TLR4-induced IFN-gamma production increases TLR2 sensitivity and drives Gram-negative sepsis in mice.

Abstract:
Gram-negative bacterial infection is a major cause of sepsis and septic shock. An important inducer of inflammation underlying both syndromes is the cellular recognition of bacterial products through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). We identified a novel antagonistic mAb (named 1A6) that recognizes the extracellular portion of the TLR4-MD-2 complex. If applied to mice before infection with clinical isolates of Salmonella enterica or Escherichia coli and subsequent antibiotic therapy, 1A6 prevented otherwise fatal shock, whereas application of 1A6 after infection was ineffective. In contrast, coapplication of 1A6 and an anti-TLR2 mAb up to 4 h after infection with Gram-negative bacteria, in combination with the start of antibiotic therapy (mimicking clinical conditions), provided robust protection. Consistent with our findings in mice, dual blockade of TLR2 and TLR4 inhibited TNF-alpha release from human peripheral blood mononuclear cells upon Gram-negative bacterial infection/antibiotic therapy. Both murine splenocytes and human PBMCs released IFN-gamma in a TLR4-dependent manner, leading to enhanced surface TLR2 expression and sensitivity for TLR2 ligands. Our results implicate TLR2 as an important, TLR4-driven sensor of Gram-negative bacterial infection and provide a rationale for blockade of...
both TLRs, in addition to antibiotic therapy for the treatment of Gram-negative bacterial infection.