Detection of microbial components by immune cells via Toll-like receptors (TLRs) with subsequent induction of inflammation is essential for the host defense. However, an overactive immune response can cause tissue damage and sepsis. Endogenous molecules hemoglobin and its derivative heme are often released into tissue compartments where there is infection in the presence of degrading blood. Hemoglobin synergizes with multiple endogenous and microbial TLR agonists to induce high levels of TNF and IL-6 from macrophages, and that this synergy is independent of TLR4 and MyD88. In contrast, heme synergizes with some but not all TLR agonists studied. Furthermore, the synergy of both hemoglobin and heme with most macrophage activators is suppressed by hemopexin, a plasma heme-binding protein. These studies suggest that hemoglobin and heme may contribute substantially to microbe-induced inflammation when bacterial or viral infection coexists with blood degradation, as well as in sterile inflammation, and that hemopexin may play a role in controlling inflammation in such settings. It may be possible to treat inflammation in some situations by administering exogenous hemopexin.