Solid State NMR Evidence for Antiparallel β-Sheet Structure Within Toxic Oligomers of Alzheimer's β-Amyloid Peptide

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Introduction

Significant genetic, pathological and biochemical evidence links Alzheimer's disease (AD) more closely to soluble aggregates (oligomers) of the β-amyloid peptide (Aβ) rather than more stable amyloid fibrils. We are interested in understanding the molecular structure of a disease-related 150kDa Aβ(1-42) oligomer produced from a structurally stable and homogenous preparation protocol.[1] Also, we aim to understand the differences between oligomers and fibrils and underlying self-assembly pathways. This understanding could contribute to disease prevention, diagnostic, and treatment strategies, as oligomers may play a central role in AD pathology.

Experimental

Oligomer samples with uniform ^{13}C labels at I32, M35, G37 and V40 and isotopic dilution were probed using ^{13}C-^{13}C 2-dimensional exchange solid state NMR spectroscopy. The measurements were based on 2D-fpRFDR and 2D-CHHC and 2D-DARR techniques [2-4] to probe peptide secondary structure and inter-side-chain proximities. In addition, we employed molecular modeling to compare the newly derived experimental constraints with previously proposed geometries for arrangement of Aβ molecules into oligomers.

Results and Discussion

The 150 kDa Aβ(1-42) oligomers exhibit β-strand secondary chemical shifts. Cross-peaks indicating close proximity between M35 H_α and G37 H_α, were observed in 2D-CHHC spectra (Fig.1), which is direct evidence of an antiparallel β-strands arrangement. Furthermore, 2D-DARR spectra indicating close intermolecular spatial proximities between I32 and V40 as well as M35 and G37 supports the C-terminal antiparallel β-sheet structures within the oligomer. Candidate C-terminal β-sheets models were constructed from part of the previously proposed oligomer geometries.

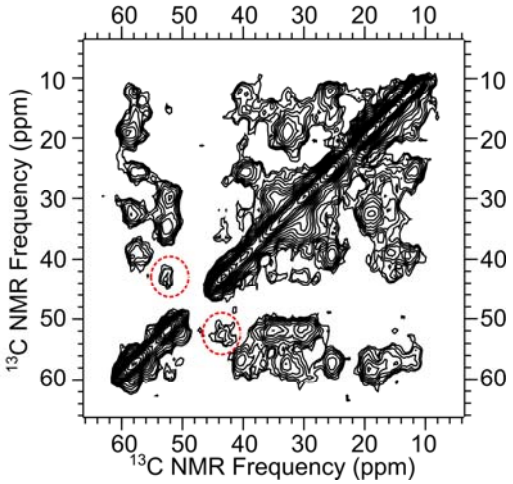

Fig.1 The aliphatic region of 2D-CHHC NMR spectrum of 150kDa Aβ(1-42) oligomer labeled with uniform ^{13}C at I32, M35, G37 and V40, showing C_α-C_α cross-peaks (in red dashed circles) between M35 and G37.

Conclusions

The results indicated that the C-terminal β-strands within the Aβ(1-42) peptide are arranged into antiparallel β-sheets when they form the 150kDa oligomer and this result could represent an aggregation pathway which differs from the fibril formation pathway.

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