Title: Molecular Chaperones in the Human Protein Disaggregation System

Abstract:
Accumulation of protein aggregates is associated with a wide array of human disorders, including neurodegeneration, diabetes, and even cancer. Our bodies, however, possess molecular chaperones which can both prevent such protein misfolding and aggregation, and also return proteins trapped in aggregates to their active state - thereby restoring lost function. Very little is known, though, of how these chaperones dissolve protein aggregates or the mechanisms which enable this process.
The human disaggregation system is comprised of Hsp70, the major system ATPase, two classes of Hsp40 (DnaJ) co-chaperones (class A and class B), and Hsp110 nucleotide exchange factor, however the functions and mechanisms of action of these players is largely unknown. Furthermore, while a collaboration between class A and class B DnaJ chaperones was shown to be strictly required for disaggregation, the nature of this interaction and its effect on protein disaggregation has remained a mystery.

Here we focus on the ubiquitous and conserved Hsp70 chaperone and investigate Hsp70 interaction with client proteins, using solution advanced NMR spectroscopy techniques as well as selective isotope-labeling methodologies. Our results establish that both bacterial and human Hsp70 chaperones interact with clients by selecting the unfolded state from a pre-existing array of interconverting structures, suggesting a conserved mode of client recognition among Hsp70s and highlighting the importance of molecular dynamics in this recognition event.
In addition, by focusing on the DnaJA-DnaJB interaction, we have detected a transient forming complex between class A and class B chaperones and have mapped the interfaces of this complex to the DnaJA and DnaJB C-terminal client-binding domains. We have also, interestingly, detected different binding modes for DnaJA1 and DnaJA2 co-chaperones to DnaJB1, providing a potential explanation for higher potency of DnaJA2-DnaJB1 complex in protein disaggregation.

Department: Structural Biology
Year of arrival to Weizmann: Summer 2016
PhD, where, when:
2006-2010, Faculty of Biology, Technion, Haifa, Israel. Supervisor : Prof. Michael Glickman.
Postdoc, where, when:
2010-2016 Department of Biochemistry and Molecular Genetics, University of Toronto, Toronto, ON, Canada. Supervisor : Prof. Lewis Kay