Correlated Segments and Fuzzy Membrane Association of Intrinsically Disordered Proteins

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Abstract

Intrinsically disordered proteins (IDPs) account for a significant fraction of any proteome and are central to numerous cellular functions. Yet how sequences of IDPs code for their conformational ensembles, conformational dynamics, and ultimately, functions is poorly understood. I will report advances from our computational and experimental studies of two membrane proteins containing intrinsically disordered regions (IDRs). For ChiZ (a component of the cell division machinery in *Mycobacterium tuberculosis*), our NMR data revealed non-uniform backbone dynamics along the sequence of the 64-residue N-terminal IDR (NT) [1]. Our molecular dynamics (MD) simulations traced the origin to correlated segments, which are stabilized by polyproline II stretches, salt bridges, cation-π interactions, and sidechain-backbone hydrogen bonds. Moreover, the extent of segmental correlation is sequence-dependent: segments in the first half of the NT sequence where internal interactions are more prevalent manifest elevated "collective" motions on the 5-10 ns timescale and suppressed local motions on the sub-ns timescale. Our NMR experiments found that NT associates with acidic membranes, but most residues remain highly dynamic, exception for a subset of Arg residues [2]. MD simulations provided crucial details on the fuzzy membrane association, stabilized mostly by salt bridges between acidic lipids and Arg residues in the second half of the NT sequence. Lastly, we used MD simulations to investigate the mechanism of Ca^{2+}-bound synaptotagmin-1 triggering membrane fusion, and produced a promising model that reconciles many conflicting experimental observations [3]. Most importantly, a conserved acidic motif within an IDR competes with the vesicle membrane for interacting with the Ca^{2+}-binding loops of the C2B domain, and flips C2B over for association with the plasma membrane, thereby bringing the two membranes closer for fusion. These findings serve as paradigms for sequence-conformation-dynamics-function relations of IDPs.

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