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Titel des Beitrags: Cellular recognition of trimyristoylated peptide or enterobacterial lipopolysaccharide via both TLR2 and TLR4.

Abstract: Evidence for specific and direct bacterial product recognition through toll-like receptors (TLRs) has been emphasized recently. We analyzed lipopeptide analogues and enterobacterial lipopolysaccharide (eLPS) for their potential to activate cells through TLR2 and TLR4. Whereas bacterial protein palmitoylated at its N-terminal cysteine and N-terminal peptides derived thereof are known to induce TLR2-mediated cell activation, a synthetic acylhexapeptide mimicking a bacterial lipoprotein subpopulation for which N-terminal trimyristoylation is characteristic (Myr(3)CSK(4)) activated cells not only through TLR2 but also through TLR4. Conversely, highly purified eLPS triggered cell activation through overexpressed TLR2 in the absence of TLR4 expression if CD14 was coexpressed. Accordingly, TLR2(-/-) macrophages prepared upon gene targeting responded to Myr(3)CSK(4) challenge, whereas TLR2(-/-)/TLR4(d/d) cells were unresponsive. Through interferon-gamma (IFNgamma) priming, macrophages lacking expression of functional TLR4 and/or MD-2 acquired sensitivity to eLPS, whereas TLR2/TLR4 double deficient cells did not. Not only TLR2(-/-) mice but also TLR4(-/-) mice were resistant to Myr(3)CSK(4) challenge-induced fatal shock.
d-Galactosamine-sensitized mice expressing defective TLR4 or lacking TLR4 expression acquired susceptibility to eLPS-driven toxemia upon IFNgamma priming, whereas double deficient mice did not. Immunization toward ovalbumin using Myr(3)CSK(4) as adjuvant was ineffective in TLR2(-/-)/TLR4(-/-) mice yet effective in wild-type, TLR2(-/-), or TLR4(-/-) mice as shown by analysis of ovalbumin-specific serum Ig concentration. A compound such as Myr(3)CSK(4) whose stimulatory activity is mediated by both TLR2 and TLR4 might constitute a preferable adjuvant. On the other hand, simultaneous blockage of both of the two TLRs might effectively inhibit infection-induced pathology.