conditions. We suggest this has relevance for *in vivo* amyloid plaque formation.

1039-Pos Board B95

A combination of modifying factors induces protein misfolding in vivo

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A current focus of research is the relationship between neurodegeneration and protein misfolding and aggregation. The microenvironment in which a protein is synthesised and functions is extremely complicated. Here, we suggest that misfolding and dysfunction of a protein in vivo may be induced by a combination of multiple factors, such as chemical modification and physical effects of the microenvironment. It is well established that in vivo, the amino acid side chains of a protein undergo diverse chemical modifications. Further, a specific amino acid side chain may be modified by a variety of different factors. Different chemical modifiers could react with a side-chain in a competitive or a cooperative manner. Protein misfolding and dysfunction may therefore be the result of multiple modifications. Consistent with this hypothesis, we found that the protein tau became misfolded and aggregated when incubated with both heparin and glucose, but not when incubated with heparin or glucose individually under the same experimental conditions. It has also been reported that acetylation can compete with and inhibit ubiquitination of the lysine ε-amino group of p53 (*Curr Opin Cell Biol* 2003, 15:164). Sporadic neurodegeneration may therefore be due to the induction of protein misfolding by a combination of modifying factors..

1040-Pos Board B96

An iterative knowledge-based scoring function for protein-protein interactions

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Using a new iterative method, we have developed a distance-dependent knowledge-based scoring function at the atomic level to predict protein-protein interactions, based on a training set of over 800 biological protein-protein dimeric structures in the Protein Data Bank. The iterative method circumvents the long-standing reference state problem in the derivation of knowledge-based scoring functions. The basic idea of our method is to improve interatomic pair potentials by iteration until they correctly discriminate experimentally determined binding modes from decoy structures for the protein-protein complexes in the training set. The iterative method is efficient and identifies 99% or more native complex structures within 30 iterative steps. The derived scoring function was then used to refine the predictions generated by ZDOCK (version 2.1) on a benchmark consisting of 99 diverse protein-protein complexes in which at least one of the components in each complex has an unbound structure. For the bound/bound test cases, our scoring function obtained a success rate of 80% under the criterion of the interface rmsd < 2.5 Å if only the top ranked structure was considered, higher than that of the shape complementarity scoring function in ZDOCK (24%). The success rate reached 92% if the top ten ranked structures were considered. For the more realistic unbound/unbound or unbound/bound test cases, our scoring function yielded a success rate of 39% if the top ten ranked structures were considered, compared to that of the shape complementarity scoring function in ZDOCK (29%). The average CPU time for refining/optimizing 2000 predicted structures for each test case with our knowledge-based scoring function is about one minute on a personal computer.

1041-Pos Board B97

The molecular mechanisms of the anti-amyloid effects of phenols

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Previous investigations demonstrated that various aromatic compounds, many of which are known antioxidants, inhibit amyloid fibril formation. Yet, the contribution of the antioxidative potency to anti-amyloid action of these compounds is not clear. In recent publications, Ono et al. (2003,2004) studied the anti-amyloid effects of eleven phenols on each of three consecutive processes: (1) seeding (formation) of nascent fibrils, (2) elongation (extension) of the fibrils, and (3) depolymerization (destabilization) of the formed assemblies. In the present study we determined the antioxidative potency of these phenols and analyzed the correlations between the effect of the studied compounds on each of the stages of amyloid fibril formation, and their antioxidative potency and physicochemical properties. These analyses reveal that the hydrophobic and/or aromatic character of the compounds makes the major contribution to the anti-formation and anti-extension effects, whereas the antioxidative potency relates mostly to the promotion of destabilization. ESR measurements conducted at different time points after addition of antioxidants to mature fibrils reveal that destabilization is accompanied by formation of free radicals. The pathophysiological implications of these findings have yet to be investigated.

1041-Pos Board B98

Depletion interaction between proteins drives the formation of protein domains of different fluidity and curvature in crowded membranes.

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Proteins packed in varying crystalline order are observed in all energy generating membranes, and it is often assumed that attractive forces are responsible for the appearance of such domains. However, it is well known in colloidal science that entropy alone is sufficient to produce ordered states of non-interacting hard bodies, as well as bulk or microphase separation through what is known as depletion-induced attraction or macromolecular crowding. Besides, colloidal bodies may also experience elastic interactions resulting from curvature mismatch. Here we investigate these colloidal effects in membranes whose shape and organization are known under physiological conditions. Photosynthetic bacteria such as *Rhodobacter (Rb.) sphaeroides* house their photosynthetic machinery in membrane invaginations consisting of peripheral light harvesting (LH2) complexes physically and functionally connected to reaction center-light harvesting (RC-LH1-PufX) complexes. We present Monte Carlo simulations of model membranes demonstrating that the size and shape asymmetry of the proteins, for example dimerisation, are sufficient to induce lateral segregation with varying order. We also show that domain formation is coupled to the local curvature of the membranes. Atomic force microscopy and polarised light spectroscopic data on mutant *Rb. sphaeroides* membranes lacking PufX, the protein that causes dimerisation of RC-LH1-X complexes, corroborate our simulations. Our results suggest that membrane shape and protein organization are primarily driven by entropy and protein geometry to create an effective supramolecular organization. Effectively, depletion interactions between the proteins in densely packed membranes results in the partitioning into fluid and ordered domains which are of key importance in photosynthesis, where both close packing and diffusion are a functional necessity.

1042-Pos Board B99

Using Pressure Perturbation for Studying the Free Energy and Conformational Landscape of Proteins Upon Aggregation and Amyloidogenesis

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Pressure tuning in combination with calorimetric, spectroscopic and structural techniques (DSC, PPC, FTIR, SAXS, AFM) revealed new insights into the pre-aggregated regime as well as mechanistic details about concurrent aggregation pathways and the differential stability of insulin aggregates. A thorough thermodynamic approach has provided a coherent and precise description of changes of the partial specific volume, heat capacity, the coefficient of thermal expansion, as well as the adiabatic and isothermal compressibility of the protein upon unfolding and aggregation. This was only possible due to a novel application of ultrasound velocimetry and pressure perturbation calorimetry. Besides pressure, also solvational perturbations, accomplished by the addition of various cosolvents such as glycerol, ethanol and TFE, have been explored. They exert pronounced and diversified effects on the unfolding, non-native assembly and fibril formation, which ultimately manifest in morphological variations of mature aggregates and fibrils (strains). The phenomenon of strains easily fits to a generalized protein energy landscape picture involving an alternative comb-shaped aggregation funnel.