Determining the critical molecular interaction responsible for tau fibril formation

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Abstract:
Abnormal aggregation of tau protein forming the paired helical filaments (PHFs) is known to be major components of neurofibrillary tangles (NFTs) in nerve cell that is considered a pathological marker for Alzheimers disease. The R2 and R3 repeats of tau protein that houses the hexapeptide region are known to initiate the tau fibril formation. Despite recent progress in understanding the structure of tau fibrils through solid-state NMR[1,2], the high-resolution structure of the tau fibril is still not available. Hence the key structural interactions that modulate the tau fibril formation remain unknown.
Using different tau repeat construct, we show that in R3, addition to the presence of the hexapeptides, the correct turn conformation upstream to it is also essential for producing prion-like fibrils that are capable of propagation. The time-dependent NMR aggregation assay of a slow fibril forming R3-S316P peptide reveals a trans to cis equilibrium shift in the peptide-bond conformation preceding P316 during the growth phase of the aggregation process. We identify S316 as the key residue in the turn that provides the templating capacity to R3 fibrils to accelerate the aggregation of the R3-S316P peptide. These results[3] and studies on the inhibitory interaction existing in longer construct of Tau will also be discussed.

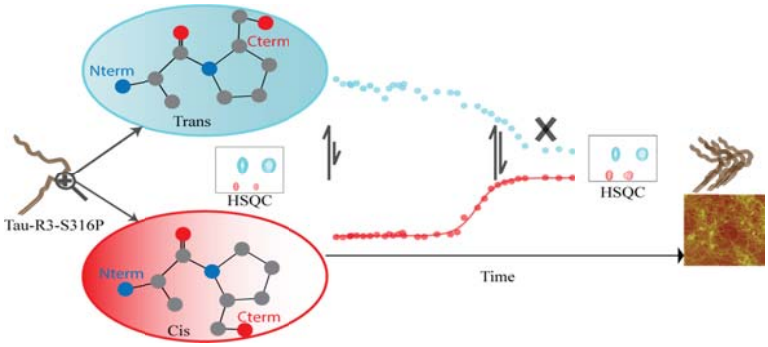

Figure: A shift in trans to cis peptide configuration at 316 amino acid position of tau is favoured for fibril formation

References and Notes:

1. Andronesi, O. C.; von Bergen, M.; Biernat, J.; Seidel, K.; Griesinger, C.; Mandelkow, E.; Baldus, M. *J. Am. Chem. Soc.* **2008**, *130*, 5922.
2. Daebel, V.; Chinnathambi, S.; Biernat, J.; Schwalbe, M.; Habenstein, B.; Loquet, A.; Akoury, E.; Tepper, K.; Muller, H.; Baldus, M.; Griesinger, C.; Zweckstetter, M.; Mandelkow, E.; Vijayan, V.; Lange, A. *J. Am. Chem. Soc.* **2012**, *134*, 13982.
3. Jiji, A. C.; Shine, A.; Vijayan, V. *Angew Chem Int Ed Engl* **2016**, *55*, 11562.