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# CYTOSKELETON NEWS

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this issue



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# The Many Faces of Tau in Neurodegeneration

### Background

Tau (tubulin-associated unit) is a microtubule-associated protein (MAP) that is predominantly expressed in neurons[1]. The functions of tau include stabilization of microtubules[1], modulation of microtubule-dependent axonal transport[2], and regulation of neurite outgrowth[3,4]. Perturbation of tau regulation can lead to the formation of intraneuronal insoluble aggregates of abnormally phosphorylated tau termed neurofibrillary tangles (NFTs). NFTs are the hallmark of a group of neurodegenerative diseases, collectively termed tauopathies[1]. Tauopathies include Alzheimer's disease (AD), corticobasal degeneration, and Pick's disease[1]. The contribution of NFTs and tau towards the neurodegenerative phenotype is still somewhat controversial and the mechanisms underlying tau aggregation still remain to be elucidated.

In this newsletter, we will focus on post-translational modifications (PTMs) of tau and their possible relevance to NFT formation, tauopathies, and neurodegeneration (Fig.1).

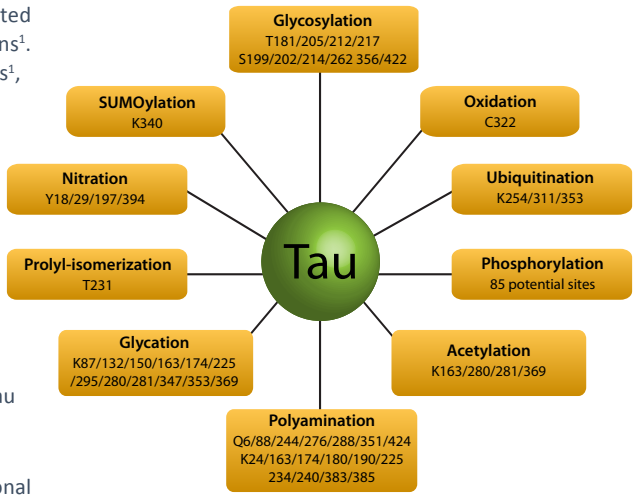


**Figure 1:** PTMs of tau and known or putative amino acid substrates[5].

### *Post-Translational Modifications of Tau*

#### Phosphorylation

A large body of work describes tau hyperphosphorylation as causative in the pathological dissociation of tau from microtubules and the subsequent aggregation of hyperphosphorylated tau and formation of NFTs[5 and references therein]. Many of the kinases/phosphatases that modify tau are identified[5]. Several of these have been proposed as therapeutic targets for the treatment of tauopathies[6]. Aberrant tau phosphorylation is currently considered the major PTM affecting NFT formation; however, the mechanisms underlying NFT formation are not yet fully understood.

#### Glycosylation

Native tau is extensively glycosylated through the addition of O-linked β-N-acetyl-glucosamine (O-GlcNAc) to serine and threonine residues[7]. O-GlcNAc is a reversible modification that is regulated through a transferase (addition) and a hydrolase (removal) enzyme[8,9]. The levels of tau O-GlcNAc are inversely related to the levels of phosphorylation, both in culture and in metabolically active rat brain slices, leading to the hypothesis that the two modifications exist in a dynamic equilibrium[10,11]. Importantly, tau from brains of AD individuals has lower levels of O-GlcNAc than healthy individuals and O-GlcNAc is completely missing in insoluble tau aggregates[10]. Such findings have lead to the hypothesis that enhanced O-GlcNAc could prevent hyperphosphorylation of tau and hence alleviate NFT formation[12]. More recently, this modification has been proposed to directly inhibit tau aggregation[13]. Current efforts to exploit this PTM therapeutically have focused on inhibition of the glycoside hydrolase (O-GlcNAcase)[12,13].

#### Acetylation

Acetylation is a reversible PTM that has recently been identified as a pathological modification on lysine residues of tau[14,15]. Immunohistochemical studies of AD brains indicate that acetylated tau is specifically associated with insoluble

## Continued from Page 1

tau aggregates. *In vitro* studies have shown that acetylation prevents tau from promoting microtubule assembly and enhances the formation of tau aggregates[15]. Acetylation also reduces proteasomal degradation of phosphorylated tau[14]. It has been proposed that targeting tau acetylation, possibly through acetyl-transferase inhibitors, could attenuate NFT formation[6,14-16].

### Ubiquitination

Non-pathologic phosphorylated tau is a target for the ubiquitin-proteasomal degradation pathway[17]. Ubiquitinated tau has also been found in tau aggregates, although, due to size limitations of the proteome pores, it is unlikely that tau aggregates are a substrate for proteosomal degradation and clearance[6]. There is some evidence that the ubiquitin ligase CHIP can protect against tau aggregation in the early stages of AD, prompting evaluation of the therapeutic potential of enhancing tau degradation[6,18].

### Prolyl-isomerization

The phosphorylated threonine residue 231 (pThr231) in tau has been shown to be a substrate for prolyl-isomerization by the peptidyl-prolyl-isomerase Pin1[19]. Pin1 recognizes pThr231-Pro (pThr231 followed by proline) tau and converts the pathogenic *cis*- to the non-pathogenic *trans*-conformation[20]. The change from *cis* to *trans* causes a conformational change in tau that facilitates the dephosphorylation of pThr231-Pro, resulting in the restoration of tau's ability to promote microtubule assembly, which is characteristic of normal tau[21]. Pin1 over-expression in AD mouse models decreases *cis* pThr231-Pro tau and Pin1 is inhibited by several mechanisms in AD, leading to the proposal that prevention of Pin1 inhibition could have therapeutic value[22].

### Other Tau PTMs and Future Directions

Several other PTMs have been identified on tau, including SUMOylation, glycation, nitration, polyamination, and oxidation, many of which are associated with NFT formation[5]. The study of non-phospho PTMs of tau is still in its infancy. Clearly, PTMs have a large influence on normal and pathogenic tau function and hold great promise as future targets for therapeutic and diagnostic applications.

## Select Tau Related Research Tools

| Protein/Kit | Source/Format | Purity | Cat. # | Amount |
|---|---|---|---|---|
| **Tubulin Protein** Lyophilized (no glycerol) | Porcine Brain | >99% | T240-A<br>T240-B | 1 x 1 mg<br>5 x 1 mg |
| **Tubulin Protein, MAP rich** | Porcine Brain | 70% tubulin 30% MAPs | ML116-A<br>ML116-B | 1 x 1 mg<br>5 x 1 mg |
| **Tau Protein** | Bovine Brain | >90% | TA01-A<br>TA01-B | 1 x 50 µg<br>3 x 50 µg |
| **Microtubule Associated Protein (MAP) Fraction** | Bovine Brain | 70% MAP2 | MAPF-A<br>MAPF-B | 1 x 100 µg<br>5 x 100 µg |
| **Tubulin for HTS Applications** | Porcine Brain | 97% | HTS03-A<br>HTS03-B | 1 x 4 mg<br>1 x 40 mg |
| **Tubulin Polymerization Assay Biochem Kit** | Turbidometric-based | >99% pure tubulin | BK006P | 24-30 assays |
| **Tubulin Polymerization Assay Biochem Kit** | Turbidometric-based | >97% pure tubulin | BK004P | 24-30 assays |
| **Tubulin Polymerization Assay Biochem Kit** | Fluorescence-based | >99% pure tubulin | BK011P | 96 assays |

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