Proton-detected Ultrafast MAS Solid-State NMR Spectroscopy of $A\beta_{42}$ Amyloid Fibrils

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Amyloid-β (Aβ) is a 39−42 residue protein produced by the cleavage of the amyloid precursor protein (APP), which subsequently aggregates to form cross-β amyloid fibrils that are a hallmark of Alzheimer's disease (AD). The most prominent forms of Aβ are $A\beta_{1-40}$ and $A\beta_{1-42}$, which differ by two amino acids (I and A) at the C-terminus. However, $A\beta_{42}$ is more neurotoxic and essential to the etiology of AD.

Here, we present an atomic resolution structure of a monomorphic form of $M_0A\beta_{1-42}$ amyloid fibrils derived from over 500 $^{13}C-^{13}C$, $^{13}C-^{15}N$ distance and backbone angle structural constraints obtained from high field magic angle spinning NMR spectra. The structure (Figure 1, PDB ID: 5KK3)[1] shows that the fibril core consists of a dimer of $A\beta_{42}$ molecules, each containing four β-strands in a S-shaped amyloid fold, and arranged in a manner that generates two hydrophobic cores that are capped at the end of the chain by a salt bridge. The outer surface of the monomers presents hydrophilic side chains to the solvent. The interface between the monomers of the dimer shows clear contacts between M35 of one molecule and L17 and Q15 of the second. Intermolecular $^{13}C-^{15}N$ constraints demonstrate that the amyloid fibrils are parallel in register. The RMSD of the backbone structure (Q15−A42) is 0.71 ± 0.12 Å and of all heavy atoms is 1.07 ± 0.08 Å. The structure provides a point of departure for the design of drugs that bind to the fibril surface and therefore interfere with secondary nucleation and for other therapeutic approaches to mitigate $A\beta_{42}$ aggregation.

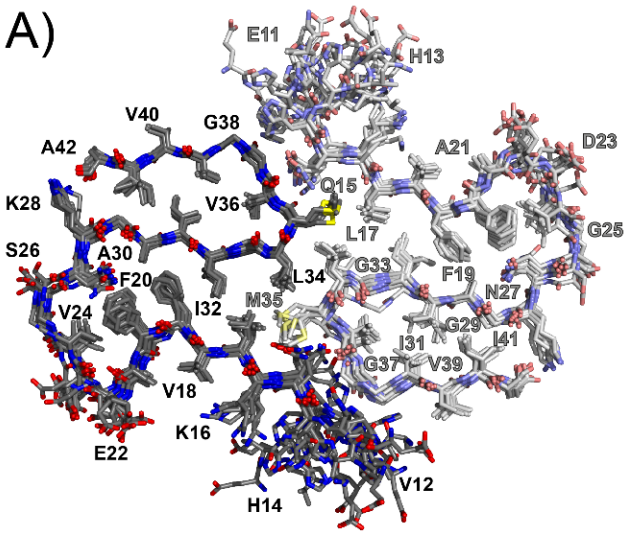

Figure 1: (A) Stick model representation of the 10 lowest energy structures. Shown is the central dimer, one monomer is in bright and one in pale colors. The structures were aligned using the backbone heavy atoms of residues Q15-A42. The structures converged to a heavy atom backbone RMSD of 0.77±0.17 Å and an RMSD of 1.11±0.14 Å for all heavy atoms.

Availability of ultrafast MAS solid-state NMR spectroscopy (>100kHz) allows for the detection of proton chemical shifts in fully protonated samples. Here, we present the progress on expanding our heteronuclear dataset of the $M_0A\beta_{1-42}$ amyloid fibril. Assignment strategies include state-of-the-art proton-detected 3D experiments such as the hCONH, hCANH, and hcoCAcoNH, among others. Furthermore, strategies to extract long-range proton-proton distances are explored.

References

1. Colvin, M. T. *et al. J. Am. Chem. Soc.* **138,** 9663–9674 (2016).

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