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## Report:

The lipopolysaccharide (LPS) of Gram negative bacteria is a well-known inducer of the innate immune response. TLR4 and MD-2 form a heterodimer that recognizes a common “pattern” in structurally diverse LPS molecules. To understand the ligand specificity and receptor activation mechanism of the TLR4-MD-2-LPS complex we determined its crystal structure using x-ray beam available at ID23-2 beam line of ESRF. LPS binding induced the formation of an “m”-shaped receptor multimer composed of two copies of the TLR4-MD-2-LPS complex arranged in a symmetrical fashion. LPS interacts with a large hydrophobic pocket in MD-2 and directly bridges the two components of the multimer. Five of the six lipid chains of LPS are buried deep inside the pocket and the remaining chain is exposed to the surface of MD-2, forming a hydrophobic interaction with the conserved phenylalanines of TLR4. The F126 loop of MD-2 undergoes localized structural change and supports this core hydrophobic interface by making hydrophilic interactions with TLR4. Comparison with the structures of tetraacylated antagonists bound to MD-2 indicates that two other lipid chains in LPS displace the phosphorylated glucosamine backbone towards the solvent area by ~5 angstrom. This structural shift allows phosphate groups of LPS to contribute to receptor multimerization by

forming ionic interactions with a cluster of positively charged residues in TLR4 and MD-2. The TLR4-MD-2-LPS structure illustrates the remarkable versatility of the ligand recognition mechanisms employed by the TLR family, which is essential for defense against diverse microbial infection.

## Related Publication

(1) Park BS, Song DH, Kim HM, Choi B-S, Lee H, Lee J-O. (2009) The structural basis of lipopolysaccharide recognition by the TLR4-MD-2 complex. *Nature* 458 (7242), 1191-1195.