tion regime and cell state dependent photobiomodulation of cadmium effects in human T cells.

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2848-Pos How Cells Decide Between Life And Death: Predictions From Stochastic Simulation

subhadip raychaudhuri

UC Davis, davis, CA, USA.

Board B151

Programmed cell death (apoptosis) is a complex cellular process that involves two separate intracellular signaling pathways, namely Type 1 and Type 2, and a wide range of signaling molecules. A clear mechanistic understanding of how apoptotic stimulus at the cell surface triggers the apoptotic signaling cascade and a cell fate decision is made is still elusive. Using a simple effective model of apoptotic signaling we show that how apoptotic signaling is differentially regulated as we vary the strength of the death stimulus at the cell surface. Specifically we show that under weak apoptotic stimulus the slower Type 2 pathway dominates the signaling where cell-to-cell stochastic fluctuations significantly deviate from the average (over many cells) behavior. Results from our simple effective model is further corroborated by an extensive stochastic simulation of the apoptotic signaling cascade. We also show that our main results are sensitive to only a few critical parameters and robust against other details of the signaling network.

Natively Unfolded Proteins

2850-Pos Bridging The Structure-function Gap: Using Fluorine NMR To Monitor Conformational Changes In Clc-ec1, A Chloride-proton Antiporter Of Known Structure

Shelley Elvington, Merritt Maduke

Stanford University, Stanford, CA, USA.

Board B153

Members of the CLC family of chloride-transport proteins are found in numerous organisms ranging from bacteria to humans, and defects in CLC family members lead to a variety of human diseases. High resolution X-ray crystallographic data are available for the prokaryotic CLC family member ClC-ec1. Inferences that can be drawn from this structure alone are limited, however, since it represents only a static picture of the protein. To understand how transporter movement occurs on a molecular basis, static structural data must be translated into a dynamic model.

Since the ^{19}F resonance is highly sensitive to its chemical environment, ^{19}F NMR is ideally suited for identifying moving parts within a protein of known structure. We have labeled ClC-ec1 with fluorinated tyrosine and measured ^{19}F spectra at pH 7.5 (low transporter activity) and pH 5.0 (high transporter activity). The appearance of new intensities in the NMR spectrum when the pH of the wild-type protein is shifted indicates that at least 1 of the 9 F-tyr residues is changing chemical environment. This change is unlikely to result from unfolding of the protein, since spectral changes are reversible upon return of the sample to pH 7.5, and the protein remains active in assays for chloride and proton flux.

Mutating one or more tyrosine residues to phenylalanine removes the corresponding resonance from the ^{19}F NMR spectrum. We have used this technique to identify the resonance corresponding to the chloride-coordinating residue Y445. Furthermore, we have shown that activity-associated movement is occurring in at least one additional region outside the chloride permeation pathway. Work is currently underway to identify which residues contribute to the observed spectral changes, and therefore which regions of ClC-ec1 are moving during ion transport.

2851-Pos High-throughput Characterization of Intrinsically Disordered Proteins from the Protein Structure Initiative

Derrick E. Johnson, Megan D. Sickmeier, Jingwei Meng, Tanguy Le Gall, Vladimir N. Uversky, A. Keith Dunker

Indiana University School of Medicine, Indianapolis, IN, USA.

Board B154

The identification of intrinsically disordered proteins (IDPs) among the targets that fail to form satisfactory crystal structures in the Protein Structure Initiative would be a key to reducing the costs and time for determining three-dimensional structures of proteins. To resolve this problem, several Protein Structure Initiative Centers were asked to send samples of both crystallizable proteins and proteins that failed to crystallize. Initially, the abundance of intrinsic disorder was evaluated via computational analysis using Predictors of Natural Disordered Regions (PONDR®) and the potential cleavage sites and corresponding fragments were determined. Then, the target proteins were analyzed for intrinsic disorder by their resistance to protease digestion. The rates of tryptic digests of sample proteins generously provided by several Centers were compared to those of myoglobin, apomyoglobin and alpha-casein as standards of ordered, partially disordered and completely disordered proteins, respectively. Results from these digestion experiments generally correlate with the results of disorder predictions. Further analysis will be performed utilizing MS-based peptide fingerprinting to establish cut sites along with urea titrations of ANS fluorescence to determine collapsed, disordered forms of proteins in their native states. In addition, spectroscopic analysis of the samples will be performed in the presence of acrylamide, TCE, TFE, TMAO, and PEG to test specific hypotheses concerning the sequence-structure relationships for IDPs. We envision developing a standard high-throughput methodology to quickly and efficiently identify IDPs. By adding to our knowledge of IDPs, we plan on using the data

collected to improve our disorder predictors as well as expand our current database for disordered proteins, DisProt (www.disprot.org).

2852-Pos Oligomerization and Membrane Interactions of α-Synuclein

Elizabeth Middleton[1], Trudy F. Ramlall[2], David Eliezer[2], Elizabeth Rhoades[1]

[1] *Yale University, New Haven, CT, USA*
[2] *Weill Medical College of Cornell University, Ithaca, NY, USA.*

Board B155

Parkinson's Disease is characterized by the presence of fibrillar deposits of alpha-Synuclein (αS) in the *substantia nigra*. αS is an intrinsically unstructured protein that becomes α-helical upon binding lipid membranes. Many studies indicate that the toxic form of αS may be pre-fibrillar oligomers formed in solution or upon binding to cell membranes. Fluorescence correlation spectroscopy (FCS) and Förster resonance energy transfer (FRET) were used to study interactions of wildtype αS and its pathological mutants, A30P and A53T, with synthetic lipid vesicles. Specifically, FCS was used to measure binding to vesicles of various lipid compositions and FRET was used to determine the conformation of the protein upon binding. The integrity of the lipid bilayer was monitored by the release of fluorescent dye trapped inside the vesicles.

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2853-Pos Hilbert-Huang Transform analysis of Steered Molecular Dynamics Simulations of the Nanomechanics of Intrinsically Disordered Muscle Proteins

Jeffrey G. Forbes[1], Norden E. Huang[2], Kuan Wang[1]

[1] *NIAMS/NIH/DHHS, Bethesda, MD, USA*
[2] *Research Center for Adaptive Data Analysis, Chungli, Taiwan.*

Board B156

Force generation, transmission and transduction are integral to many cellular processes, such as cell migration, cell fusion and cellular proliferation. Most key players in the contractile machineries possess intrinsically disordered domains that perform essential force sensing and signal transduction functions. These disordered domains exist as ensembles of rapidly equilibrating conformations that manifest as unique elasticity when subjected to external force. We are performing systematic structural and nanomechanical analysis of intrinsically disordered domains in the force generating and bearing molecules. Steered molecular dynamics simulations to intrinsically disordered proteins revealed that computationally accessible velocities can yield force spectra that are surprisingly similar to experimental curves. The wealth of molecular information contained in the SMD trajectories are being analyzed by the Hilbert-Huang Transform (HHT), an adaptive empirical method of data analysis, that has been particularly useful for non-stationary and non-linear data (typical from physical and natural processes). An empirical mode decomposition resolve the data into intrinsic oscillation modes that contain information without a priori assumption of periodicity and a subsequent Fourier or Hilbert transform is then used for feature extraction from this (1/t or 1/distance)-energy space.

The results of the HHT analysis of representative members of several classes of intrinsically disordered proteins including titin PEVK (PPII helices), nebulin repeats (transient a helices), myosin S2 (disordered coiled coil) and calmodulin (calcium induced ordering) will be presented. In particular, we show that SMD is able to accurately simulate experimental force spectra of titin PEVK at a simulation velocity of 0.0005 nm/ps. The structural and HHT analysis clearly support the role of salt bridges as "molecular Velcro®" in regulating the elasticity of the titin PEVK segment.

2854-Pos Inducing Order in ChiZ, a Natively Disordered Membrane Protein from Mycobacterium tuberculosis

jacob Moore[1], Ashwini Chauhan[2], Malini Rajagopalan[2], Timothy A. Cross[1]

[1] *Florida State University, Tallahassee, FL, USA*
[2] *University of Texas Health Center, Tyler, TX, USA.*

Board B157

ChiZ is a cell wall hydrolase enzyme expressed in Mycobacterium tuberculosis that has been implicated in regulation of cell division. Enzymes of this nature are hypothesized to play significant roles in bacterial pathogenesis, making it an attractive target for drug therapy research. ChiZ is a 17kDa single-span membrane protein consisting of three separate domains: C-terminal LysM domain, transmembrane domain, and N-terminal domain. We show here that the N-terminal domain of this protein is responsible for cleavage of peptidoglycan. NMR, circular dichroism, and PONDR results indicate that this catalytic domain of this membrane protein is natively unstructured. This work also discusses substrate-binding experiments indicating that this functional domain begins to fold in the presence of various substrates. Additionally, work is being performed to characterize the active site(s) of ChiZ as it relates to cleaving peptidoglycan.

2855-Pos Intrinsic Disorder and Protein Evolution: Probable Amino Acid Sequences of the Last Universal Ancestor's Proteins

Wai Chan[1], Christopher Oldfield[2], Sai Harish Babu Karne[3], Vladimir Uversky[2,4], Pedro Romero[3,2], Keith Dunker[2]

[1] *Department of Biology, School of Science, Indiana University-Purdue University at Indianapolis, Indianapolis, IN, USA*
[2] *Center for Computational Biology and Bioinformatics, Department of Biochemistry and Molecular Biology, School of Medicine, Indiana University-Purdue University at Indianapolis, Indianapolis, IN, USA*

[3] *School of Informatics, Indiana University –Purdue University at Indianapolis, Indianapolis, IN, USA*
[4] *Institute for Biological Instrumentation, Russian Academy of Sciences, Moscow, Russian Federation.*

Board B158

Recent research has been done in determining the order of amino acids that are in existence. According to a paper by Trifonov E.N., the order that the amino acids came into existence is: G, A, D, V, P, S, E, (L, T), R, (I, Q, N), H, K, C, F, Y, M, W. ((2004) Journal of Biomolecular Structure and Dynamics 22, 1). The ones that came earlier are normally referred to as "Ancient" amino acids while the most recent amino acids are "Modern" amino acids. Analysis of the order of the amino acids suggests that many of the "Ancient" amino acids are disorder-promoting residues in "Modern" proteins. This would imply that "Ancient" proteins are more likely to be unfolded compared to "Modern" proteins. This experiment sets out to verify if this link is true.

A group of orthologous proteins was obtained from the Clusters of Orthologous Groups (COGs) database. These groups of COGs were chosen based on the paper by Brooks et al. ((2002) Mol. Biol. Evol. *19*, 1645) because they came from well conserved proteins and from 8 diverse organisms. A protein profile of these COGs was created. Then the Last Universal Ancestor (LUA)'s amino acid frequencies calculated by Brooks' paper and recalculated by Sai Harish and et al. was used to calculate the probable protein profile of the LUA. Using various predictors of "disorderness", the profiles can then be compared to determine if there is a significant difference.

The results are expected to show that these "Ancient" proteins are more likely to be unfolded because the LUA have higher composition of amino acids that promote "disorderness" therefore more likely to create unfolded proteins.

2856-Pos Intrinsic Disorder And Protein Evolution:Amino Acid Composition Of Proteins In Last Universal Ancestor

Sai Harish Babu Karne[1], Pedro Romero[1,2], Janna White[1], Wai Chan[3], Christopher J. Oldfield[1,2], Vladimir N. Uverskey[2,4], A. Keith Dunker[1,2]

[1] *School of Informatics, Indiana University –Purdue University at Indianapolis, Indianapolis, IN, USA*
[2] *Center for Computational Biology and Bioinformatics, Department of Biochemistry and Molecular Biology, School of Medicine, Indiana University-Purdue University at Indianapolis,, Indianapolis, IN, USA*
[3] *Department of Biology, School of Science, Indiana University-Purdue University at Indianapolis, Indianapolis, IN, USA*
[4] *Institute for Biological Instrumentation, Russian Academy of Sciences, Pushchino, Russian Federation.*

Board B159

Studies on the origin and early evolution of genetic code revealed a consensus chronological order of appearance of amino acids, G/A, V/D, P, S, E/L, T, R, N, K, Q, I, C, H, F, M, Y, W (Trifonov E.N. (2000) Gene *261*, 139). Surprisingly, many of the early amino acids (such as G, D, E, P, and S) are disorder-promoting, as they are very abundant in modern intrinsically disordered proteins. On the other hand, the major order-promoting residues (C, W, Y, and F) were added to the genetic code late. This strongly suggests that primordial proteins were likely to be intrinsically disordered. To test this hypothesis we applied a method introduced by Brooks et al (Mol. Biol. Evol. 2002 *19*:1645) to evaluate the amino acid composition of proteins in LUA (Last Universal Ancestor). To this end, a set of proteins from the database of Clusters of Orthologous Groups of proteins (COGs) was analyzed. This database represents a phylogenetic classification of the proteins encoded in complete genomes (http://www.ncbi.nlm.nih.gov/COG). Each COG set includes proteins that are inferred to be orthologs (direct evolutionary counterparts). The current release consists of 138,458 which form 4873 COGs and comprise 75% of the 185,505 proteins from 66 species: 50 bacterial genomes, 13 archaeal genomes, and three genomes of unicellular eukaryotes. All proteins in these COGs were divided on enzymes and non-enzymes and the method proposed by Dawn J Brook's team was applied to these two subsets to derive amino acid compositions of primordial enzymes and non-enzymes in LUA. Analysis revealed that both groups of proteins are highly enriched in disorder, with non-enzymes being much more disordered than enzymes.

2857-Pos Dynamical Properties Of Unstructured FG-Nucleoporins

Michael E. Colvin[1], Edmond Y. Lau[2], V.V. Krishnan[3], Michael Rexach[4]

[1] *University of California, Merced, CA, USA*
[2] *Lawrence Livermore National Laboratory, Livermore, CA, USA*
[3] *Fresno State University, Fresno, CA, USA*
[4] *University of California, Santa Cruz, CA, USA.*

Board B160

The FG-nucleoporins (FG-nups) are natively-unfolded protein domains with repeated phenylalanine-glycine motifs that play key roles in nucleocytoplasmic transport. We have used classical molecular dynamics (MD) simulations to analyze the dynamical properties of a number of FG-nups and FG-nup mutants. As a control, we have also performed similar simulations on denatured forms of a natively folded protein. For each protein we have performed replica exchange molecular dynamics and multiple replicates of conventional MD. From the resulting MD trajectories we have measured the rates of change of standard metrics for protein structure and compactness. We have also analyzed the dynamical properties of the FG-nups using both established metrics for characterizing polymers and newly developed metrics for quantifying the rates of structural change and internal structural correlation. These new metrics include time autocorrelation functions of different descriptors of protein structure and statistical analysis of correlations between inter-residue distances in the protein. These results indicate that FG domains do not adopt fixed secondary or tertiary structures, but do exhibit varying degrees of residual order. The diversity of the dynamical properties in the FG-nups studied suggests that different FG-nups may have different roles in enabling proper transport of materials to and from the nucleus.

2858-Pos Genetically Engineered Model of Naturally Unfolded Fibrillogenic Proteins

Natalya I. Topilina, Vladimir V. Ermolenkov, Seiichiro Higashiya, John T. Welch, Igor K. Lednev

SUNY at Albany, Albany, NY, USA.

Board B161

A *de novo* 140-amino acid residue polypeptide YE8 with a regular 16 amino acid repeat sequence, $(GA)_3GY(GA)_3GE$ exhibits remarkable unfolding/folding properties and, as well, forms fibrillar structures providing the excellent model for an unfolded fibrillogenic protein. Deep UV Resonance Raman spectroscopy was employed to investigate the polypeptide structural transformations during the folding and fibrillation process. We found that the YE8 polypeptide shows all the properties of a typical amyloid fibril-forming protein including a pronounced directing or templating effect. A strong concentration dependence for β-sheet formation correlates with the lag time. However despite the ability of repetitive unit GAGAGAG to form highly regular β-sheet structure, there was no evidence for intramolecular promoting of folding by YE8 polypeptide. AFM, TEM, CD and fluorescence spectroscopy were also used in this work.

2859-Pos Investigation of the Dynamics and Mobility of Full-Length MARCKS, an Intrinsically Disordered Protein, using SDSL-EPR

Mandy E. Blackburn, Elizabeth L. Brooks, Safi Smith, Gail E. Fanucci

Univeristy of Florida, Gainesville, FL, USA.

Board B162

MARCKS is an intrinsically disordered protein (IDP) involved in relaying messages between multiple signaling pathways via mutually exclusive interactions involving the effector domain (ED). The ED is a 25 residue domain located near the center of the protein that contains 13 basic residues, five hydrophobic residues, and three phosphorylation sites. MARCKS is known to bind to calmodulin (CaM, a protein involved in calcium based signaling pathways; acidic membrane surfaces), and phosphatidylinositols (which are poly-valent acidic lipids involved in multiple signaling pathways). Results from a site-directed spin-labeling (SDSL) EPR spectroscopy characterization of the dynamics of the N and C termini and ED of full-length MARCKS upon binding to acidic vesicles and Ca 2+ − CaM are presented. For these experiments, full-length MARCKS protein was expressed and isolated from E. coli. To ensure removal of nucleic acid contamination, a demonstrated problem for proteins that contain basic regions obtained recombinantly from E. coli [1], a novel fluorescence based assay was developed. Details of protein purification and YOYO assay are also presented.

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2860-Pos Modeling the Unfolded State of a Microtubule Binding Repeat in Tau Protein Austin

V. Huang, Collin M. Stultz

MIT, Somerville, MA, USA.

Board B163

Tau is a natively unfolded protein that forms intracellular aggregates in the brains of patients with Alzheimer's disease. To decipher the mechanism underlying the formation of tau aggregates, we developed a novel approach for constructing models of natively unfolded proteins. The method, Energy-minima Mapping and Weighting (EMW), samples local energy minima of subsequences within a natively unfolded protein and then constructs ensembles from these energetically favorable conformations that are consistent with a given set of experimental data. Using EMW, we generated ensembles that are consistent with secondary chemical shift measurements obtained on 13C enriched forms of tau. By focusing on structural features that are common to the various ensembles, we obtained novel insights into the structural ensembles of wild-type and mutant forms of tau.

2861-Pos Structure Of The Full Length HIV-1 Integrase In Complex With LEDGF And DNA By Cryo Electron Microscopy

Fabrice Michel[1], Corinne Crucifix[1], Florence Granger[1], Jean Francois Mouscadet[2], Marina Gottikh[3], Alexis Nazabal[4], Stephane Emiliani[5], Richard Benarous[5], Dino Moras[1], Patrick Schultz[1], Marc Ruff[1]

[1] *IGBMC, Illkirch, France*
[2] *ENS, Cachan, France*
[3] *Belozersky Insitute of Physico-Chemical Biology, Moscow, Russian Federation*
[4] *ETH, Zurich, Switzerland*
[5] *Institut Cochin, Paris, France.*

Board B164

Integration of the human immunodeficiency virus type 1 (HIV-1) cDNA into the human genome is catalyzed by the viral integrase protein that requires the lens epithelium-derived growth factor (LEDGF), a cellular transcriptional coactivator. In the presence of LEDGF, integrase forms a stable complex *in vitro* and importantly becomes soluble by contrast with integrase alone which aggregates and precipitates. Using cryo-electron microscopy (EM) and single-particle reconstruction, we obtained three-dimensional structures of the wild type full length integrase-LEDGF complex with and

without DNA at 14 A resolution. The stoichiometry of the complex was found to be $(integrase)_4$-$(LEDGF)_2$ and existing atomic structures were unambiguous positioned in the EM map. *In vitro* functional assays reveal that LEDGF increases integrase activity likely in maintaining a stable and functional integrase structure. Upon DNA binding, IN undergoes large conformational changes. Cryo-EM structure underlines the path of viral and target DNA and a model for the concerted DNA integration in a highly bent human DNA is proposed.

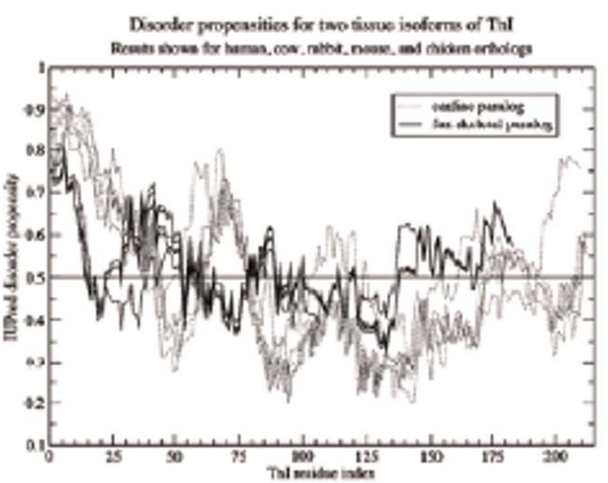
2862-Pos Tissue Isoforms Of Troponin I Vary In Their Predicted Intrinsic Disorder

Ryan M.B. Hoffman, Brian D. Sykes

University of Alberta, Edmonton, AB, Canada.

Board B165

Intrinsic disorder (ID) prediction algorithms were used to assess the distribution and extent of ID in the three tissue isoforms of troponin I (TnI). Consistent with previous experimental findings in the fast skeletal system, all prediction approaches identified the termini as intrinsically disordered. The N-terminal extension unique to the cardiac isoform, a known site of integration of multiple signaling cascades, was predicted to be very highly disordered. Only one predictor (DISOPRED2) gave largely similar results across the tissue isoforms; the majority of prediction approaches (including the predictors based on physical models of ID, FoldIndex and IUPred) evince tissue-specific variation in the stability of TnI. VSL2B showed the largest variation in ID between the isoforms. An unexpected finding was that the largest variability in predicted ID was found for the coiled-coil-forming region, and that the inhibitory region of TnI had large predicted differences in ID, comparing different isoforms. The results are interpreted in terms of the mechanistic role of the coiled-coil forming region, in the context of the known structure-function relationships of the thin filament.



2863-Pos Single-molecule And Ensemble Studies Of Alpha-synuclein Multistate Folding And Membrane Interaction

Allan Chris M. Ferreon, Yann Gambin, Edward A. Lemke, Ashok A. Deniz

The Scripps Research Institute, La Jolla, CA, USA.

Board B166

Alpha-synuclein, a natively unfolded protein expressed predominantly in the human brain and concentrated in presynaptic nerve terminals, has been implicated in the pathogenesis of several neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, all characterized by protein misfolding and the formation of fibrillar aggregates. To better understand the mechanism of alpha-synuclein misfolding and fibrillation, the conformational properties of the protein were investigated using a combination of ensemble and single-molecule techniques.

Protein transitions induced by changes in temperature, pH and concentration of a lipid-mimetic (SDS) were monitored by far-UV CD spectroscopy. Our ensemble data suggested a model of the alpha-synuclein folding landscape involving multiple conformational states.

In order to directly probe the different alpha-synuclein conformational states and intermediates, a dual cysteine mutant of the protein was site-specifically labeled with donor and acceptor fluorescent dyes, and used in single-molecule FRET (smFRET) experiments. The evolution of FRET distributions as a function of SDS concentration enabled us to clearly distinguish several protein conformations. Fluorescence correlation spectrocopy (FCS) was employed to characterize the dynamics of each state. Our single-molecule data revealed that alpha-synuclein binds tightly to SDS bilayers, and that its folding state is sensitive to membrane curvatures. In addition, smFRET enabled us to follow protein conformational changes induced by binding to phospholipid vesicles of different lipid compositions. Our results highlight the complex landscape of alpha-synuclein binding-induced folding, with implications for its misfolding and biological activity.

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2864-Pos Analysis Of Multiple Specificity In P53 And 14-3-3

Christopher J. Oldfield[1], Jingwei Meng[1], Jack Y. Yang[1,2], Vladimir N. Uversky[1,3], A. Keith Dunker[1]

[1] *Indiana University-Perdue University at Indianapolis, Indianapolis, IN, USA*

[2] *Harvard Medical School, Boston, MA, USA*

[3] *Russian Academy of Sciences, Pushchino, Russian Federation.*

Board B167

Proteins are involved in many interactions with other proteins leading to networks that regulate a wide variety of physiological processes. Some of these proteins, called hub proteins or hubs, bind

to many different protein partners. It has been proposed that hub function may be facilitated by intrinsic protein disorder. Intrinsically disordered proteins (IDPs) lack a stable three-dimensional structure under physiological conditions and many such proteins have been characterized by several biophysical methods. Additionally, IDPs are estimated to be abundant within various proteomes, particularly eukaryotes, and carry out a variety of molecular functions without the prerequisite of a specific, stable structure. It is thought that IDPs can facilitate hub function through an ability to mediate binding diversity, where one of the proposed mechanisms for this is multiple recognition - i.e. recognition of multiple molecular partners through use of the same binding residues - through contextual folding of IDPs. Despite the importance of hub proteins, the molecular basis of multiple recognition has not been well studied.

Here we present a detailed examination of two divergent examples of hub proteins to illustrate the mechanisms by which intrinsic disorder can mediate binding diversity:

1. p53, which uses different disordered regions to bind to different partners and which also has several individual disordered regions that each bind to multiple partners, and
2. 14–3–3, which is a structured protein that associates with many different intrinsically disordered partners.

For both examples, three-dimensional structures of multiple complexes reveal that the flexibility and plasticity of intrinsically disordered protein regions as well as induced-fit changes in the structured regions are both important for binding diversity. These data support the conjecture that hub proteins often utilize intrinsic disorder to bind to multiple partners and provide detailed information about induced fit in structured regions.

2865-Pos Osmolyte-induced Folding Of Alpha-synuclein Probed By Tryptophan Fluorescence Spectroscopy

Gertjan Veldhuis

University of Twente, Enschede, The Netherlands.

Board B168

Osmolytes are small organic compounds well-known for their ability to aid in protein stabilization and folding. From a medical point of view these simple chemical chaperones receive an ongoing interest as they may be potentially interesting candidates for drug targeting and treatment of human diseases related to protein aggregation or conformational misfolding. A vast number of neurodegenerative diseases are accompanied by deposits of proteins into amyloid-like structures. In many cases the proteins belong to the class of intrinsically disordered proteins, lacking specific stable secondary structure, at least under *in vitro* conditions, that is, in dilute aqueous solutions. Intrigued by the ability of osmolytes to stabilize or rescue (partially) denatured proteins, we set out to explore the structural implications of a particular set of osmolytes on a model intrinsically disordered protein, alpha-Synuclein, involved in the etiology of Parkinson's disease. Osmolyte-induced folding was monitored by spectroscopic investigation of single-Trp mutants of alpha-Synuclein with tryptophan residues engineered at various positions along the polypeptide chain. The onset of folding, accompanied by a blue-shift in the fluorescence emission maximum and a gain in secondary structural elements measured by CD, was not only dependent on the concentration of the osmolytes employed, but also on the chemical nature. Interestingly, osmolyte-induced folding was probed equally well by all single-Trp mutants and occurred for each particular osmolyte at similar concentrations, irrespective of the position of the Trp. This suggests that the folding is a phenomenon of the whole polypeptide instead of being just local effects. The magnitude of the blue-shift, however, did show a clear dependency on the position of the Trp, indicating that some parts of the protein became highly buried whereas others remained close to the surface of the compacted species.

2866-Pos How PUMA Attacks Its Prey: Understanding The Molecular Basis Of PUMA-Induced Cell Death

John C. Fisher, Jerry E. Chipuk, Douglas R. Green, Richard W. Kriwacki

St. Jude. Children's Research Hospital, memphis, TN, USA.

Board B169

PUMA, a member of the pro-apoptotic BH3-only proteins, has been shown to be essential for p53 induced apoptosis in response to genotoxic stress, but the mechanism(s) through which PUMA induces mitochondrial outer membrane permeabilization (MOMP) has been subject to extensive study and much debate. Here we show that PUMA is an intrinsically unstructured protein free in solution. While PUMA is completely devoid of tertiary structure, we show using NMR and circular dichroism spectroscopy that the 25 residue segment corresponding to the BH3 domain exhibits slight helical propensity in solution. Furthermore, we report the 2.9Å crystal structure of a 25 amino acid PUMA BH3 domain peptide bound to the anti-apoptotic BCL-xL protein. The PUMA BH3 domain undergoes a disorder-to-order transition upon binding BCL-xL and assumes a rigid helical conformation. Reminiscent of previously determined BCL-xL/BH3 structures, the structure of the BCL-xL surface-exposed hydrophobic groove changes to accommodate the PUMA BH3 helix; however, the extent of structural rearrangement seen for BCL-xL in the PUMA bound crystal structure differs quite drastically from other BCL-xL/BH3 structures. The results of our structural studies of PUMA and the PUMA/BCL-xL complex provide important insights into the molecular basis of p53-dependent PUMA-induced apoptosis and into the mechanistic basis regarding the BCL-xL, p53, PUMA tripartite nexus.

2867-Pos Stabilizing and Destabilizing Interactions between Intrinsically Unstructured N and C Terminal Regions and Homeodomain of NK-2 Class Homeoproteins

Jeong Ho Ju[1], Takeshi Tomita[2], Edward P. Gelmann[1], Shioko Kimura[2], James M. Gruschus[2]

[1] *Columbia University, New York, NY, USA*
[2] *National Institutes of Health, Bethesda, MD, USA.*

Board B170

NK-2 class homeoproteins are transcription factors that orchestrate organogenesis during embryonic development, and maintain organ cells in their differentiated state in adults, suppressing carcinogenesis. They consist of roughly 80% flexible random coil and a single, well-ordered DNA binding domain, the homeodomain. NMR and CD spectroscopy results for the NKX 2–1, NKX 2–5, and NKX 3–1 proteins are presented. Stabilizing interactions occur between the homeodomain and motifs in the N-terminal flexible random coil region, while destabilizing interactions occur with motifs in the C-terminal region. These motif interactions appear to be modulated by phosphorylation, affecting homeodomain stability and, consequently, protein turnover in the cell. Thus, these N and C-terminal motifs and their interacting kinases could be targets for therapies aimed at boosting tumor suppression by promoting stabilizing and inhibiting destabilizing homeodomain interactions, leading to increased protein levels in the cell.

Molecular Modeling

2868-Pos Polymers at High Solution Concentration, in Polymer Brushes, and in Mesoscopic Channels

V. Adrian Parsegian[1], Joel A. Cohen[2], Rudi Podgornik[1], Per Lyngs Hansen[3], Sergey M. Bezrukov[1]

[1] *NIH, Bethesda, MD, USA*
[2] *Univ Pacific, San Francisco, CA, USA*
[3] *Univ Southern Denmark, Odense, Denmark.*

Board B171

In high-concentration solutions, stressed between lipid bilayers, squeezed into narrow channels, when does a polymer feel the walls? When is a polymer or oligomer so self-crowded that neither its length nor the walls matter? When will it act as it does in a des Cloizeaux regime where compressive properties depend only on the density of monomers (with its characteristic 9/4 power dependence on concentration)?

Measurements of forces between bilayers with attached PEG oligomers [1–3] together with measurements of polymer partitioning between a channel and the outside solution [4,5], show that within a small enough space, an oligomer or a polymer can even forget its length. At high enough monomer density it, paradoxically, forgets the walls that confine it. This becomes dramatically clear when large polymers are able to enter nanoscale pores.

A unity of thinking emerges between behaviors on the nanometer and centimeter scales.

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2870-Pos 3D Structure of the Unliganded gp120 Based on Structural Homology and Molecular Dynamics Symulations

Octavian O. Calborean, Dan F. Mihailescu

Faculty of Biology, University of Bucharest, Bucharest, Romania.

Board B173

Infection with HIV-1 begins with the docking of the viral envelope protein gp120 to CD4 receptors expressed on the the host cell surface. Understanding of the conformational states available to the HIV-1 envelope glycoprotein gp120 is critical to any rational attempt to design inhibitors and vaccines. The full-length HIV-1 gp120 has eluded structural analysis. However, deletion of the V1, V2 and V3 variable loops and the N- and C-termini of gp120 from HIV-1 and from simian immunodeficiency virus (SIV), resulting in gp120 core protein have been crystallized. The objective of gp120 molecular modeling is to derive the complete 3D structure of the free (unliganded) biomolecule using experimental elements belonging to different strains of the virus, characterized in different crystallization conditions and at different resolutions.

The reconstruction procedure is based on primary data experimentally derived from X-ray crystallography or NMR of certain major components from the gp120 molecular puzzle:

(i) the unliganded, completely glycosylated, V3 loop-missing SIV structure;
(ii) structures liganded to CD4 and antibody (HIV);
(iii) the liganded structure containing V3 loop (HIV);
(iv) V3 loop and C5 domain in solution.

The 3D structures were modelled by protein structure homology. The alignments between the primary structures of known states and the ∼60 strains modelled were manually adjusted and then each