Cellular recognition of tri-/di-palmitoylated peptides is independent from a domain encompassing the N-terminal seven leucine-rich repeat (LRR)/LRR-like motifs of TLR2.

Abstract:

Toll-like receptors (TLRs) mediate microbial pattern recognition in vertebrates. A broad variety of agonists has been attributed to TLR2 and three TLRs, TLR4, TLR2, and TLR5, have been demonstrated to bind microbial products. Distinct agonists might interact with different subdomains of the TLR2 extracellular domain. The TLR2 extracellular domain sequence includes 10 canonical leucine-rich repeat (LRR) motifs and 8-10 additional and potentially functionally relevant LRR-like motifs. Thus, the transfection of TLR2 LRR/LRR-like motif deletion constructs in human embryonic kidney 293 cells and primary TLR2-deficient mouse fibroblasts was performed for analysis of the role of the regarding domains in specific pattern recognition. Preparations applied as agonists were highly purified soluble peptidoglycan, lipoteichoic acid, outer surface protein A from Borrelia burgdorferi, synthetic mycoplasmal macrophage-activating lipoprotein-2, tri- palmitoyl-cysteinyI-ser~l-(lysyl)3-lysine (P3CSK4), dipalmitoyl-CSK4 (P2-CSK4), and monopalmitoyl-CSK4 (PCSK4) as well as lipopolysaccharide and inactivated bacteria. We found that a block of the N-terminal seven LRR/LRR-like motifs was not involved in TLR2-mediated cell activation by P3CSK4 and P2CSK4 ligands mimicking triacylated and diacylated...
bacterial polypeptides, respectively. In contrast, the integrity of the TLR2 holoprotein was compulsory for effective cellular recognition of other TLR2 agonists applied, including PCSK4. The formation of a functionally relevant subdomain by a region including the N-terminal seven LRR/LRR-like motifs rather than by single LRRs is suggested by our results. They further imply that TLR2 contains multiple binding domains for ligands that may contribute to the characterization of its promiscuous molecular pattern recognition.

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