A deeper understanding of mechanism of biological processes from thermodynamic point of view can facilitate greatly the understanding of life and rational drug design in the post-genomic times.

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Molecular Motions of Proteins Play Crucial Role in their Function

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Proteins, which are the materials central to cellular function, should not be regarded simply as static pictures as determined by X-ray crystallography. They are dynamic entities in cellular solution with functions governed ultimately by their dynamic character (1). Therefore a complete understanding of the structure-function relationship of a protein requires an analysis of its dynamic behavior and molecular motion.

Using molecular dynamics (MD) simulation or CONCOORD (2) approach, the dynamic behaviors of HIV-1 gp120 envelope glycoprotein and serine protease proteinase K were investigated. Apart from analyses of the conventional structural properties during simulations, the essential dynamics analysis method was used to study the large concerted motions of these two proteins, including the influence of ligand bindings or residue mutations on molecular motions. The results revealed that i) the proteinase K shows relatively rigid internal core with some highly flexible surface loops forming the substrate-binding region, supporting the induce-fit or conformational selection mechanism of substrate binding (3); ii) the removal of Ca^{2+} cations from proteinase K increases the global conformational flexibility, decreases the local flexibility of substrate-binding region and does not influence the thermal motion of catalytic triad, thus explaining the experimentally determined decreased thermal stability, reduced substrate affinity and almost unchanged catalytic activity upon Ca^{2+} removal (4); iii) the substrate binding affects the large concerted motions and flexibility behavior of proteinase K suggesting that the variations in substrate-pocket motions can be connected to substrate binding, catalysis and product release (5); amino acid mutations 375 S/W and 423 I/P of HIV-1 gp120 have distinct effects on molecular motions of gp120 (6), facilitating 375 S/W mutant to adopt the CD4-bound conformation while 423 I/P mutant to prefer for CD4-unliganded state (7). Analyzing the dynamic character of proteins not only is important for the characterization of the functional properties of proteins but also facilitates the reasonable interpretation of experimentally determined structural, biochemical and biological data.

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Origins of the Mechanical Stability of the C2 Domains in Human Synaptotagmin 1

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Synaptotagmin 1 (Syt1) induces the buckling of plasma membrane during neurotransmitter release at the synapse (1). Therefore, elucidating the mechanical properties of Syt1 is essential for understanding its biological function in synaptic response. Syt1 contains two homologous cytoplasmic domains, C2A and C2B. We employed a self-organized polymer (SOP) model of a protein chain (2) to carry out molecular simulations, implemented on a CPU and on a GPU (Graphics Processing Unit) (3), using experimental pulling speeds. The forced unfolding of isolated C2A and C2B domains occurs under comparable forces starting from their C-terminal ends, but according to different pathways. Our results for the behavior of the C2A domain correlate very well with dynamic spectroscopy experimental studies (4, 5), but no direct measurements of the mechanical behavior of the isolated C2B domain exist to date. Thus, to confirm the presence of the pathways generated with the SOP model, we also carried out implicit solvent model simulations. Atomic force microscopy (AFM) experiments found an increase in the critical unfolding force of C2B when joined with C2A in the Syt1 molecule (4), which was proposed to result from the contribution of the C2A-C2B interface. However, our simulations reveal that the presence of an intact interface does not lead to the unfolding of Syt1 according to the AFM experiments. In contrast, we discovered that the presence of linkers used in the experimental set-up plays a crucial role in the behavior of this synaptic protein complex and, their inclusion in simulations as well leads to data that fully matches the experiments. Interestingly, we found that the stabilization effect of the linker on the C2B domain alters not only the critical force, but also the unfolding pathways of both C2 domains. Our findings provide insights into the relative conformation variability of the C2 domains and the origins of stability of the Syt1 protein.