Dokumenttyp: journal article

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Titel des Beitrags: Antagonistic antibody prevents toll-like receptor 2-driven lethal shock-like syndromes.

Abstract: Hyperactivation of immune cells by bacterial products through toll-like receptors (TLRs) is thought of as a causative mechanism of septic shock pathology. Infections with Gram-negative or Gram-positive bacteria provide TLR2-specific agonists and are the major cause of severe sepsis. In order to intervene in TLR2-driven toxemia, we raised mAb's against the extracellular domain of TLR2. Surface plasmon resonance analysis showed direct and specific interaction of TLR2 and immunostimulatory lipopeptide, which was blocked by T2.5 in a dose-dependent manner. Application of mAb T2.5 inhibited cell activation in experimental murine models of infection. T2.5 also antagonized TLR2-specific activation of primary human macrophages. TLR2 surface expression by murine macrophages was surprisingly weak, while both intra- and extracellular expression increased upon systemic microbial challenge. Systemic application of T2.5 upon lipopeptide challenge inhibited release of inflammatory mediators such as TNF-alpha and prevented lethal shock-like syndrome in mice. Twenty milligrams per kilogram of T2.5 was sufficient to protect mice, and administration of 40 mg/kg of T2.5 was protective even 3 hours after the start of otherwise lethal challenge with Bacillus subtilis. These results indicate that epitope-specific binding of exogenous ligands
precedes specific TLR signaling and suggest therapeutic application of a neutralizing anti-TLR2 antibody in acute infection.