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Tau post-translational modifications: Therapeutic targets for Alzheimer's disease

Introduction

Worldwide, more than 47 million people have been diagnosed with dementia, and the majority of these cases are caused by Alzheimer's disease (AD); aside from the social burden, this neurodegenerative disease has an associated cost of 1.09% of the global gross domestic product[1]. Severe cognitive impairment that leads to deficits in skilled movements, language, and recognition are pathophysiological hallmarks of AD. On a molecular level, neuropathological hallmarks include formation of beta-amyloid plaques and neurofibrillary tangles (NFTs) comprised of paired helical filaments of hyper-phosphorylated Tau proteins. This newsletter focuses on the mechanistic control of Tau by post-translational modifications (PTMs) and the development of novel AD therapeutics based on regulating the PTM status of Tau[2] (Fig. 1).

Tau: Phosphorylation

Increased levels of total Tau in the cerebral spinal fluid (CSF) are associated with AD and other neurodegenerative diseases; thus, total Tau levels have been defined as a marker for neuronal damage and degeneration rather than a specific marker for AD[3]. Conversely, increased levels of tau phosphorylated at T181 in CSF are uniquely linked to AD, making it one of the few specific biomarkers for AD diagnosis. For confirmation of AD pathology post-mortem, NFTs are routinely used, and recent evidence suggests that tau oligomers are detectable at early Braak stages of AD; furthermore, NFT maturation and distribution correlate with cognitive decline in AD, suggesting that NFTs have a critical role in AD pathogenesis[4].

The PTM phosphorylation regulates physiological Tau interactions with microtubules[4], but in AD, Tau is hyper-phosphorylated, which is a driving, regulatory mechanism in Tau mislocalization, dysfunction, aggregation, and NFT formation[5,6]. Tau hyper-phosphorylation can occur on as many as 45 residues, some of which are distinct from normal Tau phosphorylation sites[3,6]. Tau hyper-phosphorylation is regulated by several kinases including cyclic-AMP-dependent protein kinase, c-Jun N-terminal kinase 3 (JNK3), glycogen synthase kinase 3 beta (GSK3B), and cyclin dependent kinase 5 (CDK5), among others[2]. JNK3, CDK5, and GSK3B inhibitors have all demonstrated neuroprotective properties *in vitro* and in animal models. GSK3B inhibitors have been tested in clinical trials, but no significant benefit was observed, leading to termination of these studies[2,7]. However, inhibition of JNK3, which was upregulated in CSF along with CDK5, may still be a viable therapy, and further investigation is ongoing. An alternative approach to regulating Tau hyper-phosphorylation is to activate the phosphatase that dephosphorylates Tau. Sodium selenite, an agonist for protein phosphatase 2 (PP2A), is in development and produces cognitive improvements in AD mouse models[8,9].

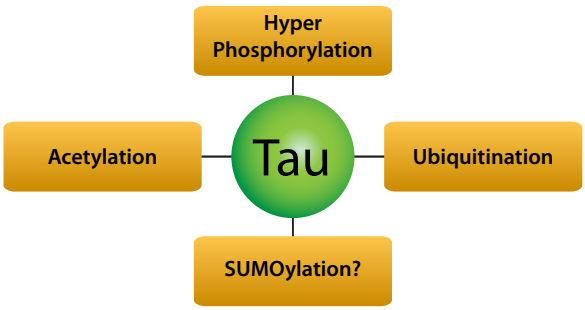

Figure 1. PTMs of Tau being targeted as Alzheimer's disease therapeutics.

Tau: Ubiquitination and SUMOylation

The PTMs ubiquitination and SUMOylation have also been identified as key regulators of Tau activity and NFT formation. The ubiquitin ligase, C-terminus of Hsc70-interacting protein (CHIP), offered significant protection against NFT formation in a mouse tauopathy model. This finding complements the inverse relationship between CHIP and pathogenic Tau in AD brains and provides evidence that ubiquitination may be an essential clearance mechanism for aggregated Tau[10]. A recent study by Luo et al. identified significant crosstalk between Tau hyper-phosphorylation and Tau SUMOylation, where either modification enhanced the other[11]. Moreover, SUMOylation of Tau prevented poly-ubiquitination and subsequent Tau degradation, possibly leading to aggregation. This study highlighted the significant crosstalk between different PTMs of

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Tau, and may provide a rationale to target alternative PTM regulatory mechanisms of Tau to ultimately regulate the hyper-phosphorylation of Tau. Indeed, PTMs that crosstalk with hyper-phosphorylation are not confined to ubiquitination and SUMOylation. Crosstalk between Tau hyper-phosphorylation and glycosylation is a well-characterized mechanism of regulation[12,13].

Tau: Acetylation

Recently, acetylation was identified as a Tau PTM elevated at early Braak stages of AD and shown to positively regulate hyper-phosphorylated Tau levels and Tau aggregation *in vitro*[14,15]. Deleting the deacetylase SIRT 1 elevated Tau acetylation, which suppressed poly-ubiquitination and subsequent protein turnover, providing additional evidence that Tau acetylation promotes AD progression[14]. These findings further highlight the importance of PTM crosstalk in Tau regulation. Building upon these studies, Min et al. identified K174 as the specific lysine critical for Tau acetylation, and defined the lysine acetyltransferase P300 as a regulator of Tau acetylation[16]. K174 was acetylated in early and late Braak stages of AD. Importantly, the prescription drug, salsalate, which decreases P300 activity, reversed Tau-mediated memory impairments and hippocampal atrophy in a mouse tauopathy model. Importantly, when salsalate was used on neurons expressing a Tau lysine acetylation mimetic, K174Q, it provided no significant benefit as shown by unchanged levels of total and phosphorylated Tau and atrophy of the hippocampus. These mutagenesis data provided additional evidence for a key role of acetylated Tau in AD progression. As this drug is already FDA approved, it will be interesting to see if it has the same benefits in treating patients with AD.

Conclusions

Pursuit of emerging AD therapeutics and subsequent drug development based on the mechanistic understanding of how PTMs regulate Tau is not an isolated event, as many pathological proteins in cancer, cardiovascular, metabolic, and other neurological diseases have dysfunctional post-translational regulation[17-19]. For example, tyrosine kinase receptors are often deregulated in cancer, and several viable cancer drugs work by controlling the receptors' ability to induce downstream PTM signaling[20]. Identification of novel regulatory PTMs for pathological proteins may aid in the development of effective, targeted therapeutics. In addition, PTM crosstalk is a fundamental mechanism to control a target protein's function. Having the right tools to identify one or more novel PTMs for a target protein will be essential to gain a complete picture of how a target protein is regulated. To assist scientists in PTM studies, Signal Seeker™ kits offer unprecedented ability to measure endogenous levels of various PTMs of target proteins in a sensitive and quantitative manner.

References

1. Prince M. et al. 2015. *World Alzheimer Report 2015*. The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost & Trends; Alzheimer's Disease International: London, UK.
2. Folch J. et al. 2016. Current Research Therapeutic Strategies for Alzheimer's Disease Treatment. *Neural Plast*. **2016**, 8501693.
3. Russell C.L. et al. 2014. Post-translational modifications in Alzheimer's disease and the potential for new biomarkers. *J. Alzheimers Dis*. **41**, 345-64.
4. Simic G. et al. 2016. Tau protein hyperphosphorylation and aggregation in Alzheimer's disease and other tauopathies, and possible neuroprotective strategies. *Biomolecules*. **6**, 6.
5. Hoover B.R. et al. 2010. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron*. **68**, 1067-81.
6. Hanger D.P. et al. 2009. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. *Trends Mol. Med*. **15**, 112-119.
7. Lovestone S. et al. 2015. A phase II trial of tideglusib in Alzheimer's disease. *J. Alzheimers Dis*. **45**, 75-88.
8. Zhang Y. et al. 2014. Silencing [Formula: see text] Rescues Tau Pathologies and Memory Deficits through Rescuing PP2A and Inhibiting GSK-3beta Signaling in Human Tau Transgenic Mice. *Front. Aging Neurosci*. **6**, 123.
9. van Eersel J. et al. 2010. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proc. Natl. Acad. Sci. USA*. **107**, 13888-93.
10. Sahara N. et al. 2005. In vivo evidence of CHIP up-regulation attenuating tau aggregation. *J. Neurochem*. **94**, 1254-1263.
11. Luo H.B. et al. 2014. SUMOylation at K340 inhibits tau degradation through deregulating its phosphorylation and ubiquitination. *Proc. Natl. Acad. Sci. USA*. **111**, 16586-16591.
12. Liu F. et al. 2004. O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*. **101**, 10804-10809.
13. Lefebvre T. et al. 2003. Evidence of a balance between phosphorylation and O-GlcNAc glycosylation of Tau proteins--a role in nuclear localization. *Biochim. Biophys. Acta*. **1619**, 167-76.
14. Min S.W. et al. 2010. Acetylation of tau inhibits its degradation and contributes to tauopathy. *Neuron*. **67**, 953-966.
15. Cohen T.J. et al. 2011. The acetylation of tau inhibits its function and promotes pathological tau aggregation. *Nat. Commun*. **2**, 252.
16. Min S.W. et al. 2015. Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. *Nat. Med*. **21**, 1154-1162.
17. Liddy K.A. et al. 2013. Functional decorations: post-translational modifications and heart disease delineated by targeted proteomics. *Genome Med*. **5**, 20.
18. Kim M.Y. et al. 2012. Role of transcription factor modifications in the pathogenesis of insulin resistance. *Exp. Diabetes Res*. **2012**, 716425.
19. Margolin D.H. et al. 2013. Ataxia, dementia, and hypogonadotropism caused by disordered ubiquitination. *N. Engl. J. Med*. **368**, 1992-2003.
20. Sullivan I. & Planchard D. 2016. Next-generation EGFR tyrosine kinase inhibitors for treating EGFR-mutant lung cancer beyond first line. *Front. Med*. (Lausanne). **3**, 76.

Signal Seeker™ Kits

Kit or Affinity Beads	Type	Reactions	Cat. #
Signal-Seeker™ Phosphotyrosine Enrichment Kit	Kit	30 10	BK160 BK160-S
Signal-Seeker™ Ubiquitin Enrichment Kit	Kit	30 10	BK161 BK161-S
Signal-Seeker™ SUMO 2/3 Enrichment Kit	Kit	30 10	BK162 BK162-S

PTM antibodies, beads, etc

Kit or Affinity Beads	Type	Reactions	Cat. #
Phosphotyrosine Affinity Beads	Beads	40-80	APY03-beads
SUMO 2/3 Affinity Beads	Beads	20-40	ASM24-beads
Ubiquitin Affinity Beads	Beads	40	UBA01-beads
Control for Ippt IgG Beads	Beads	10	CIG01-beads
Control for Ubiquitin Affinity Beads	Beads	10	CUB02