Introduction: Role of Tau in Neurodegenerative Diseases

The aggregation of the microtubule-stabilizing protein tau has been identified as an important constituent in the formation of amyloid plaques characteristic of neurodegenerative diseases such as Alzheimer’s disease. Monomeric tau protein is an intrinsically disordered protein, which has a propensity to aggregate at three (or four depending on isoform) microtubule binding regions eventually forming beta-sheet strands. While the characteristics/structure of tau protein before and after aggregation has been characterized by a number of methods, the transient intermediate states have been far more difficult to study.

Our studies use Δtau187, which spans amino acids 255-441 of the human tau variant. We probe the structural changes associated with the early stages of tau aggregation with tools utilizing site-specific electron spin labeling. We are in particular interested in whether the hydration water is restructured or relinquished before or during oligomer formation, and whether this is correlated with the microtubule binding regions of tau protein. The layer of protein around a protein can provide information about the accessibility to various sites and is critical for oligomer and beta sheet formation.

ESEEM Study of the Initial Stages of Tau Protein Aggregation

ESEEM is one of the few techniques which can provide structure information for disordered systems. Roughly, ESEEM can provide the distances and number of nuclei around a protein spin. We use samples with deuterated water which allows us to specifically detect the deuterium from solvent molecules and suppress ESEEM from the protein backbone.

Spin-Spin Relaxation (T2) Measurements

T2 relaxation is caused by dipolar interactions between electrons as well as interactions with matrix nuclei. As you can see from the data above, the T2 dramatically decreases when aggregation of Δtau187 is induced. This is primarily caused by electron-electron dipolar interactions on adjacent tau proteins. In other words, the tau proteins immediately form an oligomer-like conformation as soon as aggregation is induced. Although more detailed measurements must be performed to determine the average size of the oligomer.

Conclusion: Proposed Mechanism for Tau Aggregation

From the DNP data, we see that there is a loss of rigidity in the solvation shell around the protein (increase in water diffusivity) upon aggregation.

From T2 measurements, we know that the protein is not in monomeric state, but a oligomeric state after inducing aggregation.

Based on these observations, we believe that a mechanism which first passes through an “aggregation-prone” intermediate state is most plausible. After a long period of time (hours) the aggregation-prone state forms fibrils by a yet unknown process.

Our proposed model is consistent with other models currently used for tau aggregation.

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