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Short Communication

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Mechanism of phosphatidylinositol-dependent membrane localization of Toll/interleukin 1 receptor domain-containing adaptor protein

Mahesh Chandra Patra

Ajou University, Suwon, Korea

Abstract:

The Toll/interleukin 1 receptor (TIR) domain-containing adaptor protein (TIRAP) regulates Toll-like receptor (TLR) 2, TLR4, TLR7, and TLR9 signaling pathways. TIRAP anchors to phosphatidylinositol (PI) 4,5-bisphosphate (PIP2) on the plasma membrane and PI (3,4,5)-trisphosphate (PIP3) on the endosomal membrane and assists in recruitment of the myeloid differentiation primary response 88 protein to activated TLRs. To date, the structure and mechanism of TIRAP's membrane association are only partially understood. Here, we modeled an all-residue TIRAP dimer using homology modeling, threading, and protein-protein docking strategies. Molecular dynamics simulations revealed that PIP2 creates a stable microdomain in a dipalmitoylphosphatidylcholine bilayer, providing TIRAP with its physiologically relevant orientation. Computed binding free energy values suggest that the affinity of PI-binding domain (PBD) for PIP2 is stronger than that of TIRAP as a whole for PIP2 and that the short PI-binding motif (PBM) contributes to the affinity between PBD and PIP2. Four PIP2 molecules can be accommodated by distinct lysine-rich surfaces on the dimeric PBM. Along with the known PI-binding residues (K15, K16, K31, and K32), additional positively charged residues (K34, K35, and R36) showed strong affinity toward PIP2. Lysine-to-alanine mutations at the PI-binding residues abolished TIRAP's affinity for PIP2; however, K34, K35, and R36 consistently interacted with PIP2 headgroups through hydrogen bond (H-bond) and electrostatic interactions. TIRAP exhibited a similar interaction pattern and binding affinity with PIP3 as it did with PIP2 through an H-bond network involving K34, K35, and R36. The present study enabled us to understand the mechanism of TIRAP's membrane association that can be useful for designing peptide-based drugs targeting TLR2-, TLR4-, TLR7-, and TLR9-mediated autoimmune diseases.

Biography:

Mahesh Chandra Patra is currently pursuing PhD degree at Ajou University, Suwon, Korea in the field of computational biology. He holds a Master's degree in Bioinformatics from Orissa University of Agriculture and Technology, Bhubaneswar, India. He has expert level knowledge of molecular dynamics simulations and python programming language. He has published 25 papers including two review articles in reputed journals. Currently, he is developing a database for therapeutically relevant clinical/preclinical agents of innate immune signaling pathways.