Catalysis of Phosphorylated Tau by Pin1 Detected via zz-Exchange

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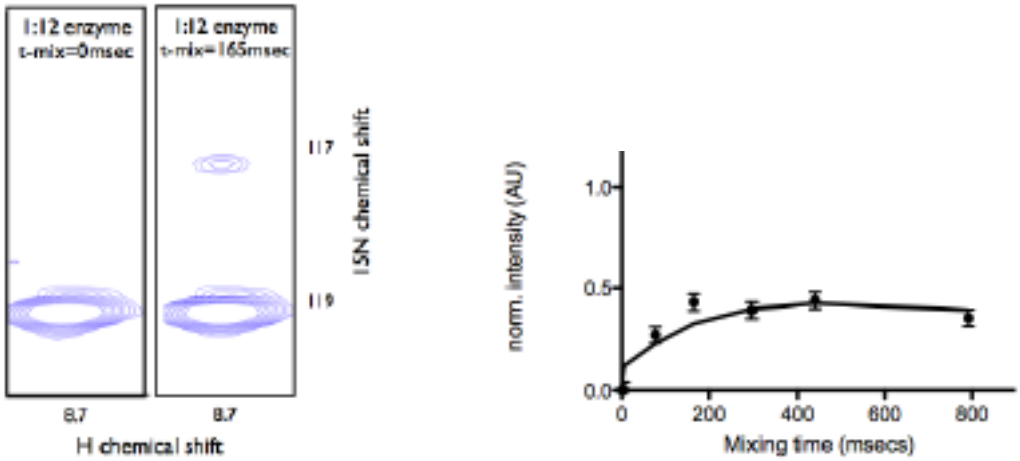
Introduction

Tau is a microtubule-associated protein expressed mostly in the axons of CNS neurons. Tau promotes tubulin polymerization by binding to and stabilizing microtubules. Tau loss-of-function has been linked to a number of degenerative diseases including progressive supranuclear palsy, Pick's disease and, most notably, to Alzheimer's disease. In vitro studies demonstrate that phosphorylated Tau protein has a lower affinity for microtubules compared to the intact protein though the exact molecular events that determine altered binding affinity and/or aggregation of Tau have not been completely elucidated. The possibility of a second regulatory mechanism arose when Lu et al discovered that the prolyl isomerase Pin1 was also a component of Alzheimer neurofibrillary tangles. Pin1 has been shown to restore the function of phosphorylated Tau in vitro and, more recently, a correlation between Pin1 and Alzheimer's disease has been detected by finding increase age-related neurodegeneration in Pin1 knockout mice. In our lab, we seek to elucidate the molecular mechanisms by which catalyzed proline isomerization of phosphorylated Tau affects its function.

Experimental

15N zz-exchange spectra of phosphorylated Tau protein in the presence of isotopically unlabeled Pin1 were collected on the 14T (600 MHz) solution state magnet at NHMFL. Spectra were collected with varying mixing times to measure the observed rate of catalyzed conformational exchange.

Results and Discussion



Left: Portion of 15N zz spectrum of phosphorylated Tau in the presence of Pin1. The main peak in this portion is the backbone NH of pSer-235. Right: catalysis of cis-trans interconversion can be detected by the appearance of an exchange peak whose intensity varies with mixing time. Our experiments show that Pin1 selectively catalyizes the cis-trans isomerization of the pSer235-Pro236 peptide bond.

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References

Labeikovsky, W. "Proline Isomerase Dynamics and the modulation of Tau function by Pin1". PhD dissertation, Brandeis University. 2008, 131pp.