flanking sequences from huntingtin. Also, we show that electrostatic repulsions due to these residues retard the rate of monomer loss and large, linear, ordered clusters are formed. Our observations provide a unifying framework, capturing all known features of the early stages of aggregation in polyglutamine containing systems.

1992-Pos Board B11

A Class of Self-Assembling Aliphatic Ultrasmall Peptides as a Model System for Understanding and Preventing Amyloidosis

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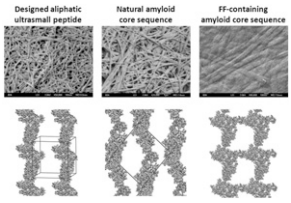
Core sequences of 4-7 residues that form amyloid fibrils have been identified within natural amyloid proteins. However, the mechanism of amyloid aggregation remains unclear. We designed a new class of aliphatic peptides (with 3-6 residues) that self-assemble in water to amyloid β-type fibers via α-helical intermediates. We compared the self-assembly of our designed peptides with core sequences in Amyloid-beta, Amylin and Calcitonin using a multimodal approach. A common feature was the appearance of α-helical intermediates before the final β-turn structures. Another amyloid-beta core sequence containing the diphenylalanine motif was chosen to evaluate the role of aromatic residues in self-assembly. The repeated occurrence of aromatic residues in core sequences has led to widespread conclusions about their key role in driving self-assembly. Surprisingly, the diphenylalanine-containing sequence did not form cross-β aggregates or involve the α-helical intermediate step. Our study puts forth a new, simplified model system to study amyloidosis and indicates that aromatic interactions are not as important as previously postulated. The results provide valuable insight into the early intermediates and factors driving self-assembly, which is necessary for developing small molecule therapeutic drugs that prevent amyloidosis.



1993-Pos Board B12

Discrete Molecular Dynamics Study of Oligomer Formation by N-Terminally Truncated Amyloid B-Protein

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Alzheimer's disease (AD) is strongly linked to amyloid b-protein (Ab). Two predominant alloforms, Ab1−40 and in particular Ab1−42, are known to form toxic oligomers. The N-terminally truncated, pyroglutamated forms of Ab1−40 and Ab1−42 are highly resistant to peptidase degradation and can seed Aβ aggregation. Discrete molecular dynamics (DMD) simulations previously captured in vitro derived distinct Ab1−40 and Ab1−42 oligomer size distributions and predicted that the more toxic Ab1−42 oligomers had more flexible and solvent exposed N-termini than Ab1−40 oligomers. Here, oligomer formation by four N-terminally truncated Ab peptides: Ab3−40, Ab3−42, Ab11−40, and Ab11−42 was examined by the DMD approach. In our simulations, the four N-terminally truncated peptides showed increased oligomerization propensity, consistent with their in vitro tendency to seed aggregation. Conformations formed by Ab11−40 had the lowest b-strand and the highest turn content. The tertiary and quaternary structure of Ab3−4X oligomers was distinctly different from that of Ab11−4X oligomers. Ab3−4X oligomers were characterized by more disordered and solvent exposed N-termini than oligomers formed by the full-length peptides. In contrast, in comparison to Ab1−4X, Ab11−4X oligomers had a more compact structure, facilitated by Val12, resulting in less flexible and less solvent exposed N-termini, suggesting reduced Ab11−4X-mediated toxicity. This unique behavior of the N-termini in Ab peptides might provide a plausible explanation for the experimentally observed increased toxicity of Ab3−4X peptides and their pyroglutamated forms.

1994-Pos Board B13

Intrinsic Disorder and Chaperon-Like Activity of Different Caseins

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Casein is the best characterized milk protein and constitutes over 70-80% of total bovine milk protein. In milk, casein exists as large micelle-like particles that comprise four unrelated proteins (αs1-, αs2-, β-, and κ-casein) and calcium phosphate. Although αs1-, αs2-, β-, and κ-casein present important structural differences, all of them adopt extremely open and flexible conformations, enough to be defined intrinsically disordered proteins (IDPs). Caseins are able to inhibiting protein aggregation and amyloid fibrils formation and this chaperon-like activity could be largely due to their structural disorder. In the present study we discuss the meaning of ''disorder'' in the case of three caseins α, β and k that have similar unordered structure and different sequence. We correlate the different type and disorder degree to the capability of preventing protein aggregation and amyloid formation. The physical-chemical parameters of α, β and k caseins were compared to those of intrinsically unfolded and ideally globular proteins. Moreover, caseins sequences were analyzed by several publicly available disorder-oriented predictors two metaservers, MeDor and meta-PRDOS, and by a neural network algorithm (PONDR). We observed that α, β and k caseins have different degree and type of disorder, depending on the parameters under analysis and criteria used by the different predictors. These data were correlated to experimental results (ThT fluorescence, CD) on the caseins effect on 1-40 β-amyloid peptide fibrillogenesis. Experiments showed that k-casein forms ordered aggregates and that it is able to significantly increase lag-time and reduce fibril amount in Aβ amyloid formation. Our results contribute to clear the role of intrinsically disordered proteins and their mechanism of action by functional order/disorder transitions, and offer insight in the field of prevention and therapy in Alzheimer diseases, and, in general, of amyloid pathologies.

1995-Pos Board B14

Cellular Polyamines Promote Amyloid-Beta Peptide Fibrillation and Modulate the Aggregation Pathways

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The cellular polyamines spermine, spermidine, and their metabolic precursor putrescine, have long been associated with cell-growth, tumor-related gene regulations, and Alzheimer's disease. Here, we show by in-vitro spectroscopy and AFM imaging, that these molecules promote aggregation of amyloid-beta (Aβ) peptides into fibrils and modulate the aggregation pathways. NMR measurements showed that the three polyamines share a similar binding mode to monomeric Aβ(1-40) peptide. Kinetic ThT studies showed that already very low polyamine concentrations promote amyloid formation: addition of 10 μM spermine (normal intracellular concentration is ~1 mM) significantly decreased the lag and transition times of the aggregation process. Spermidine and putrescine additions yielded similar but weaker effects. CD measurements demonstrated that the three polyamines induce different aggregation pathways, involving different forms of induced secondary structure. This is supported by AFM images showing that the three polyamines induce Aβ(1-40) aggregates with different morphologies. The results reinforce the notion that modulation of the Aβ peptide aggregation pathways towards minimally toxic ones by addition of suitable ligands may be a possible therapeutic strategy for Alzheimer's disease.

1996-Pos Board B15

Cyclic N Terminal Fragment of Amylin Forms Non Amyloid Fibers: Implications for Intra- and Inter-Molecular Interactions in Amylin

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Islet amyloid polypeptide (IAPP), also known as amylin, is a 37-residue intrinsically disordered hormone peptide that is secreted together with insulin by the beta cells of the pancreas, and is involved in glucose regulation and gastric emptying. IAPP is implicated in the pathogenesis of diabetes type II, due to its deposition in the form of amyloid fibers in the beta cells of the pancreas, where insulin is produced. IAPP contains a highly conserved, functional disulfide bond that confers a short ring-like structure (N_loop) to the N-terminus of the peptide. Removal of this functional element alters both the mass per length distributions of hIAPP fibers and the kinetics of fibril formation. The mechanism by which the N_loop affects hIAPP aggregation is not yet understood,

but it is important for rationalizing the kinetics and potentially developing inhibitors.
Using a nanosecond laser spectroscopy technique, able to measure rates of end-to-end contact formation in disordered proteins, Vaiana et al. have shown that the N_loop induces compact states in IAPP, implying attractive interactions between the N_loop and the disordered linear chain. Here we report that the isolated N_loop (residues 1-8 of hIAPP) forms extremely long and stable non β-sheet fibers in solution under the same conditions in which human amylin (hIAPP) forms amyloid fibers. We discuss the effect of peptide cyclization on intra- and inter-protein interactions, and its possible implication in the function and pathological aggregation of IAPP. Our findings indicate a potential role of direct N_loop-N_loop interactions in hIAPP aggregation, which has not been previously explored.

1997-Pos Board B16
Energy Centrality Relationship Reduces False Positive Prediction in Protein Docking
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Interacting protein networks are responsible for a multitude of biological functions. These Functionally-Linked Interacting Proteins (FLIPs) occur at specific interfaces. The structures of most FLIPs are identified via X-ray crystallography, which can also reveal contacts that are functionally uncorrelated (FunCs) and the result of aggregation during crystallization. We hypothesize the Energy Centrality Relationship (ECR) concept that evolutionary pressure to maintain FLIPs will generate signature characteristics that can discriminate between aggregation and association. In our ECR analysis, we assess the amino acid energetic variation upon computational alanine scanning as a function of distance from the centroid of the interface. Here, we show that positional and energetic correlation patterns can discriminate FLIP/FunC and when clustered can differentiate between proteins belonging to different FLIP/FunC sub-categories. In addition, by generating docking decoys for structures of representatives of protein functional categories, we demonstrate ECR also greatly reduces false positives in quaternary structure prediction.

1998-Pos Board B17
Residue Interaction Network: An Approach to Identify Functionally Important Residues for Protein:Protein Interactions
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Proteins play an important role in various cellular processes, directly or by interacting with other proteins and macromolecules. The structural stability and interaction capability are important for their efficient functioning, but identifying the residues most important to those functions remains a problem. Here, we use a Network Analysis (NA) approach for identifying such important residues in our interacting protein database, FLIPdb. A residue network can be defined as all the residues within a contact distance, regardless of bonded or non-bonded interactions. Other studies done by using Network Analysis connectivity parameters show that active sites and functionally important residues in monomeric proteins can be identified. In this work, a residue network was constructed in which the amino acid residue Cμ atom positions represent the nodes and the edges are residues whose nodes are within 9 Å. Analysis of network centrality parameters such as *degree centrality, closeness*, and *betweeness* indicate that the network characteristics of residues in quaternary interactions are differentiable from those of other residues.

1999-Pos Board B18
Mathematical Modeling of Amyloid Beta Fibril Formation: Equilibria & Stability
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Protein misfolding and concomitant aggregation towards amyloid formation is the underlying biochemical commonality among a wide range of human pathologies. Amyloid formation involves the conversion of proteins from their native monomeric states (intrinsically disordered or globular) to well-organized, fibrillar aggregates in a nucleation-dependent manner. Understanding the mechanism of aggregation is important not only to gain better insight into amyloid pathology but also to simulate and predict molecular pathways. One of the main impediments in doing so is the highly stochastic nature of interactions that complicates the development of meaningful insights. In this study, we have utilized a well-characterized intermediate along the amyloid-β peptide aggregation called 'protofibrils' as a model system to investigate the molecular pathways by which they form fibrils using stability and perturbation analysis. Investigation of protofibril aggregation limits both the number of species to be modeled (monomers, and protofibrils), as well as the reactions to two (elongation by monomer addition, and protofibril-protofibril lateral association). Our new model is a reduced order four species model grounded in mass action kinetics. Our prior study required 3200 reactions, which makes determining the reaction parameters prohibitively difficult. using this model, along with a linear perturbation argument, we rigorously determine stable ranges of rate constants for the reactions and ensure they are physically meaningful. This was done by finding the ranges in which the perturbations vanish in a five-parameter sweep, which includes the monomer and protofibril equilibrium concentrations and three of the rate constants. These results are presented and discussed.

2000-Pos Board B19
Developing a Brownian Dynamics Algorithm to Simulate Protein Aggregation
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Protein aggregation is strongly linked to a number of neuro-degenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease.
Alpha-synuclein (α-syn) is an intrinsically disordered protein found mainly in neuronal tissue. Its secondary structure is a function of the surrounding environment, the protein being disordered in a solvent, curling up into an alpha-helix near a membrane and stretching into beta sheets in fibrils or amyloids. The latter form accumulates in Lewy bodies, which are implicated in the ontogenesis of Parkinson's disease.
To study protein aggregation we are developing a highly coarse grained model, by representing protein segments as soft rigid bodies of various shapes with attractive patches on their surfaces. To simulate their dynamics, we have implemented a recently proposed Brownian Dynamics (BD) algorithm.
We present results on simulations of single particles, demonstrating that both translational and rotational diffusion coefficients, as well as the equilibrium probability densities, are in good agreement with theory. In addition we show preliminary results studying the aggregation and self-assembly of these particles.

2001-Pos Board B20
Modelling the Inhibition of Amyloid-β Aggregation causing Alzheimer's Disease using D-Peptides
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The development of Alzheimer's disease (AD), a leading cause of dementia in the elderly, is characterised by brain neurons degeneration, which according to recent evidence results mainly from prefibrillar amyloid-β peptide (Aβ) assemblies. Structural and mechanistic aspects of these neurotoxic oligomeric provide an important basis for the design of aggregation disrupting molecules such as D3, a D-enantiomeric peptide recently identified by mirror-image phage display and shown to both reduce plaque load and improve cognitive deficits in transgenic mice. We have employed a number of computational approaches to examine the nature of interactions between D3 and different Aβ species (monomer and oligomer). using an implementation of the global- optimization approach employing Monte Carlo sampling with energy minimization, 6000 D3-Aβ monomer and 4000 D3-Aβ pentamer complexes were independently generated, and scored according to calculated binding energies. The best 100 complexes in each category were then subjected to molecular dynamics simulation in explicit water and the Aβ-D3 interactions monitored . The interaction energies were decomposed into residue-residue contributions showing that the association is driven by electrostatic attraction involving D3's arginines and the negatively charged residues populating the Aβ N-terminal segment, GLU22 and ASP23 in particular. Our findings are in agreement with dot blot experiments which showed fluorescein isothiocyanate- labeled D3 as mainly binding to Aβ's N-terminal portion. The effect of D3 on Aβ's structure was investigated and shown to destroy the β-sheet in the Aβ pentamer.

2002-Pos Board B21
Modeling Variants of Alzheimer's Ion Channels in the Lipid Bilayer formed by an Aggregation-Intermediate β-Hairpin and E22Δ Mutant
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We modeled Alzheimer's $A\beta_{1-42}$ ion channel in a β-barrel structure embedded in the lipid bilayer using explicit molecular dynamics (MD) simulations. Our Aβ barrels consist of multimeric chains of $A\beta_{1-42}$ peptide. Wild-type $A\beta_{1-42}$