Insights into structure and dynamics of inter-domain interactions in proteins by NMR and molecular dynamics simulations

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NMR spectroscopy has undergone a revolution in recent years with the advent of several new methods overcoming the problems of sensitivity and resolution. The ability of NMR to couple structure and dynamics is unique and several new methods have been developed in this direction. One of the challenging problems has been to study inter-domain interactions in multi-domain and multifunctional proteins. In our laboratories, we are currently using NMR to study the structure and dynamics of the molecular chaperone machinery involving Hsp70. One of the components in this system is the family of J-proteins that are obligate partners of Hsp70s, stimulating their ATPase activity and thus allowing them to function in multiple cellular processes. Most J-proteins are functionally diverse which is attributed to their heterogeneous multidomain organization consisting of an N-terminal J-domain and a variable C terminal domain. The flexible linker between the two domains renders them difficult for X-ray crystallographic studies. We recently solved the 3D structure of a two-domain Zn^{2+}-binding human J-protein co-chaperone by NMR. While the two domains (N- and C-terminal) were found to fold independently of each other, binding of ligand in the C-terminal domain affected the function of the N-terminal domain. To further understand this intriguing behavior we carried MD simulations which revealed hinge-type bending motion between the two domains. Results of this work illustrating the complementary nature of NMR and molecular dynamics simulations in understanding inter-domain interactions will be presented.