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Keynote 7, Prof. Mei Hong: Structure and Dynamics of Amyloid Proteins from Solid-State NMR: Glucagon & Tau

Protein misfolding into amyloid fibrils is common not only in neurodegenerative diseases but also in pharmaceutical sciences, where many peptide-based drugs have the tendency to fibrillize, thus impeding solution formulation of the drug. Using solid-state NMR spectroscopy, we have investigated the structure and dynamics of two amyloid fibrils, one formed by the peptide hormone glucagon, which is used to treat diabetic hypoglycemia, and the other formed by the microtubule-binding protein tau, which is found in many neurodegenerative diseases. The glucagon fibril structure is unique among all amyloid proteins known to date: the 𝛽-sheet is antiparallel rather than parallel hydrogen-bonded, contains two coexisting molecular conformations in a single ultrastructural morphology, and has an extraordinary 𝛽-strand length of 10 nm. The 1.7 Å resolution structure reveals many stabilizing interactions for the fibril, thus suggesting future strategies for designing glucagon analogs that resist fibril formation. Compared to glucagon, the 40 kDa full-length four-repeat tau protein forms a much more complex amyloid fibril, with the majority of the protein being dynamically disordered. Using an extensive set of multidimensional correlation solid-state NMR techniques, we have determined the repeat domains that constitute the 𝛽-sheet core, and show that this core has a single molecular conformation. This monomorphic nature for an in-vitro tau fibril is fully consistent with the monomorphic nature of brain-derived tau fibrils known to date, suggesting that in vitro fibrillized tau is a good model for studying in vivo tau fibrils. Further, the segments outside the rigid core, which appear as a "fuzzy coat"in electron micrographs, are heterogeneously dynamic. The repeats excluded from the rigid core exhibits partial mobility and 𝛽-sheet character, while the proline-rich domains undergo large-amplitude anisotropic motions. These results suggest the structure and dynamics of tau in diseases such as progressive supranuclear palsy, and open the path for designing tau inhibitors and imaging agents.

Presenter: Prof. HONG, Mei (MIT, USA)

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