these conditions, the predominant toxin complex that assembles is octameric. Incubation in blood causes heptameric LT complexes to lose greater than 90% cytotoxicity, whereas octameric LT complexes retain their activity. To understand the molecular mechanism of the apparent differential loss of toxin activity, we determined the pH-threshold of conversion to the channel state for each oligomeric complex. We find that the octameric toxin has a lower pH-threshold for channel formation than the heptamer. A consequence of this is that heptamers are inactivated by premature conversion to the channel state, whereas the octamers remain in the functional prechannel state. We propose that assembly of two oligomeric Atx complexes may provide a regulation mechanism for anthrax toxin cytotoxicity in both assembly at cell-surfaces and in the bloodstream. The assembly of octameric toxin complexes at the cell surface may alleviate potential assembly bottlenecks incurred by the mechanism of assembly via PA dimers, while in the bloodstream they may serve to maintain cytotoxicity during anthrax pathogenesis.

2342-Pos

An Atomic View of Fibril Structure Using Solid State NMR Approaches

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Amyloidosis is a clinical disorder caused by extracellular deposition of proteins that are normally soluble in their native conformation, but suffer conformational modifications resulting in insoluble and abnormal fibrils that impair organ function. Parkinson's disease and Alzheimer's disease are the two most common diseases associated with amyloidosis. However, many important diseases such as Prion and Huntington diseases are also amyloidogenic. To understand protein aggregation is crucial to improve the knowledge about protein-protein interactions and protein hydration and thus the thermodynamic behavior related to folding and misfolding.

The limitations of many biophysical and biochemical approaches to study fibril formation have slowed the advance in the understanding of how soluble proteins undergo conformational changes that result in aggregation. Techniques such as Atomic Force Microscopy and Transmission Electron Microscopy taken together with X-Ray Crystallography have provided some details about fibril morphology and distance correlations among monomeric units. However, samples composed of fibrils are huge, heterogeneous and extremely difficult to crystallize, which implies in a limitation to use Crystallography and Solution-State NMR. As atomic resolution models require information about the spatial coordinates of atoms, Solid-State NMR (ssNMR) has emerged as the uniquely technique able to provide these information. Improvements in distance measurements, torsion angle determination, improved decoupling sequences, and higher Magic Angle Spinning frequencies allow ssNMR to become an important tool for structural studies of fibrillar architecture. Fibrils have been shown to adopt β-sheet conformation organized in parallel or anti-parallel fashion associated with in- or out of register structures. Despite the many challenges that have been overcome, many questions remain unanswered and more improvements need to be made.

2343-Pos

Molecular Structure of Type II Collagen

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The naturally crystalline arrangement of collagen molecules within the fibrils of some tissues, allows the use of fiber diffraction methods for structural characterization. This method has the potential to give structural information about collagen type II with minimum interference from sample preparation and may give the opportunity to produce relatively detailed three-dimensional visualization of the fibrils sub-structure. Towards this end, experiments with Multiple Isomorphous Replacement (MIR) were carried out to so that a one-dimensional electron density map of native collagen structure may be determined. Several experiments were performed at the BioCAT facility at Argonne National Laboratory with variations of: sample holder designs, sample preparation procedures, heavy atoms for MIR, temperatures and setups for small and medium angle diffraction. Some more optimum combinations of these produced data of resolution 15 Å or better in the axial direction. Using these data, a subsequent study that also made use of AFM and TEM techniques, revealed that the parameters of collagen type II fibrils from lamprey notochord are very similar if not the same as collagen type II fibrils in mammalian tissues: 30 nm in diameter, axial periodicity of 67 nm, amino acid charge distribution is the same. Analysis of the X-ray diffraction derived one dimensional electron density map showed that the telopeptides, which are crucial for fibrillogenesis and organization of collagen type II tissues, have a very specific folded conformation, reminiscent of that seen in the C-telopeptide of type I collagen. The folded telopeptide conformations provide a clear picture of the intermolecular crosslink locations within the contributing collagen monomers within the 67 nm D-period. This type of structural information is essential for understanding the mechanisms of tissue development and disease pathologies.

2344-Pos

Tandem Repeats Domain in Candida Albicans Als Adhesins

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Yeast adhesins are involved in binding interactions to other cells, substrates and surfaces. Als adhesins in *Candida albicans* consists of 8 homologous proteins. The proteins are composed of an N terminal signal sequence, three Ig-like domains, a threonine rich (T) region, tandem repeats (TR), a glycosylated stalk and C-terminal GPI-anchor to the cell wall. Tandem repeats in the *C. albicans* Als adhesins consist of 2 to 36 copies of a 36-residue sequence.

Tandem repeat domain structures from six Als adhesins were modeled by Rosetta and LINUS. Both methods produced a three-stranded antiparallel β-sheet. This is consistent with circular dichroism (CD) secondary structure and atomic force microscopy domain measurements. Models of glycosylated TR domains show carbohydrates surrounding hydrophobic patches. This is the basis of protein-protein and protein-substrate interactions. In addition, the presence of tandem repeats led to enhanced non-saturable binding to polystyrene and other TR domains. Interestingly, TR domains do not affect the isosbestic point in thermal CD experiments.

This modeling structure and function of the tandem repeats in Als proteins can be applied to repeat regions in other yeast adhesins proteins.

2345-Pos

Structure-Based Models for Alpha-Helical to Beta-Helical Conformation Change in the C-Terminal of the Mammalian Prion Protein

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We employ all atom structure-based models with mixed basis contact maps to explore where there are any significant geometric or energetic constraints limiting conjectured conformational transitions between the alpha-helical (αH) and the left handed beta helical (LHβH) conformations for the C-terminal (residues 166-230) of the mammalian prion protein. The LHβH structure has been proposed to describe infection oligomers(1) and one class of in vitro grown fibrils(2,3), as well as possibly self-templating the conversion of normal cellular prion protein to the infectious form. The structure-based model uses GROMACS based molecular dynamics with a two-dimensional weighted histogram analysis method (WHAM) being applied to study projected energy surfaces. Our preliminary results confirm that the kinetics of the conformation change are not strongly limited by the large scale geometry modification, and evidence exists for a pathway linking the two conformations with a common folding intermediate, also suggested by all atom unfolding simulations(4).

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(4) See S. Dai and D.L. Cox, abstract elsewhere for this meeting

*Research supported in part by the International Institute for Complex Adaptive Matter, NSF Grant DMR-0844115

2346-Pos

Silk Fiber Mechanics from Models at Different Length Scales

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Silk is one of the most resilient fibers in nature. Consisting of an amorphous matrix cross-linked by beta-sheet rich crystalline units, silk is a hierarchically organized material the molecular details of which remain largely unknown. In order to decipher the structural determinants of its mechanical properties, we model silk at different length scales by combining molecular dynamics simulations, force distribution analysis, novel force-based coarse-grain models, and finite element methods. We predict the distinct mechanics of anti-parallel versus parallel silk crystals as force-bearing cross-links [1], and the impact of chain entanglement and crystallinity on fiber mechanics [2]. Our predictions can serve as a guide for the design of artificial silk protein analogues.