

Tau Interacts with the C-terminal Region of α -synuclein, Promoting α -synuclein Aggregation

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Introduction

Extracellular deposits or intracellular inclusions of misfolded proteins are associated with numerous neurodegenerative diseases. It is known that several neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease, feature the co-existence of the aggregates of α -synuclein and tau proteins. Multiple protein aggregates have also been found from the patients of the same disease, while aggravating frequently the disease symptoms. In addition, co-incubation of the two proteins, α -synuclein and tau, was shown to promote mutual aggregation and simultaneously enhance toxicity *in vivo*.¹ However, structural details about the mechanism of fibril formation are not known yet. In this study, we analyzed the α -synuclein aggregates that are formed in the presence of 441-residue full-length tau by solution-state NMR spectroscopy.

Experimental

We used solution-state NMR spectroscopy to explore the interactions between the tau and α -synuclein proteins. The two-dimensional (2D) ^1H - ^{15}N heteronuclear single-quantum (HSQC) NMR experiments were carried out at 15° C after incubating the samples at 37° C. NMR experiments were carried out on the NHMFL's Bruker 800 MHz instrument equipped with a 5-mm cell inverse detection triple-resonance ^1H -X-Y cryogenic probe. NMR data were processed using NMRPipe and the processed data were analyzed using the software NMRViewJ.

Results, Discussion and conclusion

From our previous studies we have noticed an accelerated mutual aggregation of α -synuclein and tau when incubated together. Our SDS-gel and TEM analysis have also evidenced co-aggregation of both proteins when incubated together. Figure 1 shows 2D $^1\text{H}/^{15}\text{N}$ HSQC NMR spectra acquired for ^{15}N -labeled α -synuclein (black), tau (red), and their mixture (blue). When these HSQC NMR spectra were overlaid, it was clearly observed for the disappearance of peaks from numerous residues of both α -synuclein and tau when they are incubated together. This observation strongly suggests the co-aggregation of α -synuclein and tau as was suggested in our previous studies. In our previous NMR studies we made a tentative conclusion that tau protein interacts with α -synuclein at the C-terminal region. Our present study reinforces our previous conclusion that because the NMR peaks in the hydrophobic region (65-90) of α -synuclein have disappeared, the hydrophobic region of α -synuclein is mainly involved in the aggregation with tau protein.

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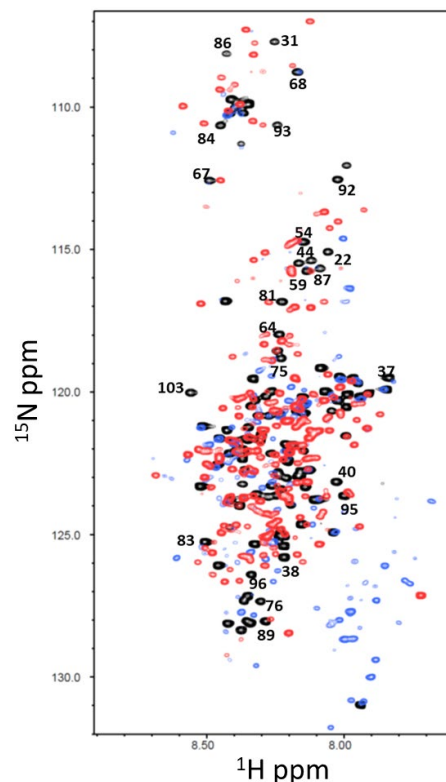


Fig. 1: Overlaid $^1\text{H}/^{15}\text{N}$ HSQC NMR spectra of α -synuclein (black), tau (red) and their mixture (blue) at 15° C