MD simulations in protein-protein interactions

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Protein-protein interactions play crucial roles for mediating cell adhesion, initiating signal transduction, as well as facilitating channel function. MD simulations are widely used to investigate protein-protein interactions between micro-structural features and macro-molecular kinetics by offering atomic, dynamic and intuitionistic profiles. Two examples are introduced here to illustrate the role of MD simulations on protein-protein interactions.

The first case is for the selectin-ligand interactions which mediate leukocyte tethering to and rolling on vascular surfaces in inflammatory and immune responses (1). Their effective binding unit is formed by C-type lectin (Lec) domain and a single epidermal growth factor (EGF)-like domain (LE in short) of selectin and SGP-3 peptide of ligand, a 19 N-terminal sulfoglycopeptide of PSGL-1 composed of three tyrosine sulfate residues Y605, Y607, and Y610, and a sLe^x-modified glycan at T616 (2). It is still fully unknown about the involvement of EGF domain in ligand recognition even though it is far from direct binding sites of the ligand. Two main standpoints exist: one is that the existence of EGF domain could stabilize Lectin domain conformation for binding ligand effectively and the other is that EGF domain could mediate the forced dissociation of selectin-ligand bond by regulating its conformation during leukocyte rolling process. We performed the molecular dynamics (MD) simulations of forced unfolding of P-LE domains and forced dissociation of P-LE/SGP-3 complex to test the conformational stability of EGF domain (3-4). The results illustrated that EGF domain and EGF-Lectin domain hinge were disrupted in both unfolding and dissociation simulations

while Lectin domain retained its conformation. We also investigated the impact of EGF domain on Lectin conformation and found that, the extension of EGF orientation relative to Lectin domain promoted the possibility of allostery of Lectin domain to a new conformation. Taken together, we proposed a hypothesis that EGF domain could regulate Lectin conformation allostery and further affect selectin-ligand interaction through mediating its conformation and orientation.

The second case is referred to the permeability of water molecules via aquarin proteins. It remains unknown about what are the specific residues to dominate the difference in water permeability between rice (*Oryza sativa*) OsPIP1s and OsPIP2s (5). A residue in the molecular aqueous pathway, Ala in OsPIP1s and Ile(Val) in OsPIP2s or named as Ala/Ile(Val) site, has been identified for modulating the permeability difference between OsPIP1 and OsPIP2 subgroups using sequence alignment, homology modeling, as well as functional measurements (personal communications with Prof. Weiai Su in Institute of Plant Physiology and Ecology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences). The dynamic structural bases for this site-related functionality, however, remain unclear. MD simulations of typical four tetramer systems, OsPIP1;1 (WT), OsPIP1;1 A103V (mutant of A by V at site 103), OsPIP2;7(WT), and OsPIP2;7 V95A (mutant of V by A at site 95), were carried out upon their respective monomeric homology models. Monomer water permeability (P_f) (3) and water-protein and water-water interactions were predicted from water transport dynamics. The results were found to be in agreement with the measurements that water permeability was enhanced for OsPIP1;1 A103V but reduced for OsPIP2;7 V95A as compared to their corresponding wild-type constructs. Upon the structural analyses, we proposed a mechanism that Ala/Ile(Val) mutation induced the orientation change of helix 2 followed by the conformational changes of key residues in NPA and ar/R regions. Their motion, in turn, modulated water-water interaction and water-protein interactions in OsPIPs and their mutants. Combining with static homology modeling, this work provided structural bases for further understanding the role of Ala/Ile(Val) site on water permeability.

Finally, MD simulations, as a powerful approach, play more and more important roles in investigating the protein-protein interactions by predicting and steering the experiments as well as providing dynamic structural bases for understanding experimental results.

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