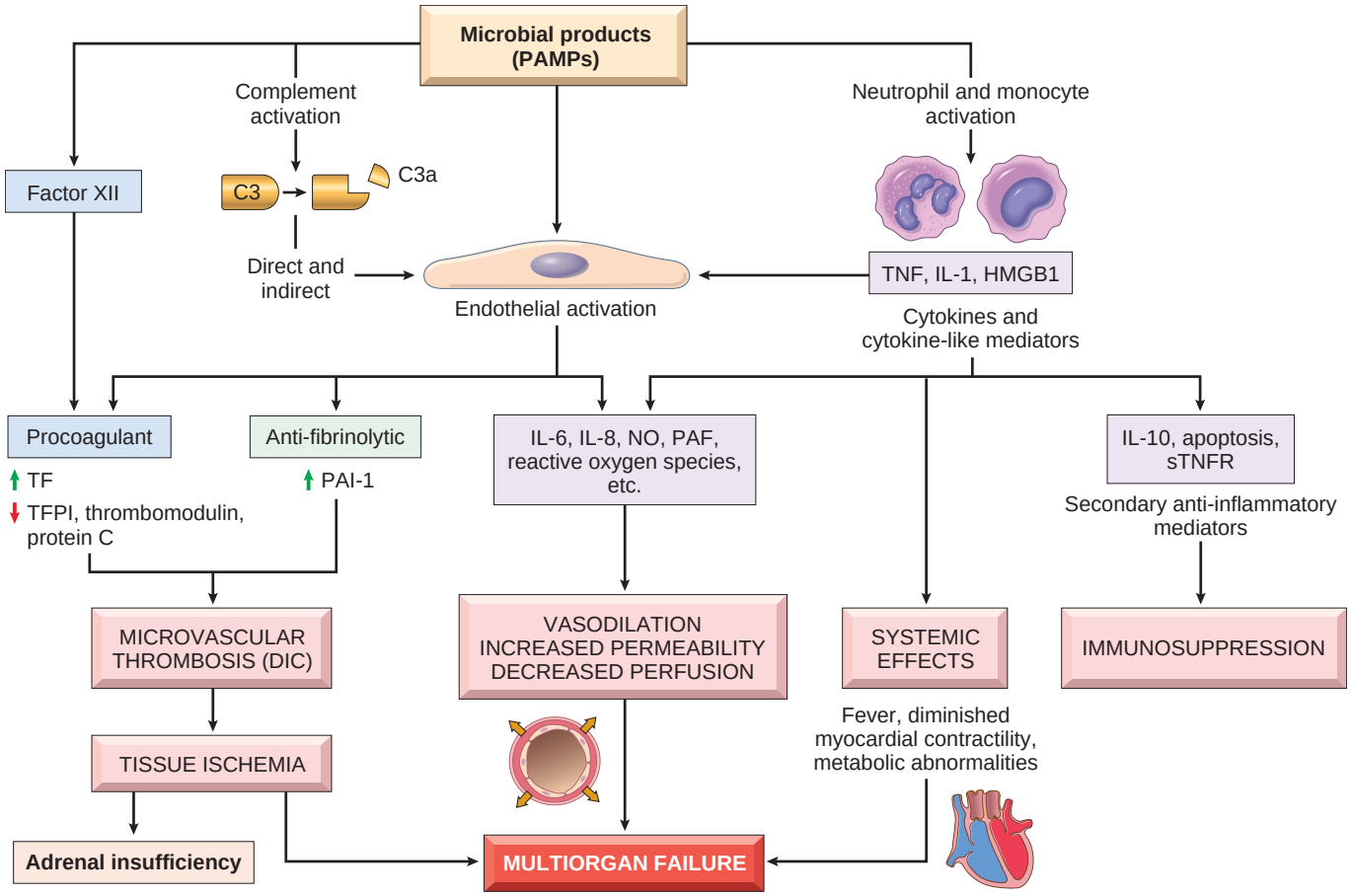

Figure 4-20 Major pathogenic pathways in septic shock. Microbial products (PAMPs, or pathogen-associated molecular patterns) activate endothelial cells and cellular and humoral elements of the innate immune system, initiating a cascade of events that lead to end-stage multiorgan failure. Additional details are given in the text. DIC, Disseminated vascular coagulation; HMGB1, high mobility group box 1 protein; NO, nitric oxide; PAF, platelet activating factor; PAI-1, plasminogen activator inhibitor 1; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

triggering pro-inflammatory responses. Likely initiators of inflammation in sepsis are signaling pathways that lie downstream of *Toll-like receptors* (TLRs, Chapter 3), which you will recall recognize a host of microbe-derived substances containing so-called pathogen-associated molecular patterns (PAMPs), as well as G-protein coupled receptors that detect bacterial peptides, and nucleotide oligomerization domain proteins 1 and 2 [NOD1, NOD2]). Upon activation, innate immune cells produce TNF, IL-1, IFN-γ, IL-12, and IL-18, as well as other inflammatory mediators such as high mobility group box 1 protein (HMGB1). Reactive oxygen species and lipid mediators such as prostaglandins and platelet activating factor (PAF) are also elaborated. These effector molecules induce endothelial cells (and other cell types) to upregulate adhesion molecule expression and further stimulate cytokine and chemokine production. The *complement cascade* is also activated by microbial components, both directly and through the proteolytic activity of plasmin (Chapter 3), resulting in the production of anaphylotoxins (C3a, C5a), chemotactic fragments (C5a), and opsonins (C3b), all of which contribute to the pro-inflammatory state. In addition, microbial components can activate coagulation directly through factor XII and indirectly through altered endothelial function (discussed below). The accompanying widespread activation of thrombin may further augment inflammation by triggering protease-activated receptors (PARs) on inflammatory cells.

The hyperinflammatory state initiated by sepsis also activates counter-regulatory immunosuppressive mechanisms, which may involve both innate and adaptive immune cells. As a result, septic patients may oscillate between hyperinflammatory and immunosuppressed states during their clinical course. Proposed mechanisms for the immune suppression include a shift from pro-inflammatory (T_H1) to anti-inflammatory (T_H2) cytokines (Chapter 6), production of anti-inflammatory mediators (e.g., soluble TNF receptor, IL-1 receptor antagonist, and IL-10), lymphocyte apoptosis, the immunosuppressive effects of apoptotic cells, and the induction of cellular anergy.

- *Endothelial activation and injury*. The pro-inflammatory state and endothelial cell activation associated with sepsis leads to widespread vascular leakage and tissue edema, which have deleterious effects on both nutrient delivery and waste removal. One effect of inflammatory cytokines is to loosen endothelial cell tight junctions, making vessels leaky and resulting in the accumulation of protein-rich edema throughout the body. This alteration impedes tissue perfusion and may be exacerbated by attempts to support the patient with