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POSTER ABSTRACT PRESENTATIONS

SESSION TITLE: APPLICATIONS OF CRYO-EM IN MEDICINE

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Abstract P-34: The Regulation of Amyloid Proteins Aggregation by Adjacent Domains

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Background: Amyloids – cross-beta fibrous protein polymers. They are associated with a variety of diseases, including Alzheimer's disease (Abeta peptide aggregation).

Almost all amyloidogenic proteins contain additional domains that regulate their aggregation. Despite the important role of domains adjacent to amyloidogenic regions in the regulation of their properties, the mechanism of their effect on the aggregation has not been well studied.

Methods: We have carried out a comparative analysis of the amyloids formation by proteins containing the predicted amyloidogenic regions and their fragments consisting only of amyloidogenic sequences. The obtained results have compared with data on the structures of domains adjacent to amyloidogenic regions. Moreover, the effect of various sequences (structured (fluorescent proteins)), unstructured (the M domain of the yeast Sup35 protein (Sup35M)), amyloidogenic (Sup35 N domain (Sup35N)) on Abeta aggregation is studied. We use a special yeast screening model, SDD-AGE, fluorescence microscopy and electron microscopy (C-DAG).

Results: We tested the ability NF-YC protein form amyloid aggregates. The full-length NF-YC does not form amyloid aggregates, while the amyloidogenic fragment aggregates. The crystal structure of NF-YC shows the amyloidogenic region adjoins the alpha-helical domain, which prevents the formation of amyloid aggregates.

Amyloid aggregation leads to disruption of the functioning of adjacent domains. The Abeta aggregation in the Abeta-eYFP leads to a drastic decrease in eYFP fluorescence. The effect depends on the fluorescent protein type (eCFP or eYFP) and on the level of protein production.

The Abeta fusion to prion domain of the Sup35 protein (Sup35N-Abeta) promotes its aggregation and allows to aggregate under conditions where Sup35 does not aggregate. However, the addition of sequences to both sides of the Abeta (Sup35N-Abeta-YFP) inhibits formation of amyloid aggregates, leading to the formation of non-amyloid-type assemblies instead (biocondensates). Introduction of the

linker (Sup35M) between Abeta and YFP (Sup35N-Abeta-Sup35M-YFP) restores its ability to amyloid aggregation.

Conclusion: Thus, mode of amyloid regions aggregation depends on the nature and location of adjacent sequences. We hypothesize the proximity to large structured domains disrupts amyloid formation aggregation due to steric hindrance, and in some case, promotes formation of alternative assemblies - bicondensates.

Key Words: amyloids • biocondensates •Abeta • Sup35

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