Mechanisms of Ageing and Development 178 (2019) 72–79

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Tauopathy: A common mechanism for neurodegeneration and brain aging

Pampa Saha, Nilkantha Sen*

Department of Neurological Surgery, University of Pittsburgh, 200 Lothrop Street, Scaife Hall, Pittsburgh, 15213, United States

ARTICLE INFO

Keywords:
Tauopathy
Tau hyperphosphorylation
Tau acetylation
Aging
Amyloid beta
Alzheimer's disease
Neurodegeneration
Cognitive dysfunction

ABSTRACT

Tau, a microtubule-associated protein promotes assembly and stability of microtubules which is related to axoplasmic flow and critical neuronal activities upon physiological conditions. Under neurodegenerative condition such as in Alzheimer's Disease (AD), tau-microtubule binding dynamics and equilibrium are severely affected due to its aberrant post-translational modifications including acetylation and hyperphosphorylation. This event results in its conformational changes to form neurofibrillary tangles (NFT) after aggregation in the cytosol. The formation of NFT is more strongly correlated with cognitive decline than the distribution of senile plaque, which is formed by polymorphous beta-amyloid (Aβ) protein deposits, another pathological hallmark of AD. In neurodegenerative conditions, other than AD, the disease manifestation is correlated with mutations of the MAPT gene. In Primary age-related tauopathy (PART), which is commonly observed in the brains of aged individuals, tau deposition is directly correlated with cognitive deficits even in the absence of Aβ deposition. Thus, tauopathy has been considered as an essential hallmark in neurodegeneration and normal brain aging. In this review, we highlighted the recent progress about the tauopathies in the light of its posttranslational modifications and its implication in AD and the aged brain.

1. Introduction

The Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder that accounts for more than 50–60% of all the dementia cases and 50% of all individuals of 85 years and above, dies due to the AD (Qiu et al., 2009; Bekris et al., 2010; Vinters, 2015; Graham et al., 2017). The two well established diagnostic hallmarks of the AD are extracellular Aβ senile plaque deposition and intracellular Neurofibrillary tangle (NFT) formation (Jellinger and Attems, 2007; Vinters, 2015; Graham et al., 2017). The overproduction of Aβ peptide from a transmembrane protein Amyloid precursor protein (APP) by the sequential action of beta and gamma-secretase eventually leads to the formation of Aβ plaques. On the other hand, hyperphosphorylation of a microtubule-associated protein Tau on its serine or threonine residues enhances its intracellular deposition that ultimately leads to form Neurofibrillary Tangle (NFT) (Lee et al., 1991; Goedert et al., 1992; Vinters, 2015; Graham et al., 2017). The aberrant hyperphosphorylation of tau disrupts its binding ability to microtubule (MT) thereby affecting MT stability and axoplasmic transports (Petrucelli et al., 2004; Kosik and Shimura, 2005; Poppek et al., 2006; Dickey et al., 2007; Green et al., 2008) (Bramblett et al., 1993; Iqbal et al., 1994; Stoothoff and Johnson, 2005). Tau-related pathology or tauopathy is not only involved in AD (Mattson, 2004; Goedert and Spillantini, 2006; Ballatore et al., 2007; Spires-Jones et al., 2009), but also found to be an integrated part of several neurodegenerative conditions such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, dementia pugilistica, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) (Spillantini and Goedert, 2013) as well as of primary age-related tauopathy in normal aging process (Crary et al., 2014).

The cognitive impairment was found to be the most common outcome of AD patients, and severity of cognitive impairment have been found to be more strongly correlated with the NFT deposition compare to that of the Aβ load in AD brain (Arriagada et al., 1992; Bierer et al., 1995). Consistent with this finding, it was shown that Aβ directly triggers tau protein phosphorylation and aggregation; if once NFT is formed, Aβ clearance cannot improve the cognitive decline (Oddo et al., 2004); however, the removal of tau can improve the cognitive function even after Aβ burden remains to be constant or increased (Chesser et al., 2013; Simic et al., 2016; Wang et al., 2018; Xin et al., 2018). Thus, Tau aggregation is considered as the more critical causal mediator of cognitive dysfunction over Aβ.

Aging is considered the most critical risk factor for almost all neurodegenerative diseases. An increasing number of studies suggest that the underlying cause and symptoms of healthy aging and age-related disorders are overlapping in various cases. Albeit many investigations

* Corresponding author.
E-mail address: senn@pitt.edu (N. Sen).

https://doi.org/10.1016/j.mad.2019.01.007
Received 26 November 2018; Received in revised form 9 January 2019; Accepted 18 January 2019
Available online 19 January 2019

have identified the underlying molecular mechanisms, but these do not suffice to combat the neurodegenerative diseases due to its multifactorial complex and progressive nature. In this review, we will focus on how tauopathy both in the degenerative and aging process takes a vital role to play in the progression of neurological abnormalities. Also, we will emphasize the importance of two prominent posttranslational modifications of tau such as phosphorylation, and acetylation that significantly contribute to the disease progression.

2. The potential role of Aβ in hyperphosphorylation of tau, tauopathy and associated cognitive dysfunction

Two groundbreaking studies in 2001 had given convincing evidence that Aβ burden in AD brain directly instigates tau aggregation by enhancing its phosphorylation (Gotz et al., 2001; Lewis et al., 2001). It was further confirmed in a study where Aβ infusion to P301 L tau transgenic mice, which carries a transgene encoding human tau with four microtubule-binding repeat domains, triggers NFT formation (Gotz et al., 2001). As a part of the mechanism it was shown that Aβ oligomers could induce phosphorylation of tau by mostly activating the cJun kinase or AKT- GSK3beta signaling pathway (Ma et al., 2009; Tokutake et al., 2012; Li et al., 2016). The recent investigation further strengthened the fact that neuritic amyloid plaques trigger the pathological conversion of tau in an AD mouse model (Li et al., 2016). Consistent with these studies another group has documented that tau aggregation and subsequent neurofibrillary degeneration was shown to be increased in JNPL3/Tg2576 double transgenic mice without an increase in Aβ load (Lewis et al., 2001). Supporting the in vivo finding; it was shown that tau phosphorylation at ser-202 and ser-396/ser-404 residues in rat hippocampal and human cortical neurons induced by Aβ fibrils, remains as either soluble or amorphous-aggregated form. (Busciglio et al., 1995). Hyperphosphorylation of tau ultimately leads to its aggregation, mislocalization, and accumulation instead of its proteasomal degradation that leads to neurofibrillary degeneration (Blurton-Jones and Laferla, 2006; Qiu et al., 2009; Bekris et al., 2010; Vinters, 2015; Graham et al., 2017).

For decades, the neurotoxic effects of Aβ and tau had been established separately until recently it has been found that in many cases Aβ-induced neurotoxicity and cognitive deficit are primarily mediated by tau protein (Mucke and Selkoe, 2012; Huber et al., 2018), and Aβ-induced cytotoxicity is absent in tau null background (Rapoport et al., 2002; Nussbaum et al., 2012). Similarly, another independent study has shown that early intervention of Aβ accumulation can prevent pTau development via the proteasomal degradation machinery (Oddo et al., 2004; Iaccarino et al., 2016). Consistent with this finding, another study shows that gamma frequency entrainment can lower initial load of Aβ and modified microglial population through the reduction of Tau phosphorylation in mice model of tauopathy where tau P301S mutant form of human microtubule-associated protein tau (MAPT) was overexpressed constitutively (Iaccarino et al., 2016). Therefore, it can be convincingly concluded that tau aggregation could be independent of Aβ load; however, a question remains unanswered whether tau phosphorylation is enough to induce cognitive dysfunction independent of Aβ.

A substantial number of efforts have been made to elucidate the underlying mechanism responsible for how tau phosphorylation contributes to cognitive dysfunctions. One of the remarkable studies has shown that tau can mediate the Aβ-induced learning and memory deficits by inducing an imbalance in the ratio of excitatory/inhibitory neurons in the brain by modulating a nonreceptor tyrosine kinase Fyn kinase (Roberson et al., 2007; Roberson et al., 2011). This notion was further confirmed by the fact that depletion of tau can prevent the synergistic effect of Aβ and Fyn on synaptic, network and cognitive impairment (Roberson et al. 2007, Roberson et al., 2011). Recently an elegant study provides a direct mechanism how phosphorylated, and mislocalized tau can induce synaptic dysfunction which underlies impairment of cognitive function. Synaptic strength depends primarily on NMDA receptor activation which is known to regulate by PSD95-Fyn-NMDA receptor complex at the postsynaptic site (Chabrier et al., 2012). PSD95, a membrane-associated guanylate kinase (MAGUK), is the major scaffolding protein in the excitatory postsynaptic density (PSD) and a potent regulator of synaptic strength, while Fyn physically associates with Tau, and can phosphorylate tyrosine residues near the amino terminus (Lee et al. 1998; Lee et al., 2004; Chabrier et al. 2012). Tau can be hyperphosphorylated upon NMDA receptor activation through a signaling cascade that is also activated by Aβ. Thus, it can be anticipated that hyperphosphorylation of tau will affect the complex formation among PSD95-Fyn-NMDA receptor complex at the postsynaptic site that will, in turn, attenuate synaptic functions. Therefore, Fyn has been linking the two critical pathologies in AD uniquely and merit it to be considered as an attractive target for AD therapeutics. However, Fyn is a challenging target, with broad expression throughout the body and significant homology with other members of the Src family kinases, which may lead to unintended off-target effects. A phase 2a proof-of-concept clinical trial in patients with AD is currently underway, providing critical first data on the potential effectiveness of targeting Fyn in AD (Nygaard et al., 2014; Nygaard, 2018).

Other studies have shown that Aβ can induce cognitive dysfunction by impairing axonal transport (Vossel et al., 2010), dendritic function (Ittner et al., 2010) and long-term potentiation (Roberson et al., 2011; Shipton et al., 2011), which are independent of the activity of Fyn kinase but dependent on Tau. Targeting tau either by chemical treatment or immunotherapy have been shown to improve cognitive function even though the Aβ levels continue to increase suggests that Tau can directly regulate cognitive dysfunction (Castillo-Carranza et al., 2015) with the severity of AD. It was shown that tau immunotherapy could reduce Aβ burden to facilitate cognitive function (Castillo-Carranza et al., 2015); further reemphasizes the fact that tau phosphorylation is much more relevant for cognitive dysfunction compared to an increase in Aβ levels.

3. Molecular mechanisms underlying post-translational modifications of tau and their correlations to tauopathy

Tau undergoes a myriad of various posttranslational modifications, such as acetylation (Cohen et al., 2011), nitration (Horiguchi et al., 2003), glycation (Ledesma et al., 1995), O-glycosylation (Arnold et al., 1996), ubiquitination (Cripps et al., 2006), SUMOylation (Dorval and Fraser, 2006), cross-linking by transglutaminase (Wilhelmus et al., 2009), isomerization (Miyasaka et al., 2005), conformational alteration and proteolytic cleavage (Gamblin et al., 2003) in addition to phosphorylation. Although, the exact function for all these post-translational modifications of tau during neurodegeneration has not been fully understood; it was found that modulating these post-translational modifications of tau affect the phosphorylation level of tau and tauopathy. In fact, most of the post-translational modifications of tau functions as the precursors of tau phosphorylation and modulation of their levels can impact the tauopathy. Therefore, these posttranslational modifications of tau offered an attractive target to reduce tauopathy other than either eliminating the phosphorylation or inducing the dephosphorylation of tau. Among these modifications, acetylation of Tau has been found to be most clinically relevant and shown to have significant influence on phosphorylation level of tau (Alonso et al., 1994; Alonso et al., 1996; Wang et al., 1996; Alonso et al., 1997; Alonso et al., 2001; Wang et al., 2007). Therefore, in this review, we will mostly highlight the current literature regarding the phosphorylation and acetylation of tau in tauopathy with the progression of AD.

3.1. Phosphorylation of Tau in AD

Under physiological condition, tau can be phosphorylated in both in WT and hAPP transgenic mice on 63 sites in both the cases (Morris

et al., 2015). However, the AD brain contains 2–3 fold higher hyperphosphorylated tau (6–8 mol P/mole of tau protein) compared to that of a healthy brain(2–3 mol P/ mole of tau protein) (Kopke et al., 1993). The mass spectrometry analysis revealed that there are at least 40 serine/threonine and two tyrosine sites for phosphorylation in PHF form of tau (Hasegawa et al., 1992; Morishima-Kawashima et al., 1995; Hanger et al., 1998).

Further studies revealed that hyperphosphorylation of tau is the net effect of the interplay between several kinases and phosphatases. Tau is phosphorylated mainly by several prolines directed protein kinases (PDPKs) mostly on serine/threonine residues followed by a proline residue. Important tau PDPKs are glycogen synthase kinase-3beta(GSK-3beta), Cyclin-dependent like kinase-5(CDK5) and dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) (Arioka et al., 1993; Morishima-Kawashima et al., 1995; Woods et al., 2001; Liu et al., 2008). Apart from the PDPKs, several non-PDPKs like calcium/calmodulin-activated protein kinase II (CaMK II), microtubule affinity regulated kinase 110 (MARK p110), protein kinase A (PKA) and casein kinase 1 (CK1) can also phosphorylate tau (Baudier and Cole, 1988; Ledesma et al., 1992; Singh et al., 1996a,b; Drewes et al., 1997; Sironi et al., 1998). The dephosphorylation of tau is mainly regulated by PP2A that accounts for ˜70% of total tau phosphatase activity in the central nervous system (Bennecib et al., 2000; Gong et al., 2000; Liu et al., 2005).

3.2. Tau acetylation in AD

Acetylation of tau recently has got special attention as a potent regulatory post-translational modification which is implicated in several tauopathies including AD pathology (Min et al., 2010; Cohen et al., 2011; Cook et al., 2014; Min et al., 2015; Hettinger and Cirrito, 2016). An NMR analysis using recombinant hTau has shown that each molecule of tau can be acetylated on an average six lysine residues (Kamah et al., 2014). Particular interest in tau acetylation is lying in the fact that, acetylation of tau can trigger tau aggregation through its hyperphosphorylation as it has been found in AD, corticobasal degeneration, progressive supranuclear palsy and in tau transgenic mice models of tauopathies (Cohen et al., 2011; Irwin et al., 2012). This study indicates the pivotal upstream regulation of tau acetylation over tau hyperphosphorylation. Thus, in that case, targeting acetylation despite phosphorylation of tau might be a more effective strategy to combat the disease root-cause and outcome.

First identification of tau acetylation and its implication with neurodegeneration came in 2010 by Li Gan and his group (Min et al., 2010). They have found multiple tau acetylation sites including three putative lysines 163,174 and 180 residues which prevent tau ubiquitination and therefore tau turn over. In this study, authors have drawn clear evidence of lysine acetyltransferase, p300 mediated tau acetylation promotes phospho-tau aggregation, and this can be blocked by deacetylation of tau by SIRT1 deacetylase (Min et al., 2010). In the subsequent year, Cohen et al. further confirmed that Lysine 280 acetylation in the MT-binding domain of tau causes impairment in tau-MT affinity and aggregation of the gain of function tau toxic species (Cohen, Guo, et al. 2011). The particular importance of acetylation of Lysine 280 residue in critical events in tauopathy was further strengthened (Irwin, Cohen, et al. 2012). Li Gan and his group further identified another novel acetylation site, Lysine 174 which is also acetylated by p300 and acetylation on Lysine174 is a potent tau modification that leads to its aggregation and cognitive deficits (Min et al., 2015). Through a recent study by Tracy et, al, they have demonstrated for the first time that acetylated tau is linked with synaptic dysfunction and cognitive decline through postsynaptic KIBRA signaling pathway, actin signaling, and AMPA receptor trafficking. They have created acetylated mimic tau by mutating K274 and K281 sites with glutamine which showed a higher level of misfolded tau aggregation along with long-term hippocampal potentiation (Tracy et al., 2016).

Moreover, it has been well demonstrated that overexpression of mutant tau at lysine 280 that mimics acetylated tau in a Drosophila transgenic species augments the phosphorylation at S262 and T212/S214 of tau (Gorsky et al., 2016). Interestingly tau has been found to have intrinsic acetyltransferase activity as well. It can be autoacetylated through cysteine residues at C291 and C322 position (Cohen et al., 2013). However, what exactly causes tau autoacetylation remains to be elusive. Most of the putative lysine residues for acetylation in the microtubule-binding domain can also be ubiquitinated implying that acetylation prevents the ubiquitination and thus proteasomal degradation and clearance of tau in pathological conditions (Min et al., 2010; Morris et al., 2015).

The extent of acetylation of tau has been found to be modified by several acetyltransferases and deacetylases in AD condition. Previously it mentioned that p300 or CBP acetyltransferases could acetylate tau and deacetylated by SIRT1 (Min et al., 2010). In contrast, a negative correlation between SIRT1 and Tau has also been identified. In this study, it was shown that pseudo acetylation on tau prevents the phosphorylation level of tau and can mitigate Aβ-mediated toxicity (Gorsky et al., 2017).

However, a missing mechanistic link between Aβ to acetylated tau in AD condition demands further investigation. In this context, very recently we reported a novel upstream mechanism that regulates tau acetylation status upon exposure to Aβ which straightforwardly connects Aβ with tau acetylation (Sen et al., 2018). Nitrosative stress has previously been implicated in the synaptic loss, neuron death in neurodegenerative conditions including AD (Nakamura and Lipton, 2009; Gu et al., 2010; Nakamura and Lipton, 2013) where nitrosylation of proteins takes place (Sen and Snyder, 2010). In this literature, we reported that Aβ-induced NO production nitrosylate GAPDH which in

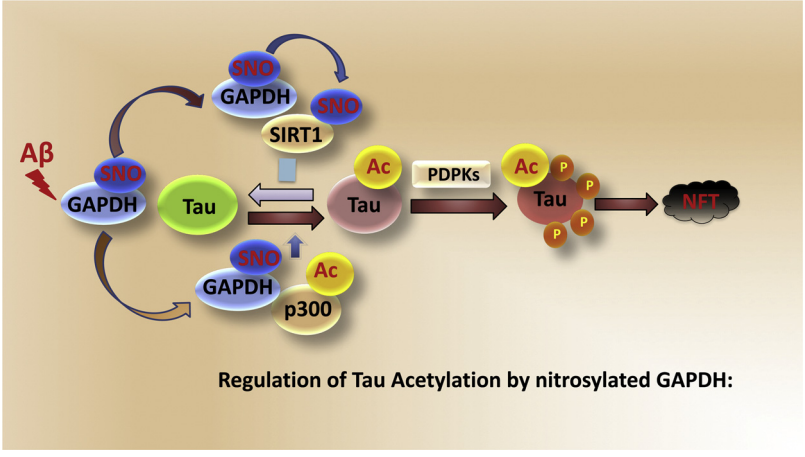

Fig. 1. Upon induction of amyloid beta, Nitrosylated GAPDH activates an acetyltransferase p300 via direct interaction. On the other hand, it inactivates a deacetylase, SIRT1 by nitrosylates SIRT1 through transnitrosylation reaction. As a result, the level of Tau acetylation remains elevated and accumulation of acetylated tau leads to tau phosphorylation and NFT in AD.

turn promote the acetylation and activation of p300 acetyltransferase which further acetylates tau protein (Sen et al. 2018) (Fig. 1). Also, nitrosylated GAPDH inactivated the deacetylase, SIRT1 by nitrosylation enhancing the possibility of more tau acetylation. So, our study presents the nitrosylated GAPDH as a double-edged sword and a very potent regulator of tau acetylation upon Aβ induction.

4. Oxidative stress and Tauopathy

An increase in oxidative stress is a characteristic feature of AD. Recent studies have substantiated that tauopathies have been associated with oxidative stress markers and neuronal damage both *in vitro* and *in vivo*. Intracellular ROS is mainly produced in mitochondrial electron transport chain (ETC), peroxisomes and endoplasmic reticulum (Abou-Sleiman et al., 2006). ROS attacks the cellular macromolecules like DNA, RNA, membrane lipids and proteins. Oxidative stress markers are closely associated with Aβ deposition in AD brain, Pick's disease as well as corticobasal degeneration (CBD) patients (Castellani et al., 1995). In other tauopathies, such as Frontotemporal lobar degeneration (FTLD) spectrum disorder and progressive supranuclear palsy (PSP), several lipid peroxidation markers, namely, malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and Thiobarbituric acid reactive substances (TBARS) were generated due to ROS (Odetti et al., 2000; Cantuti-Castelvetri et al., 2002; Martinez et al., 2008). Other studies have shown that fatty acid oxidation product also can induce the NFT formation in AD condition (Patil and Chan, 2005).

The direct evidence of oxidative stress and impairment of tau function was shown in a study where overexpression of wild-type tau in N2a neuroblastoma cells confers greater susceptibility to oxidative stress and manifests the toxicity through impairment of microtubule-associated peroxisome transportation (Stamer et al., 2002). These studies raised the possibility that oxidative stress may have a direct influence on Tauopathies. Indeed, it was demonstrated that the oxidative damage induced tau phosphorylation which leads to its aggregation (Ledesma et al., 1994; Yan et al., 1994, Perez et al., 2000, Reynolds et al., 2006). In a chronic oxidative stress model where M17 neuroblastoma cells were treated with buthionine sulfoximine (BSO), resulted in an increase in the level of phosphorylated tau in concomitant with an inhibition of glutathione synthesis (Su et al., 2010). Further studies revealed that ROS induced by 1,2-diacetyl benzene (DAB; a neurotoxic metabolite of 1,2-diethyl benzene) cause hyperphosphorylation of tau by activating GSK-3® in the hippocampus that leads to impaired memory in mice (Lovell et al., 2004). In another study, where Tau was overexpressed in human embryonic kidney 293 (HEK293) cells, tau was shown to be phosphorylated at ser396, ser404, and Thr231 residues after induction of oxidative stress by treatment with H2O2 (Chiara et al., 2012). Consistent with this finding, a recent study demonstrates that sodium orthovanadate, which is commonly used to induce oxidative stress, causes an augmentation in hyperphosphorylation of tau at Ser396 significantly; however, it was decreased upon resveratrol treatment in rat hippocampal slices (Jhang et al., 2017). Resveratrol is known to function as an activator of a protein deacetylase SIRT1(Borra et al., 2005; Mohar and Malik, 2012), which can reduce the oxidative stress by promoting the level of antioxidants through activation of several transcription factors such as Foxo3a (Giannakou and Partridge, 2004; Daitoku et al., 2011). Considering that GSK-3® or JNK/p38kinse are major kinases to phosphorylate Tau, it was shown that inhibiting GSK-3® or JNK/p38kinse can improve streptozotocin-induced oxidative stress and cognitive impairment by reducing tau phosphorylation and tauopathy (Guo et al., 2017).

Furthermore, oxidative stress has been found to be a critical regulator in tau-induced neurodegeneration in Drosophila where ROS is the vital element that causes tau phosphorylation through p38-MAPK pathway activation (Dias-Santagata et al., 2007). Apart from the activation of kinases responsible for tau phosphorylation induced by oxidative stress, there are several pieces of evidence where the level of a dephosphorylating enzyme of tau, such as PP2 A activity was decreased upon the oxidatively stressed condition (Zhang et al., 2014). This data suggests that oxidative stress triggers tau hyperphosphorylation both by activating kinases and deactivating phosphatases with the severity of AD.

Since tau acetylation is upstream of tau phosphorylation; it opens an excellent scope of investigation on whether oxidative stress can directly modulate tau acetylation or not. In this respect we would like to hypothesize that oxidative stress might have some direct effect on p300/CBP acetyltransferase mediated tau acetylation because elsewhere it has been reported that p300/CBP interacts and acetylates its various substrates in the presence of ROS (Dansen et al., 2009; Sun et al., 2009; Jain et al., 2012). Oxidative stress has been shown to affect the deacetylating activity of SIRT1(Salminen et al., 2013), which is critical for the regulation of tau acetylation and subsequent tau phosphorylation. Thus, it might also be worth investigating whether oxidative stress induced SIRT1 inactivation has any direct role on tau acetylation and therefore abnormal aggregation.

4.1. Tauopathies in neurodegenerative disorders other than AD: a perspective from genetic manipulation

Implications of tau pathology in neurodegenerative diseases other than AD has started to explore in late 1980, and the first evidence was observed in the study reported by Dr. Pollock and his associates. In this study, it was shown that filamentous aggregates in Tau are common in Pick's disease which is under the group of disorders known as frontotemporal lobar degeneration (FTLD), and progressive supranuclear palsy (PSP) (Pollock et al., 1986). Further characterization of these diseases it was revealed that tau was hyperphosphorylated without any significant pathology of either Aβ and α-synuclein. The subsequent molecular, biochemical studies provide insight into the tau hyperphosphorylation, and it was shown that all six tau isoforms were present in sarkosyl extracts in equal ratios of R3 and R4 isoforms which were composed of typical tau triplets of 60, 64 and 69 kDa, and additional minor bands of 72/74 kDa. Eventually, this characteristic pattern of tau phosphorylation was evidenced in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Niemann-Pick disease type C, Down syndrome and dementia pugilistica (Sergeant, Delacourte et al. 2005). In other neurodegenerative disorders, such as PSP (Flament et al., 1991), corticobasal degeneration (CBD; (Ksiezak-Reding et al., 1994), argyrophilic grain disease (AgD; (Simic, 2002)), and some cases of FTDP-17, sarkosyl extracts revealed that tau protein was separated as doublets of 64 and 69 kDa, which is a typical feature of class II tauopathies where isoforms with 4R predominates. On the other hand, the Pick's disease is characterized by the presence of pathological tau doublets of 60 and 64 kDa and contain mainly 3R tau isoforms (class III tauopathy) whereas in myotonic dystrophy type I (DM1) or Steinert's disease a major insoluble tau band of 60 kDa, and minor 64 and 69 kDa bands have been identified (Delacourte et al., 1996; Buee et al., 2000; Jovanov-Milosevic et al., 2012; Jadhav et al., 2015). Despite having all the characterization of Tau, the direct relevance of tau dysfunction and filament formation in these diseases has not been shown yet.

Further genetic studies shed some light into this relevancy, and it was reported that autosomal dominantly inherited form of FTD with parkinsonism and amyotrophy (disinhibition-dementia-parkinsonism-amyotrophy complex, DDPAC) is in the same chromosome 17q21.2 region where *MAPT* gene is present(Wilhelmsen et al., 1994). Consistent with this finding, another group has shown that the genetic defect in MSTD (multiple system tauopathy with presenile dementia) mapped to chromosome 17q21-22 (Murrell et al., 1997), where *MAPT* gene is present. MSTD is characterized by the presence of 4R tau and solubility of tau was dependent on its isoforms. More specifically, it was shown that increased splicing of exon 10 of the *MAPT* gene might be the cause of familial MSTD (Foster et al., 1997). Sequencing results found

that conversion of a guanine (G) to adenine (A) transition at position +3 of the intron following exon 10 is critical to segregate the disease (Spillantini et al., 1998). However, tauopathy is not dependent only one mutations; other independent studies have shown that two exonic mutations (P301L and V337M) (Poorkaj et al., 1998), or missense mutations (G272V, P301L, and R406W) in exon 10 significantly contributes to the tauopathy (Hutton et al., 1998). Reversing these mutations was able to reduce the ability of tau to promote microtubule assembly (Hasegawa et al., 1998; Hong et al., 1998); suggesting that these mutations directly contribute to the tauopathy. Considering that these mutations in the *MAPT* gene can significantly contribute to the tauopathy independent of Aβ changes; these mutations can be implicated in neurodegenerative diseases other than AD.

5. Tauopathy in healthy brain aging

Tau deposition is also typical in the aged brain, specifically, in primary age-related tauopathy (PART) (Bouras et al., 1993; Ikeda et al., 1993; Bancher and Jellinger, 1994; Itoh et al., 1996; Jellinger and Attems, 2007; Crary et al., 2014). Clinically, PART can be either correlated or associated with other neurodegenerative conditions such as tangle predominant senile dementia (TPSD), tangle only dementia, preferential development of NFT without senile plaques, or senile dementia of the neurofibrillary tangle type (SD-NFT) (Crary et al., 2014). Even though PART is commonly observed in the brains of aged individuals and universally detectable at autopsy among elderly individuals, the diagnosis of PART in the aged patient remains challenging. However, identifying the association between tauopathy with PART opens the possibility of using tau imaging as a diagnostic tool to detect PART in the clinical settings.

Several efforts have been made to elucidate the underlying molecular mechanism to establish a correlation between common aging mechanisms with tau deposition. Among them, an alteration in the kinase activity of Mammalian target of rapamycin (mTOR) has been shown to have a significant effect on aging. Because, the reduced signaling of mTOR kinase and inhibition by rapamycin have been demonstrated to extend the lifespan of yeast, worms, and flies (Schieke and Finkel, 2006; Harrison et al., 2009; Bishop, Lu et al. 2010). As a part of the mechanism, it was shown that inhibition of mTOR leads to an increase in autophagy which can reduce protein aggregation and tauopathies in neurodegenerative condition (Ravikumar et al., 2004; Bishop, Lu et al. 2010). Secondly, in the healthy aging brain, impairment of proteasomal degradation machinery leads to unwanted protein aggregates, and this phenomenon also gives a link between aging process with tau accumulation (Fischer et al., 2009). Thirdly, aging leads to either downregulate or inactivates a protein deacetylase, SIRT1, which is essential to reduce oxidative stress and maintain the level of neurotrophic factors such as BDNF to keep the brain healthy (Rogina and Helfand, 2004; Boily et al., 2008; Mair and Dillin, 2008). In AD, an inactivation of SIRT1 results in an induction of acetylation of Tau which serves as a precursor for tau phosphorylation and tauopathy. Thus, we cannot rule the possibility that inactivation of SIRT1 in the aged brain, specifically in PART, will result in an increase in acetylation of Tau and pathology associated with Tau.

6. Conclusion

Although substantial progress has been made to understand the pathological aspects of tau phosphorylation in several preclinical models of neurodegenerative disorders, targeting tau phosphorylation to improve cognitive deficiencies remains abortive. Thus, identification of novel post-translational modification of Tau such as tau acetylation which occurs well ahead of tau phosphorylation provides a unique opportunity to address the tau phosphorylation. Specifically, tau acetylation at K280 has the most promising target to treat the tauopathy because of its direct correlation with tau phosphorylation. However, it is not clear whether tau acetylation can directly affect oxidative stress or neuroinflammation independent of tau phosphorylation. Also, reducing tau acetylation is clinically challenging because Tau acetylation depends on activation and inactivation of an acetyltransferase p300 and a protein deacetylase SIRT1. Both proteins have several substrates other than Tau, and these substrates are functionally relevant to numerous physiological aspects in a cell. Thus, attenuating their activities may result in adverse effects instead of providing neuroprotection. Therefore, it would be much more meaningful to attenuate the aberrant activation of p300 and SIRT1. Our recent study offers an insight where nitrosylation of GAPDH has been shown to be responsible for both aberrant activation of p300 and inactivation of SIRT1. Also, blocking GAPDH-nitrosylation using Omigapil, which is being tested for patients of muscular dystrophy have shown promising results to prevent tau acetylation. In the future, much more studies are needed to specifically target the Tau acetylation which contributes to the pathology upon activation of neurological disorders including AD or the aged brain.

Acknowledgments

This work was partly supported by the National Institutes of Health (Grants RO1NS094516 and RO1EY025622 to N.S.), funding from the University of Pittsburgh and Copeland Foundation to N.S.

References

Abou-Sleiman, P.M., Muqit, M.M., Wood, N.W., 2006. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nat. Rev. Neurosci. 7 (3), 207–219.
Alonso, A.C., Zaidi, T., Grundke-Iqbal, I., Iqbal, K., 1994. Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 91 (12), 5562–5566.
Alonso, A.C., Grundke-Iqbal, I., Iqbal, K., 1996. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nat. Med. 2 (7), 783–787.
Alonso, A.D., Grundke-Iqbal, I., Barra, H.S., Iqbal, K., 1997. Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule-associated proteins 1 and 2 and the disassembly of microtubules by the abnormal tau. Proc. Natl. Acad. Sci. U. S. A. 94 (1), 298–303.
Alonso, A.D., Zaidi, T., Novak, M., Barra, H.S., Grundke-Iqbal, I., Iqbal, K., 2001. Interaction of tau isoforms with Alzheimer's disease abnormally hyperphosphorylated tau and in vitro phosphorylation into the disease-like protein. J. Biol. Chem. 276 (41), 37967–37973.
Arioka, M., Tsukamoto, M., Ishiguro, K., Kato, R., Sato, K., Imahori, K., Uchida, T., 1993. Tau protein kinase II is involved in the regulation of the normal phosphorylation state of tau protein. J. Neurochem. 60 (2), 461–468.
Arnold, C.S., Johnson, G.V., Cole, R.N., Dong, D.L., Lee, M., Hart, G.W., 1996. The microtubule-associated protein tau is extensively modified with O-linked N-acetylglucosamine. J. Biol. Chem. 271 (46), 28741–28744.
Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T., Hyman, B.T., 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42 (3 Pt 1), 631–639.
Ballatore, C., Lee, V.M., Trojanowski, J.Q., 2007. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat. Rev. Neurosci. 8 (9), 663–672.
Bancher, C., Jellinger, K.A., 1994. Neurofibrillary tangle predominant form of senile dementia of Alzheimer type: a rare subtype in very old subjects. Acta Neuropathol. 88 (6), 565–570.
Baudier, J., Cole, R.D., 1988. Interactions between the microtubule-associated tau proteins and S100b regulate tau phosphorylation by the Ca2+/calmodulin-dependent protein kinase II. J. Biol. Chem. 263 (12), 5876–5883.
Bekris, L.M., Yu, C.E., Bird, T.D., Tsuang, D.W., 2010. Genetics of Alzheimer disease. J. Geriatr. Psychiatry Neurol. 23 (4), 213–227.
Bennecib, M., Gong, C.X., Grundke-Iqbal, I., Iqbal, K., 2000. Role of protein phosphatase-2A and -1 in the regulation of GSK-3, cdk5 and cdc2 and the phosphorylation of tau in rat forebrain. FEBS Lett. 485 (1), 87–93.
Bierer, L.M., Hof, P.R., Purohit, D.P., Carlin, L., Schmeidler, J., Davis, K.L., Perl, D.P., 1995. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch. Neurol. 52 (1), 81–88.
Bishop, N.A., Lu, T., Yankner, B.A., 2010. Neural mechanisms of ageing and cognitive decline. Nature 464 (7288), 529–535.
Blurton-Jones, M., Laferla, F.M., 2006. Pathways by which Abeta facilitates tau pathology. Curr. Alzheimer Res. 3 (5), 437–448.
Boily, G., Seifert, E.L., Bevilacqua, L., He, X.H., Sabourin, G., Estey, C., Moffat, C., Crawford, S., Saliba, S., Jardine, K., Xuan, J., Evans, M., Harper, M.E., McBurney, M.W., 2008. SirT1 regulates energy metabolism and response to caloric restriction in mice. PLoS One 3 (3), e1759.
Borra, M.T., Smith, B.C., Denu, J.M., 2005. Mechanism of human SIRT1 activation by resveratrol. J. Biol. Chem. 280 (17), 17187–17195.
Bouras, C., Hof, P.R., Morrison, J.H., 1993. Neurofibrillary tangle densities in the

hippocampal formation in a non-demented population define subgroups of patients with differential early pathologic changes. Neurosci. Lett. 153 (2), 131–135.
Bramblett, G.T., Goedert, M., Jakes, R., Merrick, S.E., Trojanowski, J.Q., Lee, V.M., 1993. Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. Neuron 10 (6), 1089–1099.
Buee, L., Bussiere, T., Buee-Scherrer, V., Delacourte, A., Hof, P.R., 2000. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res. Brain Res. Rev. 33 (1), 95–130.
Busciglio, J., Lorenzo, A., Yeh, J., Yankner, B.A., 1995. Beta-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron 14 (4), 879–888.
Cantuti-Castelvetri, I., Keller-McGandy, C.E., Albers, D.S., Beal, M.F., Vonsattel, J.P., Standaert, D.G., Augood, S.J., 2002. Expression and activity of antioxidants in the brain in progressive supranuclear palsy. Brain Res. 930 (1-2), 170–181.
Castellani, R., Smith, M.A., Richey, P.L., Kalaria, R., Gambetti, P., Perry, G., 1995. Evidence for oxidative stress in Pick disease and corticobasal degeneration. Brain Res. 696 (1-2), 268–271.
Castillo-Carranza, D.L., Guerrero-Munoz, M.J., Sengupta, U., Hernandez, C., Barrett, A.D., Dineley, K., Kayed, R., 2015. Tau immunotherapy modulates both pathological tau and upstream amyloid pathology in an Alzheimer's disease mouse model. J. Neurosci. 35 (12), 4857–4868.
Chabrier, M.A., Blurton-Jones, M., Agazaryan, A.A., Nerhus, J.L., Martinez-Coria, H., LaFerla, F.M., 2012. Soluble abeta promotes wild-type tau pathology in vivo. J. Neurosci. 32 (48), 17345–17350.
Chesser, A.S., Pritchard, S.M., Johnson, G.V., 2013. Tau clearance mechanisms and their possible role in the pathogenesis of Alzheimer disease. Front. Neurol. 4, 122.
Chiara, F., Gambalunga, A., Sciacovelli, M., Nicolli, A., Ronconi, L., Fregona, D., Bernardi, P., Rasola, A., Trevisan, A., 2012. Chemotherapeutic induction of mitochondrial oxidative stress activates GSK-3alpha/beta and Bax, leading to permeability transition pore opening and tumor cell death. Cell Death Dis. 3, e444.
Cohen, T.J., Guo, J.L., Hurtado, D.E., Kwong, L.K., Mills, I.P., Trojanowski, J.Q., Lee, V.M., 2011. The acetylation of tau inhibits its function and promotes pathological tau aggregation. Nat. Commun. 2, 252.
Cohen, T.J., Friedmann, D., Hwang, A.W., Marmorstein, R., Lee, V.M., 2013. The microtubule-associated tau protein has intrinsic acetyltransferase activity. Nat. Struct. Mol. Biol. 20 (6), 756–762.
Cook, C., Stankowski, J.N., Carlomagno, Y., Stetler, C., Petrucelli, L., 2014. Acetylation: a new key to unlock tau's role in neurodegeneration. Alzheimers Res. Ther. 6 (3), 29.
Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., Alafuzoff, I., Arnold, S.E., Attems, J., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., Gearing, M., Grinberg, L.T., Hof, P.R., Hyman, B.T., Jellinger, K., Jicha, G.A., Kovacs, G.G., Knopman, D.S., Kofler, J., Kukull, W.A., Mackenzie, I.R., Masliah, E., McKee, A., Montine, T.J., Murray, M.E., Neltner, J.H., Santa-Maria, I., Seeley, W.W., Serrano-Pozo, A., Shelanski, M.L., Stein, T., Takao, M., Thal, D.R., Toledo, J.B., Troncoso, J.C., Vonsattel, J.P., White 3rd, C.L., Wisniewski, T., Woltjer, R.L., Yamada, M., Nelson, P.T., 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 128 (6), 755–766.
Cripps, D., Thomas, S.N., Jeng, Y., Yang, F., Davies, P., Yang, A.J., 2006. Alzheimer disease-specific conformation of hyperphosphorylated paired helical filament-Tau is polyubiquitinated through Lys-48, Lys-11, and Lys-6 ubiquitin conjugation. J. Biol. Chem. 281 (16), 10825–10838.
Daitoku, H., Sakamaki, J., Fukamizu, A., 2011. Regulation of FoxO transcription factors by acetylation and protein-protein interactions. Biochim. Biophys. Acta 1813 (11), 1954–1960.
Dansen, T.B., Smits, L.M., van Triest, M.H., de Keizer, P.L., van Leenen, D., Koerkamp, M.G., Szypowska, A., Meppelink, A., Brenkman, A.B., Yodoi, J., Holstege, F.C., Burgering, B.M., 2009. Redox-sensitive cysteines bridge p300/CBP-mediated acetylation and FoxO4 activity. Nat. Chem. Biol. 5 (9), 664–672.
Delacourte, A., Robitaille, Y., Sergeant, N., Buee, L., Hof, P.R., Wattez, A., Laroche-Cholette, A., Mathieu, J., Chagnon, P., Gauvreau, D., 1996. Specific pathological Tau protein variants characterize Pick's disease. J. Neuropathol. Exp. Neurol. 55 (2), 159–168.
Dias-Santagata, D., Fulga, T.A., Duttaroy, A., Feany, M.B., 2007. Oxidative stress mediates tau-induced neurodegeneration in Drosophila. J. Clin. Invest. 117 (1), 236–245.
Dickey, C.A., Kamal, A., Lundgren, K., Klosak, N., Bailey, R.M., Dunmore, J., Ash, P., Shoraka, S., Zlatkovic, J., Eckman, C.B., Patterson, C., Dickson, D.W., Nahman Jr, N.S., Hutton, M., Burrows, F., Petrucelli, L., 2007. The high-affinity HSP90-CHIP complex recognizes and selectively degrades phosphorylated tau client proteins. J. Clin. Invest. 117 (3), 648–658.
Dorval, V., Fraser, P.E., 2006. Small ubiquitin-like modifier (SUMO) modification of natively unfolded proteins tau and alpha-synuclein. J. Biol. Chem. 281 (15), 9919–9924.
Drewes, G., Ebneth, A., Preuss, U., Mandelkow, E.M., Mandelkow, E., 1997. MARK, a novel family of protein kinases that phosphorylate microtubule-associated proteins and trigger microtubule disruption. Cell 89 (2), 297–308.
Fischer, D.F., van Dijk, R., van Tijn, P., Hobo, B., Verhage, M.C., van der Schors, R.C., Li, K.W., van Minnen, J., Hol, E.M., van Leeuwen, F.W., 2009. Long-term proteasome dysfunction in the mouse brain by expression of aberrant ubiquitin. Neurobiol. Aging 30 (6), 847–863.
Flament, S., Delacourte, A., Verny, M., Hauw, J.J., Javoy-Agid, F., 1991. Abnormal Tau proteins in progressive supranuclear palsy. Similarities and differences with the neurofibrillary degeneration of the Alzheimer type. Acta Neuropathol. 81 (6), 591–596.
Foster, N.L., Wilhelmsen, K., Sima, A.A., Jones, M.Z., D'Amato, C.J., Gilman, S., 1997. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. Ann. Neurol. 41 (6), 706–715.
Gamblin, T.C., Chen, F., Zambrano, A., Abraha, A., Lagalwar, S., Guillozet, A.L., Lu, M., Fu, Y., Garcia-Sierra, F., LaPointe, N., Miller, R., Berry, R.W., Binder, L.I., Cryns, V.L., 2003. Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 100 (17), 10032–10037.
Giannakou, M.E., Partridge, L., 2004. The interaction between FOXO and SIRT1: tipping the balance towards survival. Trends Cell Biol. 14 (8), 408–412.
Goedert, M., Spillantini, M.G., 2006. A century of Alzheimer's disease. Science 314 (5800), 777–781.
Goedert, M., Spillantini, M.G., Cairns, N.J., Crowther, R.A., 1992. Tau proteins of Alzheimer paired helical filaments: abnormal phosphorylation of all six brain isoforms. Neuron 8 (1), 159–168.
Gong, C.X., Lidsky, T., Wegiel, J., Zuck, L., Grundke-Iqbal, I., Iqbal, K., 2000. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain. Implications for neurofibrillary degeneration in Alzheimer's disease. J. Biol. Chem. 275 (8), 5535–5544.
Gorsky, M.K., Burnouf, S., Dols, J., Mandelkow, E., Partridge, L., 2016. Acetylation mimic of lysine 280 exacerbates human Tau neurotoxicity in vivo. Sci. Rep. 6, 22685.
Gorsky, M.K., Burnouf, S., Sofola-Adesakin, O., Dols, J., Augustin, H., Weigelt, C.M., Gronke, S., Partridge, L., 2017. Pseudo-acetylation of multiple sites on human Tau proteins alters Tau phosphorylation and microtubule binding, and ameliorates amyloid beta toxicity. Sci. Rep. 7 (1), 9984.
Gotz, J., Chen, F., van Dorpe, J., Nitsch, R.M., 2001. Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. Science 293 (5534), 1491–1495.
Graham, W.V., Bonito-Oliva, A., Sakmar, T.P., 2017. Update on Alzheimer's disease therapy and prevention strategies. Annu. Rev. Med. 68, 413–430.
Green, K.N., Steffan, J.S., Martinez-Coria, H., Sun, X., Schreiber, S.S., Thompson, L.M., LaFerla, F.M., 2008. Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. J. Neurosci. 28 (45), 11500–11510.
Gu, Z., Nakamura, T., Lipton, S.A., 2010. Redox reactions induced by nitrosative stress mediate protein misfolding and mitochondrial dysfunction in neurodegenerative diseases. Mol. Neurobiol. 41 (2-3), 55–72.
Guo, X.D., Sun, G.L., Zhou, T.T., Wang, Y.Y., Xu, X., Shi, X.F., Zhu, Z.Y., Rukachaisirikul, V., Hu, L.H., Shen, X., 2017. LX2343 alleviates cognitive impairments in AD model rats by inhibiting oxidative stress-induced neuronal apoptosis and tauopathy. Acta Pharmacol. Sin. 38 (8), 1104–1119.
Hanger, D.P., Betts, J.C., Loviny, T.L., Blackstock, W.P., Anderton, B.H., 1998. New phosphorylation sites identified in hyperphosphorylated tau (paired helical filament-tau) from Alzheimer's disease brain using nanoelectrospray mass spectrometry. J. Neurochem. 71 (6), 2465–2476.
Harrison, D.E., Strong, R., Sharp, Z.D., Nelson, J.F., Astle, C.M., Flurkey, K., Nadon, N.L., Wilkinson, J.E., Frenkel, K., Carter, C.S., Pahor, M., Javors, M.A., Fernandez, E., Miller, R.A., 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460 (7253), 392–395.
Hasegawa, M., Morishima-Kawashima, M., Takio, K., Suzuki, M., Titani, K., Ihara, Y., 1992. Protein sequence and mass spectrometric analyses of tau in the Alzheimer's disease brain. J. Biol. Chem. 267 (24), 17047–17054.
Hasegawa, M., Smith, M.J., Goedert, M., 1998. Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. FEBS Lett. 437 (3), 207–210.
Hettinger, J.C., Cirrito, J.R., 2016. Bad Ac-etylated Tau. Neuron 90 (2), 205–206.
Hong, M., Zhukareva, V., Vogelsberg-Ragaglia, V., Wszolek, Z., Reed, L., Miller, B.I., Geschwind, D.H., Bird, T.D., McKeel, D., Goate, A., Morris, J.C., Wilhelmsen, K.C., Schellenberg, G.D., Trojanowski, J.Q., Lee, V.M., 1998. Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. Science 282 (5395), 1914–1917.
Horiguchi, T., Uryu, K., Giasson, B.I., Ischiropoulos, H., LightFoot, R., Bellmann, C., Richter-Landsberg, C., Lee, V.M., Trojanowski, J.Q., 2003. Nitration of tau protein is linked to neurodegeneration in tauopathies. Am. J. Pathol. 163 (3), 1021–1031.
Huber, C.M., Yee, C., May, T., Dhanala, A., Mitchell, C.S., 2018. Cognitive Decline in Preclinical Alzheimer's Disease: Amyloid-Beta versus Tauopathy. J. Alzheimers Dis. 61 (1), 265–281.
Hutton, M., Lendon, C.L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., Pickering-Brown, S., Chakraverty, S., Isaacs, A., Grover, A., Hackett, J., Adamson, J., Lincoln, S., Dickson, D., Davies, P., Petersen, R.C., Stevens, M., de Graaff, E., Wauters, E., van Baren, J., Hillebrand, M., Joosse, M., Kwon, J.M., Nowotny, P., Che, L.K., Norton, J., Morris, J.C., Reed, L.A., Trojanowski, J., Basun, H., Lannfelt, L., Neystat, M., Fahn, S., Dark, F., Tannenberg, T., Dodd, P.R., Hayward, N., Kwok, J.B., Schofield, P.R., Andreadis, A., Snowden, J., Craufurd, D., Neary, D., Owen, F., Oostra, B.A., Hardy, J., Goate, A., van Swieten, J., Mann, D., Lynch, T., Heutink, P., 1998. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 393 (6686), 702–705.
Iaccarino, H.F., Singer, A.C., Martorell, A.J., Rudenko, A., Gao, F., Gillingham, T.Z., Mathys, H., Seo, J., Kritskiy, O., Abdurrob, F., Adaikkan, C., Canter, R.G., Rueda, R., Brown, E.N., Boyden, E.S., Tsai, L.H., 2016. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540 (7632), 230–235.
Ikeda, K., Kondo, H., Fujishima, T., Kase, K., Mizutani, Y., 1993. [A case of atypical senile dementia of Alzheimer type]. No To Shinkei 45 (5), 455–460.
Iqbal, K., Zaidi, T., Bancher, C., Grundke-Iqbal, I., 1994. Alzheimer paired helical filaments. Restoration of the biological activity by dephosphorylation. FEBS Lett. 349 (1), 104–108.
Irwin, D.J., Cohen, T.J., Grossman, M., Arnold, S.E., Xie, S.X., Lee, V.M., Trojanowski, J.Q., 2012. Acetylated tau, a novel pathological signature in Alzheimer's disease and other tauopathies. Brain 135 (Pt 3), 807–818.
Itoh, M., Yamada, R., Yoshida, N., Suematsu, T., Oka, M. Matsushita, Otomo, E., 1996.

Dementia characterized by abundant neurofibrillary tangles and scarce senile plaques: a quantitative pathological study. Eur. Neurol. 36 (2), 94–97.
Ittner, L.M., Ke, Y.D., Delerue, F., Bi, M., Gladbach, A., van Eersel, J., Wolfing, H., Chieng, B.C., Christie, M.J., Napier, I.A., Eckert, A., Staufenbiel, M., Hardeman, E., Gotz, J., 2010. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell 142 (3), 387–397.
Jadhav, S., Cubinkova, V., Zimova, I., Brezovakova, V., Madari, A., Cigankova, V., Zilka, N., 2015. Tau-mediated synaptic damage in Alzheimer's disease. Transl. Neurosci. 6 (1), 214–226.
Jain, S., Wei, J., Mitrani, L.R., Bishopric, N.H., 2012. Auto-acetylation stabilizes p300 in cardiac myocytes during acute oxidative stress, promoting STAT3 accumulation and cell survival. Breast Cancer Res. Treat. 135 (1), 103–114.
Jellinger, K.A., Attems, J., 2007. Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. Acta Neuropathol. 113 (2), 107–117.
Jhang, K.A., Park, J.S., Kim, H.S., Chong, Y.H., 2017. Resveratrol Ameliorates Tau Hyperphosphorylation at Ser396 Site and Oxidative Damage in Rat Hippocampal Slices Exposed to Vanadate: Implication of ERK1/2 and GSK-3beta Signaling Cascades. J. Agric. Food Chem. 65 (44), 9626–9634.
Jovanov-Milosevic, N., Petrovic, D., Sedmak, G., Vuksic, M., Hof, P.R., Simic, G., 2012. Human fetal tau protein isoform: possibilities for Alzheimer's disease treatment. Int. J. Biochem. Cell Biol. 44 (8), 1290–1294.
Kamah, A., Huvent, I., Cantrelle, F.X., Qi, H., Lippens, G., Landrieu, I., Smet-Nocca, C., 2014. Nuclear magnetic resonance analysis of the acetylation pattern of the neuronal Tau protein. Biochemistry 53 (18), 3020–3032.
Kopke, E., Tung, Y.C., Shaikh, S., Alonso, A.C., Iqbal, K., Grundke-Iqbal, I., 1993. Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. J. Biol. Chem. 268 (32), 24374–24384.
Kosik, K.S., Shimura, H., 2005. Phosphorylated tau and the neurodegenerative foldopathies. Biochim. Biophys. Acta 1739 (2-3), 298–310.
Ksiezak-Reding, H., Morgan, K., Mattiace, L.A., Davies, P., Liu, W.K., Yen, S.H., Weidenheim, K., Dickson, D.W., 1994. Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration. Am. J. Pathol. 145 (6), 1496–1508.
Ledesma, M.D., Correas, I., Avila, J., Diaz-Nido, J., 1992. Implication of brain cdc2 and MAP2 kinases in the phosphorylation of tau protein in Alzheimer's disease. FEBS Lett. 308 (2), 218–224.
Ledesma, M.D., Bonay, P., Colaco, C., Avila, J., 1994. Analysis of microtubule-associated protein tau glycation in paired helical filaments. J. Biol. Chem. 269 (34), 21614–21619.
Ledesma, M.D., Bonay, P., Avila, J., 1995. Tau protein from Alzheimer's disease patients is glycated at its tubulin-binding domain. J. Neurochem. 65 (4), 1658–1664.
Lee, V.M., Balin, B.J., Otvos Jr, L., Trojanowski, J.Q., 1991. A68: a major subunit of paired helical filaments and derivatized forms of normal Tau. Science 251 (4994), 675–678.
Lee, G., Newman, S.T., Gard, D.L., Band, H., Panchamoorthy, G., 1998. Tau interacts with src-family non-receptor tyrosine kinases. J. Cell. Sci. 111 (Pt 21), 3167–3177.
Lee, G., Thangavel, R., Sharma, V.M., Litersky, J.M., Bhaskar, K., Fang, S.M., Do, L.H., Andreadis, A., Van Hoesen, G., Ksiezak-Reding, H., 2004. Phosphorylation of tau by fyn: implications for Alzheimer's disease. J. Neurosci. 24 (9), 2304–2312.
Lewis, J., Dickson, D.W., Lin, W.L., Chisholm, L., Corral, A., Jones, G., Yen, S.H., Sahara, N., Skipper, L., Yager, D., Eckman, C., Hardy, J., Hutton, M., McGowan, E., 2001. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 293 (5534), 1487–1491.
Li, T., Braunstein, K.E., Zhang, J., Lau, A., Sibener, L., Deeble, C., Wong, P.C., 2016. The neuritic plaque facilitates pathological conversion of tau in an Alzheimer's disease mouse model. Nat. Commun. 7, 12082.
Liu, F., Grundke-Iqbal, I., Iqbal, K., Gong, C.X., 2005. Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Eur. J. Neurosci. 22 (8), 1942–1950.
Liu, F., Liang, Z., Wegiel, J., Hwang, Y.W., Iqbal, K., Grundke-Iqbal, I., Ramakrishna, N., Gong, C.X., 2008. Overexpression of Dyrk1A contributes to neurofibrillary degeneration in Down syndrome. FASEB J. 22 (9), 3224–3233.
Lovell, M.A., Xiong, S., Xie, C., Davies, P., Markesbery, W.R., 2004. Induction of hyperphosphorylated tau in primary rat cortical neuron cultures mediated by oxidative stress and glycogen synthase kinase-3. J. Alzheimers Dis. 6 (6), 659–671 discussion 673-681.
Ma, Q.L., Yang, F., Rosario, E.R., Ubeda, O.J., Beech, W., Gant, D.J., Chen, P.P., Hudspeth, B., Chen, C., Zhao, Y., Vinters, H.V., Frautschy, S.A., Cole, G.M., 2009. Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. J. Neurosci. 29 (28), 9078–9089.
Mair, W., Dillin, A., 2008. Aging and survival: the genetics of life span extension by dietary restriction. Annu. Rev. Biochem. 77, 727–754.
Martinez, A., Carmona, M., Portero-Otin, M., Naudi, A., Pamplona, R., Ferrer, I., 2008. Type-dependent oxidative damage in frontotemporal lobar degeneration: cortical astrocytes are targets of oxidative damage. J. Neuropathol. Exp. Neurol. 67 (12), 1122–1136.
Mattson, M.P., 2004. Pathways towards and away from Alzheimer's disease. Nature 430 (7000), 631–639.
Min, S.W., Cho, S.H., Zhou, Y., Schroeder, S., Haroutunian, V., Seeley, W.W., Huang, E.J., Shen, Y., Masliah, E., Mukherjee, C., Meyers, D., Cole, P.A., Ott, M., Gan, L., 2010. Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron 67 (6), 953–966.
Min, S.W., Chen, X., Tracy, T.E., Li, Y., Zhou, Y., Wang, C., Shirakawa, K., Minami, S.S., Defensor, E., Mok, S.A., Sohn, P.D., Schilling, B., Cong, X., Ellerby, L., Gibson, B.W., Johnson, J., Krogan, N., Shamloo, M., Gestwicki, J., Masliah, E., Verdin, E., Gan, L., 2015. Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Nat. Med. 21 (10), 1154–1162.
Miyasaka, T., Watanabe, A., Saito, Y., Murayama, S., Mann, D.M., Yamazaki, M., Ravid, R., Morishima-Kawashima, M., Nagashima, K., Ihara, Y., 2005. Visualization of newly deposited tau in neurofibrillary tangles and neuropil threads. J. Neuropathol. Exp. Neurol. 64 (8), 665–674.
Mohar, D.S., Malik, S., 2012. The Sirtuin System: The Holy Grail of Resveratrol? J. Clin. Exp. Cardiolog. 3 (11).
Morishima-Kawashima, M., Hasegawa, M., Takio, K., Suzuki, M., Yoshida, H., Titani, K., Ihara, Y., 1995. Proline-directed and non-proline-directed phosphorylation of PHF-tau. J. Biol. Chem. 270 (2), 823–829.
Morris, M., Knudsen, G.M., Maeda, S., Trinidad, J.C., Ioanoviciu, A., Burlingame, A.L., Mucke, L., 2015. Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. Nat. Neurosci. 18 (8), 1183–1189.
Mucke, L., Selkoe, D.J., 2012. Neurotoxicity of amyloid beta-protein: synaptic and network dysfunction. Cold Spring Harb. Perspect. Med. 2 (7), a006338.
Murrell, J.R., Koller, D., Foroud, T., Goedert, M., Spillantini, M.G., Edenberg, H.J., Farlow, M.R., Ghetti, B., 1997. Familial multiple-system tauopathy with presenile dementia is localized to chromosome 17. Am. J. Hum. Genet. 61 (5), 1131–1138.
Nakamura, T., Lipton, S.A., 2009. Cell death: protein misfolding and neurodegenerative diseases. Apoptosis 14 (4), 455–468.
Nakamura, T., Lipton, S.A., 2013. Emerging role of protein-protein transnitrosylation in cell signaling pathways. Antioxid. Redox Signal. 18 (3), 239–249.
Nussbaum, J.M., Schilling, S., Cynis, H., Silva, A., Swanson, E., Wangsanut, T., Tayler, K., Wiltgen, B., Hatami, A., Ronicke, R., Reymann, K., Hutter-Paier, B., Alexandru, A., Jagla, W., Graubner, S., Glabe, C.G., Demuth, H.U., Bloom, G.S., 2012. Prion-like behaviour and tau-dependent cytotoxicity of pyroglutamylated amyloid-beta. Nature 485 (7400), 651–655.
Nygaard, H.B., 2018. Targeting fyn kinase in Alzheimer's disease. Biol. Psychiatry 83 (4), 369–376.
Nygaard, H.B., van Dyck, C.H., Strittmatter, S.M., 2014. Fyn kinase inhibition as a novel therapy for Alzheimer's disease. Alzheimers Res. Ther. 6 (1), 8.
Oddo, S., Billings, L., Kesslak, J.P., Cribbs, D.H., LaFerla, F.M., 2004. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron 43 (3), 321–332.
Odetti, P., Garibaldi, S., Norese, R., Angelini, G., Marinelli, L., Valentini, S., Menini, S., Traverso, N., Zaccheo, D., Siedlak, S., Perry, G., Smith, M.A., Tabaton, M., 2000. Lipoperoxidation is selectively involved in progressive supranuclear palsy. J. Neuropathol. Exp. Neurol. 59 (5), 393–397.
Patil, S., Chan, C., 2005. Palmitic and stearic fatty acids induce Alzheimer-like hyperphosphorylation of tau in primary rat cortical neurons. Neurosci. Lett. 384 (3), 288–293.
Perez, M., Cuadros, R., Smith, M.A., Perry, G., Avila, J., 2000. Phosphorylated, but not native, tau protein assembles following reaction with the lipid peroxidation product, 4-hydroxy-2-nonenal. FEBS Lett. 486 (3), 270–274.
Petrucelli, L., Dickson, D., Kehoe, K., Taylor, J., Snyder, H., Grover, A., De Lucia, M., McGowan, E., Lewis, J., Prihar, G., Kim, J., Dillmann, W.H., Browne, S.E., Hall, A., Voellmy, R., Tsuboi, Y., Dawson, T.M., Wolozin, B., Hardy, J., Hutton, M., 2004. CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. Hum. Mol. Genet. 13 (7), 703–714.
Pollock, N.J., Mirra, S.S., Binder, L.I., Hansen, L.A., Wood, J.G., 1986. Filamentous aggregates in Pick's disease, progressive supranuclear palsy, and Alzheimer's disease share antigenic determinants with microtubule-associated protein, tau. Lancet 2 (8517), 1211.
Poorkaj, P., Bird, T.D., Wijsman, E., Nemens, E., Garruto, R.M., Anderson, L., Andreadis, A., Wiederholt, W.C., Raskind, M., Schellenberg, G.D., 1998. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann. Neurol. 43 (6), 815–825.
Poppek, D., Keck, S., Ermak, G., Jung, T., Stolzing, A., Ullrich, O., Davies, K.J., Grune, T., 2006. Phosphorylation inhibits turnover of the tau protein by the proteasome: influence of RCAN1 and oxidative stress. Biochem. J. 400 (3), 511–520.
Qiu, C., Kivipelto, M., von Strauss, E., 2009. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin. Neurosci. 11 (2), 111–128.
Rapoport, M., Dawson, H.N., Binder, L.I., Vitek, M.P., Ferreira, A., 2002. Tau is essential to beta -amyloid-induced neurotoxicity. Proc. Natl. Acad. Sci. U. S. A. 99 (9), 6364–6369.
Ravikumar, B., Vacher, C., Berger, Z., Davies, J.E., Luo, S., Oroz, L.G., Scaravilli, F., Easton, D.F., Duden, R., O'Kane, C.J., Rubinsztein, D.C., 2004. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat. Genet. 36 (6), 585–595.
Reynolds, M.R., Lukas, T.J., Berry, R.W., Binder, L.I., 2006. Peroxynitrite-mediated tau modifications stabilize preformed filaments and destabilize microtubules through distinct mechanisms. Biochemistry 45 (13), 4314–4326.
Roberson, E.D., Scearce-Levie, K., Palop, J.J., Yan, F., Cheng, I.H., Wu, T., Gerstein, H., Yu, G.Q., Mucke, L., 2007. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 316 (5825), 750–754.
Roberson, E.D., Halabisky, B., Yoo, J.W., Yao, J., Chin, J., Yan, F., Wu, T., Hamto, P., Devidze, N., Yu, G.Q., Palop, J.J., Noebels, J.L., Mucke, L., 2011. Amyloid-beta/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. J. Neurosci. 31 (2), 700–711.
Rogina, B., Helfand, S.L., 2004. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. Proc. Natl. Acad. Sci. U. S. A. 101 (45), 15998–16003.
Salminen, A., Kaarniranta, K., Kauppinen, A., 2013. Crosstalk between oxidative stress and SIRT1: impact on the aging process. Int. J. Mol. Sci. 14 (2), 3834–3859.
Schieke, S.M., Finkel, T., 2006. Mitochondrial signaling, TOR, and life span. Biol. Chem. 387 (10-11), 1357–1361.

Sen, N., Snyder, S.H., 2010. Protein modifications involved in neurotransmitter and gasotransmitter signaling. Trends Neurosci. 33 (11), 493–502.
Sen, T., Saha, P., Sen, N., 2018. Nitrosylation of GAPDH augments pathological tau acetylation upon exposure to amyloid-beta. Sci. Signal. 11 (522).
Sergeant, N., Delacourte, A., Buee, L., 2005. Tau protein as a differential biomarker of tauopathies. Biochim. Biophys. Acta 1739 (2-3), 179–197.
Shipton, O.A., Leitz, J.R., Dworzak, J., Acton, C.E., Tunbridge, E.M., Denk, F., Dawson, H.N., Vitek, M.P., Wade-Martins, R., Paulsen, O., Vargas-Caballero, M., 2011. Tau protein is required for amyloid {beta}-induced impairment of hippocampal long-term potentiation. J. Neurosci. 31 (5), 1688–1692.
Simic, G., 2002. Pathological tau proteins in argyrophilic grain disease. Lancet Neurol. 1 (5), 276.
Simic, G., Babic Leko, M., Wray, S., Harrington, C., Delalle, I., Jovanov-Milosevic, N., Bazadona, D., Buee, L., de Silva, R., Di Giovanni, G., Wischik, C., Hof, P.R., 2016. Tau Protein Hyperphosphorylation and Aggregation in Alzheimer's Disease and Other Tauopathies, and Possible Neuroprotective Strategies. Biomolecules 6 (1), 6.
Singh, T.J., Grundke-Iqbal, I., Iqbal, K., 1996a. Differential phosphorylation of human tau isoforms containing three repeats by several protein kinases. Arch. Biochem. Biophys. 328 (1), 43–50.
Singh, T.J., Zaidi, T., Grundke-Iqbal, I., Iqbal, K., 1996b. Non-proline-dependent protein kinases phosphorylate several sites found in tau from Alzheimer disease brain. Mol. Cell. Biochem. 154 (2), 143–151.
Sironi, J.J., Yen, S.H., Gondal, J.A., Wu, Q., Grundke-Iqbal, I., Iqbal, K., 1998. Ser-262 in human recombinant tau protein is a markedly more favorable site for phosphorylation by CaMKII than PKA or PhK. FEBS Lett. 436 (3), 471–475.
Spillantini, M.G., Goedert, M., 2013. Tau pathology and neurodegeneration. Lancet Neurol. 12 (6), 609–622.
Spillantini, M.G., Murrell, J.R., Goedert, M., Farlow, M.R., Klug, A., Ghetti, B., 1998. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc. Natl. Acad. Sci. U. S. A. 95 (13), 7737–7741.
Spires-Jones, T.L., Stoothoff, W.H., de Calignon, A., Jones, P.B., Hyman, B.T., 2009. Tau pathophysiology in neurodegeneration: a tangled issue. Trends Neurosci. 32 (3), 150–159.
Stamer, K., Vogel, R., Thies, E., Mandelkow, E., Mandelkow, E.M., 2002. Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. J. Cell Biol. 156 (6), 1051–1063.
Stoothoff, W.H., Johnson, G.V., 2005. Tau phosphorylation: physiological and pathological consequences. Biochim. Biophys. Acta 1739 (2-3), 280–297.
Su, B., Wang, X., Lee, H.G., Tabaton, M., Perry, G., Smith, M.A., Zhu, X., 2010. Chronic oxidative stress causes increased tau phosphorylation in M17 neuroblastoma cells. Neurosci. Lett. 468 (3), 267–271.
Sun, Z., Chin, Y.E., Zhang, D.D., 2009. Acetylation of Nrf2 by p300/CBP augments promoter-specific DNA binding of Nrf2 during the antioxidant response. Mol. Cell. Biol. 29 (10), 2658–2672.
Tokutake, T., Kasuga, K., Yajima, R., Sekine, Y., Tezuka, T., Nishizawa, M., Ikeuchi, T., 2012. Hyperphosphorylation of Tau induced by naturally secreted amyloid-beta at nanomolar concentrations is modulated by insulin-dependent Akt-GSK3beta signaling pathway. J. Biol. Chem. 287 (42), 35222–35233.
Tracy, T.E., Sohn, P.D., Minami, S.S., Wang, C., Min, S.W., Li, Y., Zhou, Y., Le, D., Lo, I., Ponnusamy, R., Cong, X., Schilling, B., Ellerby, L.M., Huganir, R.L., Gan, L., 2016. Acetylated Tau Obstructs KIBRA-Mediated Signaling in Synaptic Plasticity and Promotes Tauopathy-Related Memory Loss. Neuron 90 (2), 245–260.
Vinters, H.V., 2015. Emerging concepts in Alzheimer's disease. Annu. Rev. Pathol. 10, 291–319.
Vossel, K.A., Zhang, K., Brodbeck, J., Daub, A.C., Sharma, P., Finkbeiner, S., Cui, B., Mucke, L., 2010. Tau reduction prevents Abeta-induced defects in axonal transport. Science 330 (6001), 198.
Wang, J.Z., Grundke-Iqbal, I., Iqbal, K., 1996. Restoration of biological activity of Alzheimer abnormally phosphorylated tau by dephosphorylation with protein phosphatase-2A, -2B and -1. Brain Res. Mol. Brain Res. 38 (2), 200–208.
Wang, J.Z., Grundke-Iqbal, I., Iqbal, K., 2007. Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration. Eur. J. Neurosci. 25 (1), 59–68.
Wang, J., Jin, W.S., Bu, X.L., Zeng, F., Huang, Z.L., Li, W.W., Shen, L.L., Zhuang, Z.Q., Fang, Y., Sun, B.L., Zhu, J., Yao, X.Q., Zeng, G.H., Dong, Z.F., Yu, J.T., Hu, Z., Song, W., Zhou, H.D., Jiang, J.X., Liu, Y.H., Wang, Y.J., 2018. Physiological clearance of tau in the periphery and its therapeutic potential for tauopathies. Acta Neuropathol. 136 (4), 525–536.
Wilhelmsen, K.C., Lynch, T., Pavlou, E., Higgins, M., Nygaard, T.G., 1994. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. Am. J. Hum. Genet. 55 (6), 1159–1165.
Wilhelmus, M.M., Grunberg, S.C., Bol, J.G., van Dam, A.M., Hoozemans, J.J., Rozemuller, A.J., Drukarch, B., 2009. Transglutaminases and transglutaminase-catalyzed cross-links colocalize with the pathological lesions in Alzheimer's disease brain. Brain Pathol. 19 (4), 612–622.
Woods, Y.L., Cohen, P., Becker, W., Jakes, R., Goedert, M., Wang, X., Proud, C.G., 2001. The kinase DYRK phosphorylates protein-synthesis initiation factor eIF2Bepsilon at Ser539 and the microtubule-associated protein tau at Thr212: potential role for DYRK as a glycogen synthase kinase 3-priming kinase. Biochem. J. 355 (Pt 3), 609–615.
Xin, S.H., Tan, L., Cao, X., Yu, J.T., Tan, L., 2018. Clearance of Amyloid Beta and Tau in Alzheimer's Disease: from Mechanisms to Therapy. Neurotox. Res. 34 (3), 733–748.
Yan, S.D., Chen, X., Schmidt, A.M., Brett, J., Godman, G., Zou, Y.S., Scott, C.W., Caputo, C., Frappier, T., Smith, M.A., et al., 1994. Glycated tau protein in Alzheimer disease: a mechanism for induction of oxidant stress. Proc. Natl. Acad. Sci. U. S. A. 91 (16), 7787–7791.
Zhang, C.E., Yang, X., Li, L., Sui, X., Tian, Q., Wei, W., Wang, J., Liu, G., 2014. Hypoxia-induced tau phosphorylation and memory deficit in rats. Neurodegener. Dis. 14 (3), 107–116.