This research was supported by grants from NSFC (No. 30860011) and Yunnan province (2007PY-22), and foundation for Key Teacher of Yunnan University.

References

1. M. Matsumura, G. Signor, and B. W. Matthews. *Nature 342*, 291-293 (1989).
2. C. S. Sevier, and C. A. Kaiser. *Nat Rev Mol Cell Biol 3*, 836-847 (2002).
3. L. M. Liang, Z. Y. Lou, F. P. Ye, J. K. Yang, S. Q. Liu, Y. N. Sun, Y. Guo, Q. L. Mi, X. W. Huang, C. G. Zou, Z. H. Meng, Z. H. Rao, and K. Q. Zhang. *FASEB J 24*, 1391-1400 (2010).
4. L. M. Liang, S. Q. Liu, J. K. Yang, Z. H. Meng, and K. Q. Zhang. *FASEB J* (2011) (in press).
5. S. Q. Liu, Z. H. Meng, Y. X. Fu, and K. Q. Zhang. *J Mol Model* 17, 289-300 (2011).
6. Y. Tao, Z. H. Rao, and S. Q. Liu. *J Biomol Struct Dyn 28*, 143-157 (2010).

Thinking into Mechanism of Protein Folding and Molecular Binding

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Protein folding and molecular binding provide the basis for life on earth. The native 3D structure of a protein is a prerequisite for its function; and the molecular binding is the fundamental principle of all biological processes (1). Therefore unraveling the mechanisms of protein folding and binding is fundamental to describing life at molecular level. Of particular interest is that protein folding and binding are similar processes because the only difference between them is the presence and absence of the chain connectivity. Among many models (such as diffusion-collision (2), hydrophobic collapse (3) and stoichiometry (4) models) proposed to describe the mechanism of these two processes, the "folding funnel" (5) model (Figure 1) is most widely accepted. In this model, protein folding can be viewed as going down the free energy hill through multiple parallel pathways towards the bottom of the funnel (6); and molecular binding can occur along rough free energy surface around the funnel bottom, especially for binding between flexible proteins/molecules. These are essentially thermodynamically controlled processes involving various types of driving forces, including the enthalpic contribution of noncovalent bond formations, entropic effects such as solvent release and burial of apolar surface area (hydrophobic effect), restrictions of degrees of freedom of protein/ligand, and loss of rotational and translational freedom of interacting partners. Briefly, these two processes, which are driven by a decrease in total Gibbs free energy (ΔG), are dictated by the mechanism of a delicate balance of the opposing effects of enthalpic (ΔH) and entropic (ΔS) contributions (equation 1).

$$\Delta \mathbf{G} = \Delta \mathbf{H} - \mathbf{T}\Delta \mathbf{S} \qquad 1$$

Here we emphasize that it is the thermodynamically driven subtle enthalpy-entropy compensation that leads to the global free energy minimum of the protein/ligand-solvent system (7), and that the specific inter-atomic interactions observed in the folded or complexed structure are to large extent the consequence of thermodynamic equilibrium but can not fully define the driving forces for folding and binding interactions.

Interestingly, we speculate that many other processes can be explained by thermodynamic enthalpy-entropy compensation, *i.e.,* the Yin and Yang balance in traditional Chinese medicine theory could correspond to the enthalpy and entropy compensation of the second law of thermodynamics; global warming can be considered as the consequence of excessive production of positive entropy (carbon dioxide) from chemically ordered fossil fuel, urging people to slow resource consumption to delay the inevitable death by entropy.

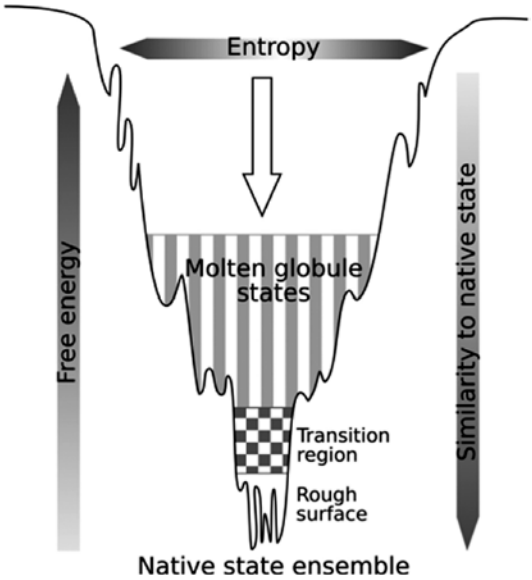

Figure 1: Schematic 2D funnel of protein folding and binding (modified from (6)).

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.

This research was supported by grants from NSFC (No. 30860011) and Yunnan province (2007PY-22), and foundation for Key Teacher of Yunnan University and SRF for ROCS, SEM.

References

1. R. Perozzo, G. Folkers, and L. Scapozza. *J Recept Signal Transduct Res 24*, 1-52 (2004).
2. M. Karplus and D. L. Weaver. *Protein Sci 3*, 650-668 (1994).
3. V. R. Agashe, M. C. Shastry, and J. B. Udgaonkar. *Nature 377*, 754-757 (1995).
4. A. Mittal, B. Jayaram, S. Shenoy, and T. S. Bawa. *J Biomol Struct Dyn 28*, 133-142 (2010).
5. P. E. Leopold, M. Montal, and J. N. Onuchic. *Proc Natl Acad Sci USA 89*, 8721-8725 (1992).
6. J. M. Yon. *J Cell Mol Med 6*, 307-327 (2002).
7. X. L. Ji and S. Q. Liu. *J Biomol Struct Dyn 28*, 621-623 (2011).

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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.

This research was supported by grants from NSFC (No. 30860011) and Yunnan province (2007PY-22), and foundation for Key Teacher of Yunnan University.