Ligand-induced interdomain mobility in PDZ tandem revealed by molecular dynamics simulations

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PSD-95 (DLG4) is one of the most studied proteins in the post-synaptic density. It is involved in organizing and regulating the distribution of membrane receptors at the post-synaptic site of nerve cells. NMDA receptor, voltage-gated potassium-channel Kv1.4 and many other membrane proteins were previously identified as its binding partners, however the exact structure and mechanism of the post-synaptic protein network remains poorly understood.

The PSD-95 protein consists of 3 PDZ domains, an SH3 and a GK domain. PDZ domains are common protein-binding modules, recognizing short C-terminal sequences. The first two PDZ domains in PSD-95 are arranged in a tandem formation, connected with a short, 4-residue linker. In the tandem arrangement, PDZ domains usually fold and function in an interdependent way.

The PDZ1-2 tandem of the PSD-95 protein was shown to possess a rigid structure in the apo-state, however ligand binding induces considerable interdomain mobility.[1] We presume that regulation of the relative orientation and dynamics of the two PDZ domains might be a key feature in organizing the distribution of the binding partners.

In order to elucidate the atomic-level mechanism of the inner motions in the PDZ tandem, we performed all-atom molecular dynamics (MD) simulations, including NMR-derived experimental dynamic parameters (NOEs and S2 order parameters) as external restraints. As a result, we obtain a number of dynamic structural ensembles of the modeled structure that properly describe its dynamics on the fast (ps-ns) timescale while maintaining good correspondence with the observable dynamic parameters. Analysis of the structural ensembles shed light on the role of the β2-β3 loop in the PDZ domains as the key to ligand-induced dynamics and interdomain communication.

[1] Wang, W., el al. (2009). Creating conformational entropy by increasing interdomain mobility in ligand binding regulation: a revisit to N-terminal tandem PDZ domains of PSD-95. JACS, 131(2), 787–96.

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