Computational insight into the mechanism of Toll-like receptor 4 activation.

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Abstract

Toll-like receptors (TLRs) are pattern recognition receptors involved in the innate immunity. In particular, TLR4 binds to lipopolysaccharides (LPS), a membrane constituent of Gram-negative bacteria, and together with MD-2 protein, forms a heterodimeric complex which leads to the activation of the innate immune system response. TLR4 activation has been associated with certain autoimmune diseases, noninfectious inflammatory disorders, and neuropathic pain. Therefore, TLR4 has risen as a promising therapeutic target, and design of TLR4 modulating drugs constitutes a highly relevant and active research area. Specific molecular features of extracellular, transmembrane, and cytoplasmic domains of TLR4 are crucial for coordinating the complex innate immune signaling pathway. Although X-ray, NMR and biological structural data is currently available for the independent TLR4 domains, the structure fragments only provide a partial view, because full-length proteins are flexible entities and dynamics play a key role in their functionality. Therefore, many structural and dynamical features of the TLR4 mode of action remain largely unknown.

Computational studies of the different independent domains composing the TLR4 were undertaken, using ab-initio calculations, homolohy modeling, protein-protein docking, all-atom molecular dynamics simulations, and thermodynamics calculations, to understand the differential domain organization of TLR4 in a wide range of membrane-aqueous environments, including liquid-disorder and liquid-order membrane models, to account for the TLR4 recruitment in lipid-rafts over activation. From the information gathered from our independent TLR4 domains studies, we finally modeled, by all-atom MD simulations, the structural assembly of plausible full-length TLR4 models embedded into a realistic plasma membrane, accounting for the active (agonist) state of the TLR4. These observations unveil relevant molecular aspects involved in the mechanism of receptor activation, and adaptor recruitment in the innate immune pathways, and will promote the discovery of new TLR4 modulators and probes.

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