SEMINAR
Wednesday 7/3/18 11:00 am
Building 211, seminar room

SPEAKER:
Dr. Rina Rosenzweig
Department of Structural Biology
Weizmann Institute of Science

TOPIC:
Molecular Chaperones in Protein Disaggregation – What Can We Learn Using NMR

The Hsp70 chaperone system is ubiquitous, highly conserved, and involved in a variety of different processes that are integral to cell health. Hsp70 function relies on nucleotide-dependent interactions with client proteins, yet its effect on substrates remained poorly understood.

We have used nuclear magnetic resonance (NMR) spectroscopy to structurally characterize a small, folding-competent protein domain (TRF1) in complex with e.coli Hsp70 (Dnak), and have found that binding of Hsp70 results in a globally unfolded conformation of their client proteins. Interestingly, despite being globally unfolded, substrates can start folding and forming local secondary structure while in complex with the chaperones. Hsp70 binding, however, did prevent non-native long-range interactions that are otherwise present in the unbound, unfolded substrate and which can lead to protein misfolding and aggregation.

By then looking directly at the substrate residues situated in the Hsp70 binding pocket, we further identified multiple conformations of TRF1 bound to Hsp70 and that there is a significant amount of heterogeneity in this bound ensemble.

Overall our results suggest that Hsp70 binding can significantly bias the folding pathway of client substrates such that local, secondary structure forms first, followed by the development of longer-range contacts between more distal parts of the protein. In addition, the promiscuous binding of Hsp70 to client proteins may serve to generate different starting points for protein folding, with some structures more amenable to proper folding than others. Furthermore, the ability of Hsp70 to recognize multiple sites in its client proteins could help
ensure that proteins that do not fold to the native state upon release still have a chance to re-enter the chaperone cycle via another site, thereby increasing their chances of ultimately folding correctly.