TIFR Centre for Interdisciplinary Sciences
21, Brundavan Colony, Narsingi, Hyderabad 500 075

Seminar

NMR Spectroscopic Insights into Hsp70 Chaperone-Substrate Interactions

Ashok Sekhar

University of Toronto, Canada

The 70 kD heat shock chaperone (Hsp70) machinery is ubiquitous, highly conserved, and forms a central hub in the cellular proteostasis network. Hsp70 is a versatile chaperone that participates in numerous cellular processes including de novo protein folding, disaggregation, protein translocation and autophagy. This diverse functionality of the Hsp70 chaperone rests on its ATP-dependent interaction with client proteins, a phenomenon that remains poorly understood at the molecular level. Here, we develop and apply cutting edge NMR methodology to characterize the conformation of a model client protein, hTRF1, bound to Hsp70. Our results demonstrate that the client protein binds Hsp70 as a highly heterogeneous ensemble, a feature that is a direct result of the promiscuity of the Hsp70 chaperone. The client protein begins exploring conformational space and forming local secondary structure in the chaperone-bound state, while Hsp70 disrupts transient long-range interactions present in the client protein. The data point to a mechanism of Hsp70-assisted protein folding, where the client protein acquires structure gradually and establishes long-range interactions in a distance-dependent manner. Moreover, the conformational heterogeneity of the bound ensemble enables the client protein to sample a number of starting conformations for folding, as a strategy for navigating kinetic traps and folding efficiently to the native state. More generally, our work emphasizes the power of NMR spectroscopy as a tool for probing the atomic resolution structural features of challenging biological systems such as sparsely populated protein states, large macromolecular complexes and dynamic conformational ensembles.

Tuesday, Aug 16th 2016

4:00 PM (Tea/Coffee at 3:45 PM)

Seminar Hall, TCIS