experimental data into Ising-like statistical mechanical models to better understand the observed structural and energetic properties of the two proteins. Two variations of the Ising-like model were implemented: the Wato-Saito-Muñoz-Eaton (WSME) model, which can be enumerated exactly using efficient transfer matrix methods, and the Baker-Finkelstein (BF) model using a double-sequence approximation. Model parameters were optimized by simultaneously fitting the complete set of data for the whole protein as well as each helix independently to reflect what was observed through experiments. In order to give a more realistic representation of protein energy, various statistical residue-specific potential matrices were tested as the inter-residue contact energy in the model. We found that different statistical potentials varied in its success to simultaneously fit all the experimental data, however all the residue-specific matrices resulted in an improvement over considering only a single parameter for the contact energy. Both the WSME and BF models were able to reproduce the equilibrium unfolding data when analyzing the hth proteins as a whole, but the WSME model could not correctly predict the folding of only the helix when analyzed independently due to the assumptions of the model. On the other hand, the BF model was capable of reproducing the experimental data for both the whole protein and the independent helices.

3403-Pos Board B131

Towards a Test of the Aggregation Hypothesis in Huntington's Disease using β-Hairpin Enhancing Motifs

Sascha Rode[1,2], Kenneth Drombosky[1,2], Ronald Wetzel[1,2].
[1]University of Pittsburgh School of Medicine, Department of Structural Biology, Pittsburgh, PA, USA, [2]University of Pittsburgh, Pittsburgh Institute for Neurodegenerative Diseases, Pittsburgh, PA, USA.

Huntington's Disease (HD), one of ten polyglutamine (polyQ) repeat diseases, is a devastating disorder caused by expansion of a polyQ-encoding CAG repeat from 37 or more in exon1 of the huntingtin (htt) gene. Although HD brains contain polyQ aggregates, and polyQ aggregation rates *in vivo* and *in vitro* increase with repeat length, there is a continued debate about the role of amyloid-like aggregates in HD. Recently we reported that aggregation of chemically synthesized, short (repeat length ~ 22), simple polyQ sequences is greatly enhanced with the addition of unnatural amino acids that encourage β-hairpin formation in the aggregation nucleus. Here we ask whether β-hairpin encouraging mutations in a short polyQ version of the htt exon1 peptide also greatly enhance aggregation. We do this while confining our study to mutations that can be introduced during ribosomal synthesis. We show here that a short polyQ sequence containing (a) L-Pro-Gly instead of the previously described D-Pro-Gly and (b) a modified tryptophan zipper motif aggregates much faster than a simple polyQ sequence of similar length. This can be traced to a decrease in the critical nucleus for amyloid formation from a value of $n^* \approx 4$ for a simple, unbroken Q_{23} sequence to $n^* \approx 1$ for similar length polyQ containing β-hairpin motifs. At the same time, the morphologies, secondary structure structures, and bioactivities of the resulting fibrils from simple and exon1 mimic polyQ were essentially identical. Importantly, incorporating these motifs into short polyQ exon1 analogs produces rapid spontaneous aggregation rates comparable to exon1 peptides with long, disease associated polyQ repeat lengths. Expression of these exon1 analogs in cells now addresses whether even short polyQ htt exon1 can be toxic if its polyQ is redesigned to promote rapid aggregation.

3404-Pos Board B132

Salt Effects on Folding of a Helical Mini Protein Villin Headpiece Subdomain HP36 Studied by Generalized-Ensemble Simulations

Takao Yoda[1], Yuji Sugita[2], Yuko Okamoto[3].
[1]Nagahama Institute of Bio-Science and Technology, Nagahama, Shiga, Japan, [2]RIKEN Advanced Science Institute, Wako, Saitama, Japan, [3]Graduate School of Science, Nagoya University, Nagoya, Aichi, Japan.

Additives dissolved in solvent are important factors that affect proteins' stability and/or folding. In this study we investigated effects of salt ions in solvent on folding events of a helical mini protein HP36. Addition of low concentrations of ions should alter electrostatic interactions among charged groups, so that populations for conformational substates of proteins should be changed. Here we compared two data sets of folding simulations of HP36 with explicit water solvent. For efficient sampling of conformational space of the protein, multicanonical replica-exchange method was adopted.

Results of the present analyses suggest that addition of ions reduces the number of nonnative, nonlocal salt bridges in the protein molecule at later stages of folding at room temperature. Especially, nonnative salt bridges between Glu5 and Arg15 and/or another between Asp4 and Lys30 have been kept in the near-native conformations in pure water. Because dehydration of the hydrophobic core of HP36 is completed only at the latest stage of folding where correct hydrophobic-core packing becomes formed, these salt bridges can prevent folding into the fully native structure of HP36 at room temperature.

3405-Pos Board B133

Simulation Model of Protein Transport and Stabilization by GroEL/ES

Apichart Linhananta.
physics, Lakehead University, Thunder Bay, ON, Canada.

In a previous communication (Linhananta et al., *Biophys. J.*, 2011, 100, 459), we reported results of a simulation model of a protein in solvents with protein-solvent contact energy parameter ε_{PS}, which represents osmolytes ($\varepsilon_{PS}>0$) and denaturants ($\varepsilon_{PS}<0$). Here a model of a three-helix-bundle (THB) protein in solvents is confined in a cylindrical cavity that mimics the GroEL/ES chaperone. The interior is characterized by the protein-wall energy, ε_{PW}, and solvent-wall energy, ε_{SW}. Simulations found a substantial increase in the folding temperature from $T^* = 4.2$ (scaled unit), for THB in vacuum, to $T^* > 6.0$ for confined THB in osmolytes. The optimum stabilization of the native state is $T^* = 6.6$, for THB in osmolytes with $\varepsilon_{PS} = 0.6$, confined by walls repulsive to THB ($\varepsilon_{PW} = 1.0$) and solvents ($\varepsilon_{SW} = 1.0$). Weight histogram analysis reveals an entropy-driven stabilization mechanism due to confinement and the osmolytes. The model is generalized to THB and solvents confined in two connected cylindrical segments. The bottom segment represents the GroEL/ES, with the interior sidewall characterized by the parameters ε_{PW} and ε_{SW}. The upper segment represents the exterior surrounding the GroEL/ES, with periodic boundary condition on the sidewall, where the protein and solvents can move through the channel connecting the two segments. For neutral solvents ($\varepsilon_{PS} = 0$) with a sidewall that is repulsive to solvents ($\varepsilon_{SW} > 0$) and attractive to the protein ($\varepsilon_{PW} < 0$), the THB protein preferentially distributes in the lower segment that represents the interior of the GroEL/ES. As the temperature increases and the protein denatures, there is an increase in the probability that the protein is found in the GroEL/ES. This highlights the roles of solvents and surface properties in the transport of unfolded proteins into the GroEL/ES.

3406-Pos Board B134

Non Local Interactions are Essential Elements of the Initiation and Guidance of the Folding Pathway of Proteins

Elisha Haas, Tomer Orevi, Gil Rahamim, Dan Amir.
Life Sciences, Bar Ilan University, Ramat Gan, Israel.

The rate of protein folding is determined by the rate of passage through the transition state, however major structural transition precede the TSE formation. We hypothesize that few non-local interactions are effective in the early phases of the folding transition prior to the cooperative transition. These interactions loosely stabilize few closed loops which form the folding noncontiguous nucleus, reduce the chain entropy and determine the course of the folding pathway (the ''loop hypothesis''). We study the order of formation of secondary structure elements and loop closure during the early phases of the folding of *E. coli* adenylate kinase (AK) by combination of rapid mixing methods and time resolved FRET spectroscopy. We find that at the initiation of folding of the AK molecule two closed loop structures in the CORE domain reach native end to end distance within a millisecond while a third loop (the N terminal loop) is closed on the microsecond time scale. Three representative CORE domain β-strands have non-native end to end distance during the first 15 ms and undergo slow change (3 sec) to native distance. Along the folding pathway of AK the fast closed N terminal loop is reopened and closed again. We conclude that non local interactions are essential factor at the early phases of the folding transition and that the folding of sub-domain elements is context dependent and should be studied in the whole molecule, *in situ*. .

3407-Pos Board B135

Computational Studies of the Formation of Peroxiredoxin Dimers

Jiajie Xiao, Freddie R. Salsbury Jr.
Department of Physics, Wake Forest University, Winston-Salem, NC 27106, USA.

The proteins in the ubiquitous peroxiredoxins (Prx) protein family play an important role in redox signaling and antioxidant defense. The biological functions of Prxs are closely related to the formation of their quaternary structures. To understand details of interactions within Prxs and their quaternary structures formations, the disassembly and unfolding processes of 1YEP (chains A and B) and 3DRN were studied as an example through molecular dynamics simulations. Hundreds of four-microsecond-long simulations using a Go-type model show that disassembly and unfolding processes are