Chapter 5

Tau in Tauopathies That Leads to Cognitive Disorders and in Cancer

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Abstract

Tau is a copious microtubule-associated protein mainly expressed in neurons; it is also expressed in non-neuronal cells. Tauopathies are neurodegenerative diseases occurring mostly within the neuronal and glial cells of the central nervous system with a conspicuous tau pathology. In tauopathies, soluble tau disconnects from microtubules and forms abnormal, aggregated filamentous assemblies of hyperphosphorylated tau. Genetic, pathological and biochemical analyses have also proved that tau protein plays a major role in the pathogenesis of several tauopathies. Cognitive disorders are a type of psychological disorders that mainly distress observation, learning, memory, and problem elucidating. Among different cognitive disorders like amnesia, dementia, and delirium tauopathies mainly involve in dementia. Though tau is a neuronal protein, it is also expressed in various non-neuronal cells, like those of the liver, kidney and muscle. The activity of non-neuronal tau, especially in cancer cells, still needs to be elucidated; tau might have significant functions in non-neuronal cells. This chapter describes the associations between tauopathies and cancer.

Keywords: tau, tauopathies, cancer, Alzheimer's disease, microtubule, phosphorylation

1. Introduction

The microtubule-associated protein tau was originally identified as a heat-stable protein that was co-purified with tubulin [1] and is solely expressed in higher eukaryotes [2–4]. Its main functions include controlling microtubule assembly [1, 5, 6], contributing to the polymerization of microtubules [7] and acting as a parameter of axonal transport [8] and axonal diameter [9]. Tau protein is also involved in the formation polarity during neuromas and in neurodegeneration [10]. It also acts as a protein framework to control the signaling pathways. Phosphorylation is the most common post-translation modification of tau protein. Hyperphosphorylation of tau

protein is detected in neurofibrillary tangles (NFTs). NFTs are noticeable in many age-dependent diseases, which are collectively called tauopathies. Tau was not only observed in the nucleoli of non-dividing cells but also in high amounts in the nuclei of cancerous cells that specified a precise protagonist of tau in dividing cells [11]. Hence, tau might have some important functions in fast-dividing cells, which in turn may have an effect on cancer pathogenesis.

In addition to neurons, tau expression has been noticed in human breast, prostate, gastric, colorectal and pancreatic cancer cell lines and tissues [12–18]. Tau is also found in patients with twisted tubulofilamentous of inclusion-body myositis [19]. The activity of non-neuronal tau, especially in cancer cells, still needs to be exemplified. The hyperphosphorylation of tau leads to Alzheimer's disease (AD) and tumor suppressor protein pRB, as well as different cell cycle activators like Cdk4, Cdk2, cyclin D, cyclin B and PCNA are present in the neurons of AD patients; this indicates re-commencement of the cell cycle, which may be a mechanism of neurodegeneration [20]. There are more associations between tauopathies and cancer, as high levels of cancer-related proteins like Fos, Jun and BRCA1 are found in AD [21, 22]. Cancer pathogenesis and tauopathies are also linked with respect to signal transduction, where the prolyl isomerase, Pin1, acts as a main factor [23]. Tauopathies also leads to cognitive discrepancies in for AD.

Tau protein activity is predominantly controlled by its phosphorylation. Two important aspects of cancer, cell signaling pathway and cell cycle progression, can be modulated by tau. Tau might work as a possible modulator of the efficacy of cancer chemotherapy drugs. In some previous experiments involving tau in different cancers, a connection between tau expression and drug resistance was noted [12, 14, 24–27], as a competition between tau and the drugs for microtubule-binding sites occurred. Deregulation of Pin1 can be a crucial protagonist in the pathogenesis of tauopathies and cancer and might be the basis for remarkable new therapies in the future [23]. Finally, there could be a good liaison between age-related tauopathies that leads to dementia that is significant category of cognitive disorders and cancer, mainly because both involve aberrant tau phosphorylation.

2. Tau in tauopathies

The main roles of tau protein are stimulating microtubule assembly and maintaining microtubule stability; these are regulated by its phosphorylation level. The preeminent activity of tau is maintained by its regular phosphorylation level, that is, 2–3 mol phosphate/mol of the protein [28]. The unusual functions of tau protein might be defined by this phosphorylation as well. Tau hyperphosphorylation reduces the microtubule binding and microtubule assembly-forming activity of tau [29, 30]. In case of in vitro experiments, cleaved tau has a high tendency to unfasten from microtubules and subsequently, to aggregate [31].

2.1. Tau gene

A particular gene, MAPT, that resides on chromosome 17q21 encodes tau protein [32]. The size of this gene is more than 50 kb and contains two differently modified haplotypes, H1 and H2 [33, 34]. Because of alternative splicing, several high and low molecular weight isoforms of tau are engendered. Normally, six isoforms of 352–441 amino acids are articulated in tau in the central nervous system (**Figure 1**), which are differentiated by the presence or absence of exons 2, 3 and 10 [3]. Exon 10-containing isoforms are known as four-repeat or 4R isoforms, whereas isoforms excluding exon 10 are known as three-repeat or 3R isoforms.

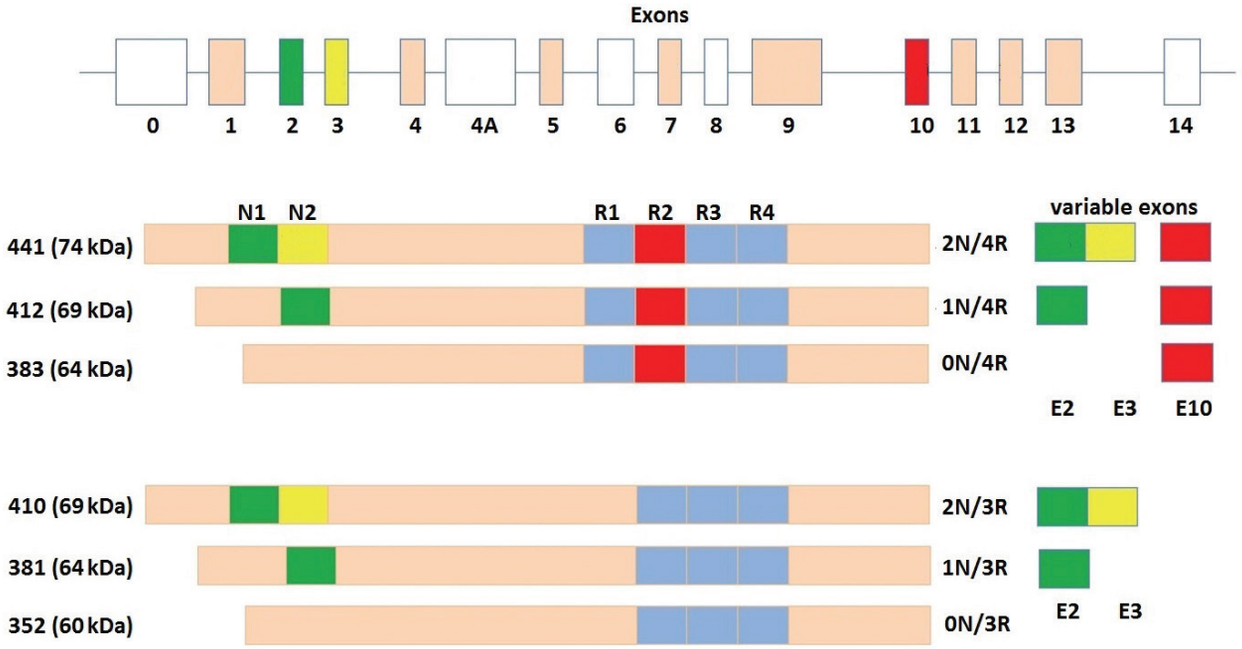

Figure 1. Graphic representation of human tau gene.

2.1.1. Post-translation of tau

There may be several types of post-translation modifications of tau protein, of which phosphorylation is the most common. Phosphorylation occurs when a phosphate group is added by esterification to one of the three amino acids, serine (S), threonine (T) and tyrosine (Y). Increase in phosphorylation decreases the affinity of tau toward microtubules and finally destabilizes cytoskeleton. There are 85 recognized phosphorylation sites described in human AD brain tissue. Among them, 53% phosphorylation sites of tau [45] are serine, 41% sites [41] are threonine while only 6% sites [5] are tyrosine [35–37]. Tau protein also comprises 11 recognized O-glycosylation sites, where the covalent attachment of oligosaccharides to a protein occurs [38]; 12 glycation sites, where non-enzymatic protein glycosylation is routinely detected in mature tissues [39–41], 1 prolyl-isomerization site, where the reaction that relocates the protein disulfide bonds occurs [42, 43]; 3 tau truncation sites, which improve the tau aggregation ability and implement neuronal apoptosis [44–46]; 4 tau nitration sites, where nitrogen oxide adjuncts to the tyrosine of an organic molecule for tau aggregation [47]; 8 tau polyamination sites, which are involved in the NFT formation process [48, 49]; 3 sites of ubiquitination, which is subordinately implicated in tau pathology [50, 51]; 1 site of sumoylation and 1 site of oxidation, which stabilizes ubiquitination and is associated in tau lesion development, respectively [52–55]; and lastly 2 sites of self-aggregation, which reconciles cell toxicity to prime for AD [56]. All of the post-translation modifications are shown in **Figure 2**. Phosphorylation impacts tau's solubility localization, and role and connections, and vulnerability to other post-translational modifications. Additionally, the hyperphosphorylation of tau simulates pathological stoichiometric tau phosphorylation and replicates the structural and functional characteristics of AD [57]. Several phosphorylated sites explicit to diseased tau were discovered by the analysis of soluble and insoluble tau fractions using mass spectrometry [58]. Tau ensures that the axonal microtubules work properly, and lets the neurons function normally, whereas

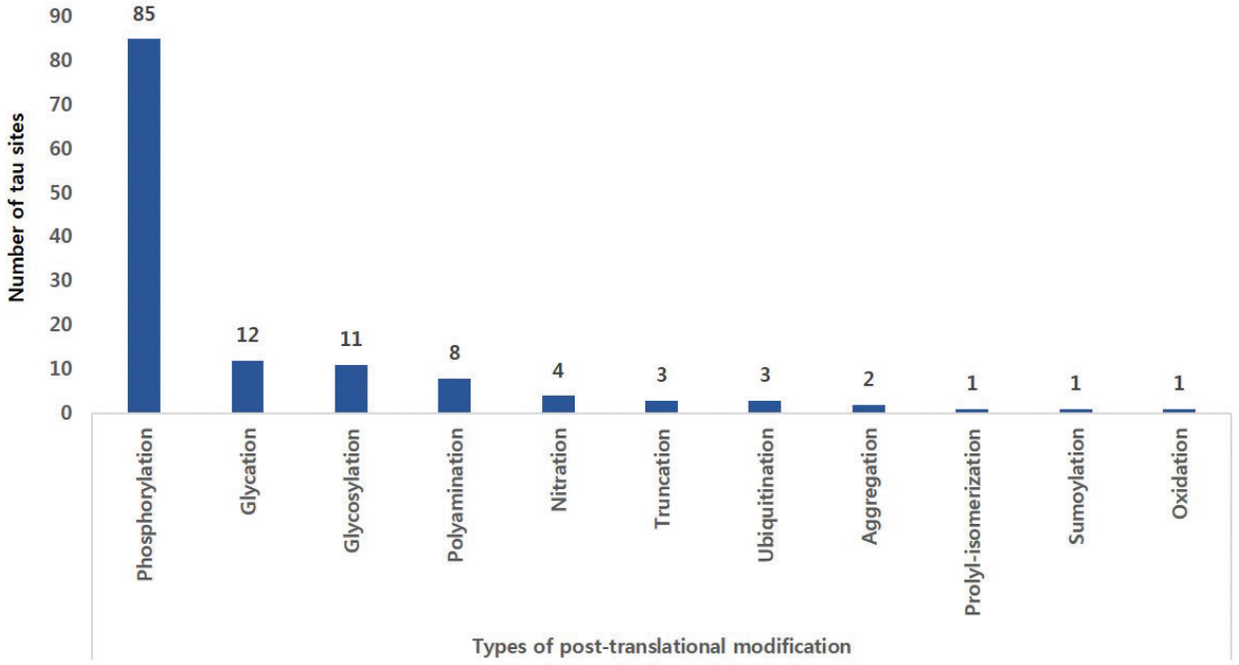

Figure 2. Number of post-translation modifications of tau protein in function.

hyperphosphorylated tau cannot ensure a well-organized microtubule binding and leads to neuronal loss due to the disassembly of microtubules.

2.2. Tauopathies

Neurodegenerative diseases that are caused by abnormally phosphorylated tau mainly in older people are collectively known as tauopathies [59]. In tauopathies, such as AD, tau is uncharacteristically hyperphosphorylated and amassed as NFTs of paired helical filaments (PHFs) [60–65]. The main obsessive mediator of the most prevalent tauopathy, AD, is misfolded tau [66]. Besides AD, several other neuronal diseases such as frontotemporal dementia, Pick's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are also related to microtubule-binding protein tau [67, 68], and these types of central nervous system disorders are called tauopathies. The brains of patients with tauopathies consist of insoluble tau deposition, and the fibrils involved, which are located mainly in the cell bodies and neuronal dendrites, are called as NFTs [69]. Though the reasons of tau aggregation are not clearly identified, the post-translation modification of tau, mainly, hyperphosphorylation, is one of the main reasons for all tauopathies. Tau is phosphorylated at various serine and threonine residues, and hyperphosphorylation subsequently reduces the binding abilities of microtubules [30, 70–72] and increases aggregation [41, 73].

A few tauopathies are briefly described below (**Table 1**).

2.2.1. Alzheimer's disease

AD is the most common type of dementia accounting for anywhere between 50 and 80% of all dementias and can cause a treacherous decline in cognition day by day. Clinically, AD is

Disease	References
Alzheimer's disease	[66, 67, 74]
Down's syndrome	[75–77]
Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17)	[78–80]
Pick's disease	[81–84]
Progressive supranuclear palsy (PSP)	[85–88]
Creutzfeldt-Jakob disease	[89, 90]
Dementia pugilistica	[91, 92]
Inclusion-body myositis	[19, 93–95]
Gerstmann-Sträussler-Scheinker disease (GSS)	[96, 97]
Amyotrophic lateral sclerosis/Parkinsonism-dementia complex	[98]
Argyrophilic grain dementia	[82, 99, 100]
Corticobasal degeneration (CBD)	[101–104]
Diffuse neurofibrillary tangles with calcification	[105, 106]
Hallervorden–Spatz disease	[107, 108]
Multiple system atrophy (MSA)	[109, 110]
Niemann-Pick disease, type C	[111–113]
Progressive subcortical gliosis	[114]
Myotonic dystrophy	[115]

Table 1. List of neurodegenerative disorders that are categorized as tauopathies.

identified by the examination of senile plaques of extracellular Aβ-amyloid peptide deposits and NFTs of intraneuronal tau deposits [116]. AD is also observed in neuropil threads and senile plaques consisting of dystrophic neurites [117]. Tau biochemical analysis revealed that all of the six isoforms of tau are present in AD and that the filaments of NFTs are in a paired helical filamentous form or in twisted ribbons at some places. The apolipoprotein E-4 allele genetically amends periodic AD [118].

2.2.2. Progressive supranuclear palsy

PSP is a neurological syndrome characterized by postural instability and mild dementia, where tangles are present mainly in the subcortical and cortical areas of the brain. PSP is caused by the accretion of NFTs and is a four-repeat tauopathy [119]. It has been reported that a mutation of the tau gene may cause autosomal dominant PSP; environmental risk factors are not involved in PSP. In sporadic cases, the H1 MAPT haplotype has been constantly connected with PSP [119], whereas a different haplotype, H2, seems to be defensive against PSP [120].

2.2.3. Pick's disease

Pick's disease is an infrequent dementia of older people that affects the frontal lobes of the brain and causes speech complications like aphasia, and behavior problems, ultimately leading to death. Pick's disease is a sporadic 3R tauopathy, where insoluble tau accumulates

mainly in neuronal cells and in glial cells, such as prickle-shaped astrocytes and twisted bodies [121]. Like PSP, Pick's disease is also associated with a mutation in the tau gene. However, Pick's disease is not a distinct entity but one of the subtypes of the variety of diseases associated with temporal dementia [122].

2.2.4. Frontotemporal dementia with Parkinsonism associated with chromosome 17 (FTDP-17)

Frontotemporal dementia with Parkinsonism associated with chromosome 17 (FTDP-17) is a neurological disorder that is a part of frontotemporal dementia, categorized by a damage of the neuron in the frontal and temporal lobes of the brain. A loss of these cells can affect personality, behavior, speech and cause motor disturbances. Mutations in the tau gene can cause this dementia. 32 tau gene mutations have been recognized in over 100 families of this syndrome [123]. Tau gene mutations associated with FTDP-17 cause anomalous filament development and an amassing of tau in neuronal and glial cells in the cerebral cortex and in the nuclei of subcortical cells. Tau mutations alter tau isoforms in FTDP-17. The mechanisms of the modifications that lead to neuronal death are yet to be discovered.

2.2.5. Corticobasal degeneration

Corticobasal degeneration (CBD) is an adult variable dementia and neurodegenerative syndrome. This is a sporadic disease accounting for one per million cases of dementia per year; the incidence of CBD is ten times lesser than that of Parkinson's disease [124]. In case of CBD, filamentous inclusions in neurons and glia having selective accumulation of hyperphosphorylated four microtubule-binding repeat tau (4R-tau) are seen [125]. The tau H1 MAPT haplotype is also stalwartly related with CBD pathology, just as it is with PSP [120].

3. Tau in cancer

Tau expression has also been noticed in different non-neuronal cells like those of the liver, kidney, muscle and so on [126, 127] Tau protein has also been expressed in human breast, prostate, gastric and pancreatic cancer cell lines and tissues [12–16]. Tau is also found in patients with twisted tubulofilaments of inclusion-body myositis [19].

As both cancer and AD are age-related diseases, and as both diseases occur mainly in developed countries with similar dietary habits, there might be some correlation between the two diseases. Additionally, tau-positive and tau-negative cancer cells show different results after treatment with chemotherapeutic agents like paclitaxel [14].

In case of breast cancer, 52% patients are tau negative [14]. An approximately same result (57%) of tau expression in breast cancer was found in a research by a different group [128]. There are a lot of experiments based on breast cancer that show different percentages of tau negative. In case of gastric cancer, 30% patients are tau negative [15], whereas 25.7% patients are tau negative in case of ovarian cancer [25]. These results suggest that tau protein expression may be diverse for different cancer sites. The causes of different cell lines expressed as tau positive or negative are not clear enough. In case of prostate cancer, androgen-independent prostate lines

show a considerably higher level of tau than androgen-dependent cells lines. Even androgen-independent derivative cell line isolated from androgen-dependent line shows higher amount of tau than that of the original cells. Also, in case of ovarian cancer cells, endometrioid carcinoma cell types express higher levels of tau protein compared to other cells. Estrogen also regulates tau protein expression [129]. A more extensive analysis will be required to confirm all of these causes of tau expression level of different cell lines.

Tau escalates the deceiving and reconnection of isolated breast tumor cells, and circulatory tumor cells might be responsible for increased risk of disease repetition. That is why the pathological assessment of tau may be useful for patients by diminishing metastasis through circulatory tumor cells mobilization [130].

Heat shock protein (Hsp90) inhibitors are used as possible cancer treatment agents as several cancer-related proteins become stable by cooperating with Hsp90. Numerous Hsp90 inhibitors reduced tau phosphorylation at different sites of phosphorylation in cells overexpressing mutated human tau [131–134].

Pin1 (peptidyl-prolyl cis/trans isomerase (PPIase)) bonds to phosphorylated tau on the Thr231-pro site and catalyzes the isomerization of pSer/Thr-pro motifs, to prompt conformational changes in tau. These changes keep back the ability of phosphorylated tau to bind microtubules and inspire microtubule-binding abilities, thereby dephosphorylating tau protein via its phosphatase, the protein phosphatase 2 (PP2A) [135]. It is noteworthy that Pin1 is overexpressed in various types of human cancers and is also an outstanding prognostic marker in different cancers [136–138]. Pin1 is a molecular target for cancer therapeutics, as its inhibition in cancer cells can elicit apoptosis and conquer the renovated phenotype [139–141].

The deficiency of active Pin1 is responsible for unusual tau accumulation whereas Pin1 controls cell cycle and is essential for cell division. Pin1 overexpression increases oncogenesis by different cell signaling pathways. There might have been an antithetical association between tauopathies and cancer explained by Pin1 [142].

Many proline-directed protein kinases, such as cyclin-dependent kinases (CDKs), mitogen-activated protein kinase (MAPKs), glycogen synthesis kinases (GSKs) and PP2A, govern the reversible phosphorylation of tau [143–145].

Tau has some roles in signal transduction. There is a high volume of proline residues found in different domains of tau [146] that can interrelate with Src homology 3 (SH3) domain [147]. Tau can also interrelate with the SH3 domain of Src, Fyn and Lck, as revealed by the Glutathione S-transferase (GST) fusion binding assay [148]. The bonding of tau to microtubules has a significant effect on the tau-Fyn interactions, as observed by the biochemical analysis of tau-Fyn binding affinity [149]. Tau could encourage the activity of Src family kinases to measure tau's binding affinity for microtubules, thus resulting in tyrosine phosphorylation. In taxol-stabilized microtubules, Fyn can perform tyrosine phosphorylation without tau; phosphorylation of tubulin increases drastically if tau is added [150]. Hence, the relationship between tau and non-microtubule proteins might have a possibly noteworthy functional significance.

Initially, tau was isolated from the brain, but shortly after that, tau availability was not limited to neurons. In one of the initial experiments, non-neuronal tau from both primary human monocytes

and U297 lymphoma cells were studied, and both total and phosphor-specific tau were observed [151]. Several other experiments also exposed the availability of tau in different cell lines and tissues. Some of those experiments were very brief and only a northern or western blot was done to show the availability of tau mRNA or protein, respectively, from the liver and kidney of mice and other tissues of rats [126, 127]. Some of the experiments detected multiple tau isoforms and pointed out the correspondence between non-neuronal tau and neuronal tau [152], whereas others showed the microtubule-binding properties of tau from hepatoma and fibroblast cells [153]. From these experiments, it is clear that tau from both neuronal and non-neuronal cells might show similar properties. In one experiment using several human cell types including HeLa cells, lymphocytes and non-transformed skin fibroblasts, tau was not only observed in the nucleoli of non-dividing cells but also observed in higher amounts in the nuclei of cancerous cells that specified a precise protagonist of tau in dividing cells [11]. Hence, tau might have some important functions in fast-dividing cells, which might have an effect on cancer.

Tau might work as a possible modulator of drug resistance. Microtubule-targeting drug estramustine-resistant [154] E4 cells expressed a massive amount of tau at both the mRNA and the protein levels, unlike DU145 cells [13]. This experiment exposed significance of the incidence of tau in non-neuronal cells; this might have a connection with signal transduction and tau's microtubule-binding properties. The expression of tau is considerably diverse in cases of residual disease or in those with a pathological complete response (pCR) in patients with breast cancer undergoing chemotherapy by the microtubule-depolymerizing drug, paclitaxel. The residual disease group expressed more tau than the pCR group [14]. siRNA knockdown tau is more vulnerable to paclitaxel treatment than the wild-type tau in case of breast cancer cells [14, 26]. A nearly similar report was published, about the relationship between tau and paclitaxel resistance in case of gastric cancer [15].

As hyperphosphorylation of tau leads to AD, and tumor suppressor pRB protein as well as different cell cycle activators like Cdk4, Cdk2, cyclin D, cyclin B and PCNA are also present in the neurons of patients with AD, there might be an insinuation of the re-commencement of the cell cycle, which could be a mechanism of neurodegeneration [20]. In case of other neurodegenerative disorders that might be caused by tau protein including FTDP-17, PSP and CBD, these cell cycle activators were found [155]. Tau phosphorylation occurred at disease-relevant sites of primary rat neurons after insertion of oncogenes [156]. This is suggested by the fact that abnormal tau-related diseases are linked to cell cycle markers in several diseases, including cancer. The aged control mouse does not express the increase of the cell cycle marker, PCNA and cyclin D; this was responsible for the sign of neurodegeneration [157]. For normal human tau-expressing transgenic mice, increased tau phosphorylation occurred, along with insoluble tau being found in the brains of aged mice [157]. This suggests that irregular cell cycle re-entry might explain the presence of tau. CNS tissue from the *Drosophila* model used to study neurodegenerative diseases exhibited an increase in the cell cycle markers, PCNA and phosphor-histone 3, as well as neuronal loss [158], which is also evidence that tau drives cell cycle re-entry. The visible neuronal loss in *Drosophila* for either wild-type or mutant tau was overturned by hindering the mammalian target-of-rapamycin (mTOR) pathway, as well as by obstructing the cell cycle in different ways [158]. This finding also links cell signaling with tau-activated neurodegeneration. There are further associations between AD and cancer, as high levels of cancer-related proteins like Fos, Jun and BRCA1 are found in AD [21, 22].

Overexpression of Pin1, which is responsible for some types of cancer, works together with tau in a phosphorylation-dependent way to carry out tau phosphorylation at Thr231 [159]. Brains of patients with AD comprise less Pin1 than aged-matched normal brains; hyperphosphorylation of tau, behavioral defects as well as other forms of neurodegeneration might have occurred, owing to the loss of Pin1 [160]. When one copy of the p73 gene, a p53 family member that regulates Pin1 [161], was missing, thus leaving only one efficient copy, age-related neurodegeneration and tau hyperphosphorylation were induced [162]. Although tau influences neuronal death, its mechanism for doing so is not clear.

Two important properties of cancer, cell signaling pathway and cell cycle progression, can be modulated by tau. As both AD and most cancers are primarily observed in aged populations, the role of tau in cancer cells may be linked with tauopathies.

Patients with AD have a lower risk of different cancers. The genes that are overexpressed in AD and Parkinson's disease-type CNS diseases were downregulated in different cancers like lung, colon and prostate cancer and vice versa [163].

4. Tau in chemotherapy

Folic acid (also called folate or vitamin B9) intensities can plummet due to the influence of certain chemotherapy drugs used for cancer treatment. Chemotherapy-initiated folic acid insufficiency prompts abnormal tau phosphorylation, which can lead to different tauopathies like AD [164].

Paclitaxel is one of the most important chemotherapy drugs for cancer treatment; it binds to beta-tubulin in the same place as tau protein. Cancer cells with a low tau expression show a higher sensitivity to paclitaxel, whereas those with a high expression of tau display a resistance to paclitaxel-related chemotherapy. In case of breast cancer, low tau expressions are favorable for paclitaxel administration during chemotherapy.

Tau-negative expression can be used to select gastric cancer patients for paclitaxel treatment, on the basis whether paclitaxel is more functional in cells with low or no tau expression [165]. Tau expression analysis should be considered for taxane-based chemotherapy for some types of bladder cancer, as tumors with low tau expression display an enhanced response to chemotherapy [166]. Tau expression is associated with the sensitivity of breast cancer cells to taxane-based chemotherapy; patients with low or no tau expression should be more responsive to chemotherapy than patients with high expression of tau [24, 167]. Tau expression is also a potential marker for response to chemotherapy and subsequent survival in lung, ovarian, pancreatic and prostate cancer.

Nowadays, some drugs used for the treatment of cancer are also used for the treatment of different neurological disorders like Parkinson's disease and AD. Nilotinib is an FDA-approved protein tyrosine kinase inhibitor (TKI), which is used for the treatment of chronic myeloid leukemia. It also targets AD, which produces neuroinflammation and misfolded proteins, to ultimately reduce cognitive damage. In Parkinson's disease, nilotinib triggers autophagy to remove hyperphosphorylated tau from the brain before they accumulate as plaques [168, 169].

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References

[1] Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. Proceedings of the National Academy of Sciences of the United States of America. 1975;**72**(5):1858-1862

[2] Cambiazo V, Gonzalez M, Maccioni RB. DMAP-85: A tau-like protein from *Drosophila melanogaster* larvae. Journal of Neurochemistry. 1995;**64**(3):1288-1297

[3] Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA. Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of Alzheimer's disease. Neuron. 1989;**3**(4):519-526

[4] Goedert M, Baur CP, Ahringer J, Jakes R, Hasegawa M, Spillantini MG, et al. PTL-1, a microtubule-associated protein with tau-like repeats from the nematode *Caenorhabditis elegans*. Journal of Cell Science. 1996;**109**(Pt 11):2661-2672

[5] Cleveland DW, Hwo SY, Kirschner MW. Purification of tau, a microtubule-associated protein that induces assembly of microtubules from purified tubulin. Journal of Molecular Biology. 1977;**116**(2):207-225

[6] Fellous A, Francon J, Lennon AM, Nunez J. Microtubule assembly in vitro. Purification of assembly-promoting factors. European Journal of Biochemistry. 1977;**78**(1):167-174

[7] Witman GB, Cleveland DW, Weingarten MD, Kirschner MW. Tubulin requires tau for growth onto microtubule initiating sites. Proceedings of the National Academy of Sciences of the United States of America. 1976;**73**(11):4070-4074

[8] Dixit R, Ross JL, Goldman YE, Holzbaur EL. Differential regulation of dynein and kinesin motor proteins by tau. Science. 2008;**319**(5866):1086-1089

[9] Harada A, Oguchi K, Okabe S, Kuno J, Terada S, Ohshima T, et al. Altered microtubule organization in small-calibre axons of mice lacking tau protein. Nature. 1994;**369**(6480):488-491

[10] Caceres A, Kosik KS. Inhibition of neurite polarity by tau antisense oligonucleotides in primary cerebellar neurons. Nature. 1990;**343**(6257):461-463

[11] Thurston VC, Zinkowski RP, Binder LI. Tau as a nucleolar protein in human nonneural cells in vitro and in vivo. Chromosoma. 1996;**105**(1):20-30

[12] Souter S, Lee G. Microtubule-associated protein tau in human prostate cancer cells: Isoforms, phosphorylation, and interactions. Journal of Cellular Biochemistry. 2009;**108**(3): 555-564

[13] Sangrajrang S, Denoulet P, Millot G, Tatoud R, Podgorniak MP, Tew KD, et al. Estramustine resistance correlates with tau over-expression in human prostatic carcinoma cells. International Journal of Cancer. 1998;**77**(4):626-631

[14] Rouzier R, Rajan R, Wagner P, Hess KR, Gold DL, Stec J, et al. Microtubule-associated protein tau: A marker of paclitaxel sensitivity in breast cancer. Proceedings of the National Academy of Sciences of the United States of Americ. 2005;**102**(23):8315-8320

[15] Mimori K, Sadanaga N, Yoshikawa Y, Ishikawa K, Hashimoto M, Tanaka F, et al. Reduced tau expression in gastric cancer can identify candidates for successful paclitaxel treatment. British Journal of Cancer. 2006;**94**(12):1894-1897

[16] Jimeno A, Hallur G, Chan A, Zhang XF, Cusatis G, Chan F, et al. Development of two novel benzoylphenylurea sulfur analogues and evidence that the microtubule-associated protein tau is predictive of their activity in pancreatic cancer. Molecular Cancer Therapeutics. 2007;**6**(5):1509-1516

[17] Huda MN, Kim DH, Erdene-Ochir E, Kim YS, Pan CH. Expression, phosphorylation, localization, and microtubule binding of tau in colorectal cell lines. Applied Biological Chemistry. 2016;**59**(6):807-812

[18] Huda MN, Erdene-Ochir E, Pan C-H. Assay for phosphorylation and microtubule binding along with localization of tau protein in colorectal cancer cells. Journal of Visualized Experiments. 2017;**128**:e55932

[19] Askanas V, Engel WK, Bilak M, Alvarez RB, Selkoe DJ. Twisted tubulofilaments of inclusion body myositis muscle resemble paired helical filaments of Alzheimer brain and contain hyperphosphorylated tau. The American Journal of Pathology. 1994;**144**(1):177-187

[20] Becker EBE, Bonni A. Cell cycle regulation of neuronal apoptosis in development and disease. Progress in Neurobiology. 2004;**72**(1):1-25

[21] Anderson AJ, Cummings BJ, Cotman CW. Increased Immunoreactivity for Jun-related and Fos-related proteins in Alzheimers-disease-association with pathology. Experimental Neurology. 1994;**125**(2):286-295

[22] Marcus DL, Strafaci JA, Miller DC, Masia S, Thomas CG, Rosman J, et al. Quantitative neuronal c-Fos and c-Jun expression in Alzheimer's disease. Neurobiology of Aging. 1998;**19**(5):393-400

[23] Lu KP. Pinning down cell signaling, cancer and Alzheimer's disease. Trends in Biochemical Sciences. 2004;**29**(4):200-209

[24] Li ZH, Xiong QY, Tu JH, Gong Y, Qiu W, Zhang HQ, et al. Tau proteins expressions in advanced breast cancer and its significance in taxane-containing neoadjuvant chemotherapy. Medical Oncology. 2013;**30**(3):591

[25] Smoter M, Bodnar L, Grala B, Stec R, Zieniuk K, Kozlowski W, et al. Tau protein as a potential predictive marker in epithelial ovarian cancer patients treated with paclitaxel/platinum first-line chemotherapy. Journal of Experimental and Clinical Cancer Research. 2013;**32**

[26] Wagner P, Wang B, Clark E, Lee H, Rouzier R, Pusztai L. Microtubule associated protein (MAP)-tau—A novel mediator of paclitaxel sensitivity in vitro and in vivo. Cell Cycle. 2005;**4**(9):1149-1152

[27] Wang Q, Wang NY, Shao GY, Qian JZ, Shen D, Fei YH, et al. Relationship between gastric cancer tau protein expression and paclitaxel sensitivity. Pathology Oncology Research. 2013;**19**(3):429-435

[28] Kopke E, Tung YC, Shaikh S, Alonso AC, Iqbal K, Grundke-Iqbal I. Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. The Journal of Biological Chemistry. 1993;**268**(32):24374-24384

[29] Lindwall G, Cole RD. Phosphorylation affects the ability of tau protein to promote microtubule assembly. The Journal of Biological Chemistry. 1984;**259**(8):5301-5305

[30] Alonso AC, Zaidi T, Grundke-Iqbal I, Iqbal K. Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1994;**91**(12):5562-5566

[31] Zhao Y, Tseng IC, Heyser CJ, Rockenstein E, Mante M, Adame A, et al. Appoptosin-mediated caspase cleavage of tau contributes to progressive supranuclear palsy pathogenesis. Neuron. 2015;**87**(5):963-975

[32] Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA. Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. Brain Research. 1986;**387**(3):271-280

[33] Andreadis A, Brown WM, Kosik KS. Structure and novel exons of the human tau gene. Biochemistry. 1992;**31**(43):10626-10633

[34] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Human Molecular Genetics. 1999;**8**(4):711-715

[35] Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Research. Brain Research Reviews. 2000;**33**(1):95-130

[36] Hanger DP, Anderton BH, Noble W. Tau phosphorylation: The therapeutic challenge for neurodegenerative disease. Trends in Molecular Medicine. 2009;**15**(3):112-119

[37] Sergeant N, Bretteville A, Hamdane M, Caillet-Boudin ML, Grognet P, Bombois S, et al. Biochemistry of Tau in Alzheimer's disease and related neurological disorders. Expert Review of Proteomics. 2008;**5**(2):207-224

[38] Martin L, Latypova X, Terro F. Post-translational modifications of tau protein: Implications for Alzheimer's disease. Neurochemistry International. 2011;**58**(4):458-471

[39] Kuhla B, Haase C, Flach K, Luth HJ, Arendt T, Munch G. Effect of pseudophosphorylation and cross-linking by lipid peroxidation and advanced glycation end product precursors on tau aggregation and filament formation. The Journal of Biological Chemistry. 2007;**282**(10):6984-6991

[40] Nacharaju P, Ko L, Yen SH. Characterization of in vitro glycation sites of tau. Journal of Neurochemistry. 1997;**69**(4):1709-1719

[41] Necula M, Kuret J. Pseudophosphorylation and glycation of tau protein enhance but do not trigger fibrillization in vitro. The Journal of Biological Chemistry. 2004;**279**(48): 49694-49703

[42] Bulbarelli A, Lonati E, Cazzaniga E, Gregori M, Masserini M. Pin1 affects tau phosphorylation in response to Abeta oligomers. Molecular and Cellular Neurosciences. 2009;**42**(1):75-80

[43] Zhou XZ, Kops O, Werner A, Lu PJ, Shen M, Stoller G, et al. Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins. Molecular Cell. 2000;**6**(4):873-883

[44] Basurto-Islas G, Luna-Munoz J, Guillozet-Bongaarts AL, Binder LI, Mena R, Garcia-Sierra F. Accumulation of aspartic acid421- and glutamic acid391-cleaved tau in neurofibrillary tangles correlates with progression in Alzheimer disease. Journal of Neuropathology and Experimental Neurology. 2008;**67**(5):470-483

[45] Fasulo L, Ugolini G, Cattaneo A. Apoptotic effect of caspase-3 cleaved tau in hippocampal neurons and its potentiation by tau FTDP-mutation N279K. Journal of Alzheimer's Disease. 2005;**7**(1):3-13

[46] Garcia-Sierra F, Mondragon-Rodriguez S, Basurto-Islas G. Truncation of tau protein and its pathological significance in Alzheimer's disease. Journal of Alzheimer's Disease. 2008;**14**(4):401-409

[47] Horiguchi T, Uryu K, Giasson BI, Ischiropoulos H, LightFoot R, Bellmann C, et al. Nitration of tau protein is linked to neurodegeneration in tauopathies. The American Journal of Pathology. 2003;**163**(3):1021-1031

[48] Murthy SN, Wilson JH, Lukas TJ, Kuret J, Lorand L. Cross-linking sites of the human tau protein, probed by reactions with human transglutaminase. Journal of Neurochemistry. 1998;**71**(6):2607-2614

[49] Halverson RA, Lewis J, Frausto S, Hutton M, Muma NA. Tau protein is cross-linked by transglutaminase in P301L tau transgenic mice. The Journal of Neuroscience. 2005;**25**(5):1226-1233

[50] Iqbal K, Grundke-Iqbal I. Ubiquitination and abnormal phosphorylation of paired helical filaments in Alzheimer's disease. Molecular Neurobiology. 1991;**5**(2-4):399-410

[51] Iqbal K, Alonso AC, Gong CX, Khatoon S, Pei JJ, Wang JZ, et al. Mechanisms of neurofibrillary degeneration and the formation of neurofibrillary tangles. Journal of Neural Transmission. Supplementum. 1998;**53**:169-180

[52] Dorval V, Fraser PE. Small ubiquitin-like modifier (SUMO) modification of natively unfolded proteins tau and alpha-synuclein. The Journal of Biological Chemistry. 2006;**281**(15):9919-9924

[53] Takahashi K, Ishida M, Komano H, Takahashi H. SUMO-1 immunoreactivity co-localizes with phospho-tau in APP transgenic mice but not in mutant tau transgenic mice. Neuroscience Letters. 2008;**441**(1):90-93

[54] Schweers O, Mandelkow EM, Biernat J, Mandelkow E. Oxidation of cysteine-322 in the repeat domain of microtubule-associated protein tau controls the in vitro assembly of paired helical filaments. Proceedings of the National Academy of Sciences of the United States of America. 1995;**92**(18):8463-8467

[55] Su B, Wang X, Lee HG, Tabaton M, Perry G, Smith MA, et al. Chronic oxidative stress causes increased tau phosphorylation in M17 neuroblastoma cells. Neuroscience Letters. 2010;**468**(3):267-271

[56] Bulic B, Pickhardt M, Schmidt B, Mandelkow EM, Waldmann H, Mandelkow E. Development of tau aggregation inhibitors for Alzheimer's disease. Angewandte Chemie (International Ed. in English). 2009;**48**(10):1740-1752

[57] Fath T, Eidenmuller J, Brandt R. Tau-mediated cytotoxicity in a pseudohyperphosphorylation model of Alzheimer's disease. The Journal of Neuroscience. 2002;**22**(22):9733-9741

[58] Hasegawa M, Morishima-Kawashima M, Takio K, Suzuki M, Titani K, Ihara Y. Protein sequence and mass spectrometric analyses of tau in the Alzheimer's disease brain. The Journal of Biological Chemistry. 1992;**267**(24):17047-17054

[59] Lee G, Leugers CJ. Tau and tauopathies. Progress in Molecular Biology and Translational Science. 2012;**107**:263-293

[60] Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. The Journal of Biological Chemistry. 1986;**261**(13):6084-6089

[61] Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proceedings of the National Academy of Sciences of the United States of America. 1986;**83**(13):4913-4917

[62] Iqbal K, Grundke-Iqbal I, Zaidi T, Merz PA, Wen GY, Shaikh SS, et al. Defective brain microtubule assembly in Alzheimer's disease. Lancet. 1986;**2**(8504):421-426

[63] Iqbal K, Grundke-Iqbal I, Smith AJ, George L, Tung YC, Zaidi T. Identification and localization of a tau peptide to paired helical filaments of Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1989;**86**(14):5646-5650

[64] Lee VM, Balin BJ, Otvos L Jr, Trojanowski JQ. A68: A major subunit of paired helical filaments and derivatized forms of normal tau. Science. 1991;**251**(4994):675-678

[65] Iqbal K, Alonso Adel C, Chen S, Chohan MO, El-Akkad E, Gong CX, et al. Tau pathology in Alzheimer disease and other tauopathies. Biochimica et Biophysica Acta. 2005;**1739**(2-3):198-210

[66] Brunden KR, Trojanowski JQ, Lee VM. Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. Nature Reviews Drug Discovery. 2009;**8**(10):783-793

[67] Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nature Reviews Neuroscience. 2007;**8**(9):663-672

[68] Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annual Review of Neuroscience. 2001;**24**:1121-1159

[69] Kidd M. Paired helical filaments in electron microscopy of Alzheimer's disease. Nature. 1963;**197**:192-193

[70] Merrick SE, Trojanowski JQ, Lee VM. Selective destruction of stable microtubules and axons by inhibitors of protein serine/threonine phosphatases in cultured human neurons. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 1997;**17**(15):5726-5737

[71] Wagner U, Utton M, Gallo JM, Miller CC. Cellular phosphorylation of tau by GSK-3 beta influences tau binding to microtubules and microtubule organisation. Journal of Cell Science. 1996;**109**(Pt 6):1537-1543

[72] Alonso AC, Grundke-Iqbal I, Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nature Medicine. 1996;**2**(7):783-787

[73] Kins S, Crameri A, Evans DR, Hemmings BA, Nitsch RM, Gotz J. Reduced protein phosphatase 2A activity induces hyperphosphorylation and altered compartmentalization of tau in transgenic mice. The Journal of Biological Chemistry. 2001;**276**(41):38193-38200

[74] Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Current Alzheimer Research. 2010;**7**(8):656-664

[75] Giaccone G, Tagliavini F, Linoli G, Bouras C, Frigerio L, Frangione B, et al. Down patients: Extracellular preamyloid deposits precede neuritic degeneration and senile plaques. Neuroscience Letters. 1989;**97**(1-2):232-238

[76] Flament S, Delacourte A, Mann DM. Phosphorylation of tau proteins: A major event during the process of neurofibrillary degeneration. A comparative study between Alzheimer's disease and Down's syndrome. Brain Research. 1990;**516**(1):15-19

[77] Yin X, Jin N, Shi J, Zhang Y, Wu Y, Gong CX, et al. Dyrk1A overexpression leads to increase of 3R-tau expression and cognitive deficits in Ts65Dn down syndrome mice. Scientific Reports. 2017;**7**(1):619

[78] Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. American Journal of Human Genetics. 1994;**55**(6):1159-1165

[79] Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: A consensus conference. Conference participants. Annals of Neurology. 1997;**41**(6):706-715

[80] Tacik P, Sanchez-Contreras M, DeTure M, Murray ME, Rademakers R, Ross OA, et al. Clinicopathologic heterogeneity in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) due to microtubule-associated protein tau (MAPT) p.P301L mutation, including a patient with globular glial tauopathy. Neuropathology and Applied Neurobiology. 2017;**43**(3):200-214

[81] Murayama S, Mori H, Ihara Y, Tomonaga M. Immunocytochemical and ultrastructural studies of Pick's disease. Annals of Neurology. 1990;**27**(4):394-405

[82] Perry G, Stewart D, Friedman R, Manetto V, Autilio-Gambetti L, Gambetti P. Filaments of Pick's bodies contain altered cytoskeletal elements. The American Journal of Pathology. 1987;**127**(3):559-568

[83] Lieberman AP, Trojanowski JQ, Lee VM, Balin BJ, Ding XS, Greenberg J, et al. Cognitive, neuroimaging, and pathological studies in a patient with Pick's disease. Annals of Neurology. 1998;**43**(2):259-265

[84] Rockenstein E, Ubhi K, Mante M, Florio J, Adame A, Winter S, et al. Neuroprotective effects of Cerebrolysin in triple repeat tau transgenic model of Pick's disease and frontotemporal tauopathies. BMC Neuroscience. 2015;**16**:85

[85] Bancher C, Lassmann H, Budka H, Grundke-Iqbal I, Iqbal K, Wiche G, et al. Neurofibrillary tangles in Alzheimer's disease and progressive supranuclear palsy: Antigenic similarities and differences. Microtubule-associated protein tau antigenicity is prominent in all types of tangles. Acta Neuropathologica. 1987;**74**(1):39-46

[86] Flament S, Delacourte A, Verny M, Hauw JJ, Javoy-Agid F. Abnormal tau proteins in progressive supranuclear palsy. Similarities and differences with the neurofibrillary degeneration of the Alzheimer type. Acta Neuropathologica. 1991;**81**(6):591-596

[87] Schmidt ML, Huang R, Martin JA, Henley J, Mawal-Dewan M, Hurtig HI, et al. Neurofibrillary tangles in progressive supranuclear palsy contain the same tau epitopes identified in Alzheimer's disease PHFtau. Journal of Neuropathology and Experimental Neurology. 1996;**55**(5):534-539

[88] Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU. Advances in progressive supranuclear palsy: New diagnostic criteria, biomarkers, and therapeutic approaches. The Lancet Neurology. 2017;**16**(7):552-563

[89] Hsiao K, Dlouhy SR, Farlow MR, Cass C, Da Costa M, Conneally PM, et al. Mutant prion proteins in Gerstmann-Straussler-Scheinker disease with neurofibrillary tangles. Nature Genetics. 1992;**1**(1):68-71

[90] Kovacs GG, Rahimi J, Strobel T, Lutz MI, Regelsberger G, Streichenberger N, et al. Tau pathology in Creutzfeldt-Jakob disease revisited. Brain Pathology. 2017;**27**(3):332-344

[91] Roberts GW, Allsop D, Bruton C. The occult aftermath of boxing. Journal of Neurology, Neurosurgery, and Psychiatry. 1990;**53**(5):373-378

[92] Areza-Fegyveres R, Rosemberg S, Castro RM, Porto CS, Bahia VS, Caramelli P, et al. Dementia pugilistica with clinical features of Alzheimer's disease. Arquivos de Neuro-psiquiatria. 2007;**65**(3B):830-833

[93] Mendell JR, Sahenk Z, Gales T, Paul L. Amyloid filaments in inclusion body myositis. Novel findings provide insight into nature of filaments. Archives of Neurology. 1991;**48**(12):1229-1234

[94] Askanas V, Engel WK, Alvarez RB. Light and electron microscopic localization of beta-amyloid protein in muscle biopsies of patients with inclusion-body myositis. The American Journal of Pathology. 1992;**141**(1):31-36

[95] Askanas V, Engel WK. Inclusion-body myositis: Muscle-fiber molecular pathology and possible pathogenic significance of its similarity to Alzheimer's and Parkinson's disease brains. Acta Neuropathologica. 2008;**116**(6):583-595

[96] Ghetti B, Tagliavini F, Masters CL, Beyreuther K, Giaccone G, Verga L, et al. Gerstmann-Straussler-Scheinker disease. II. Neurofibrillary tangles and plaques with PrP-amyloid coexist in an affected family. Neurology. 1989;**39**(11):1453-1461

[97] Ishizawa K, Komori T, Shimazu T, Yamamoto T, Kitamoto T, Shimazu K, et al. Hyperphosphorylated tau deposition parallels prion protein burden in a case of Gerstmann-Straussler-Scheinker syndrome P102L mutation complicated with dementia. Acta Neuropathologica. 2002;**104**(4):342-350

[98] Steele JC. Parkinsonism-dementia complex of Guam. Movement Disorders. 2005; **20**(Suppl 12):S99-S107

[99] Braak H, Braak E. Argyrophilic grains: Characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. Neuroscience Letters. 1987;**76**(1):124-127

[100] Itagaki S, McGeer PL, Akiyama H, Beattie BL, Walker DG, Moore GR, et al. A case of adult-onset dementia with argyrophilic grains. Annals of Neurology. 1989;**26**(5):685-689

[101] Paulus W, Selim M. Corticonigral degeneration with neuronal achromasia and basal neurofibrillary tangles. Acta Neuropathologica. 1990;**81**(1):89-94

[102] Ksiezak-Reding H, Morgan K, Mattiace LA, Davies P, Liu WK, Yen SH, et al. Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration. The American Journal of Pathology. 1994;**145**(6):1496-1508

[103] Mori H, Nishimura M, Namba Y, Oda M. Corticobasal degeneration: A disease with widespread appearance of abnormal tau and neurofibrillary tangles, and its relation to progressive supranuclear palsy. Acta Neuropathologica. 1994;**88**(2):113-121

[104] Wakabayashi K, Oyanagi K, Makifuchi T, Ikuta F, Homma A, Homma Y, et al. Corticobasal degeneration: Etiopathological significance of the cytoskeletal alterations. Acta Neuropathologica. 1994;**87**(6):545-553

[105] Kosaka K. Diffuse neurofibrillary tangles with calcification: A new presenile dementia. Journal of Neurology, Neurosurgery, and Psychiatry. 1994;**57**(5):594-596

[106] Kosaka K. Response to 'Challenging the concept of diffuse neurofibrillary tangles with calcification (Kosaka-Shibayama disease). Psychiatry and Clinical Neurosciences. 2017;**71**(1):70-71

[107] Eidelberg D, Sotrel A, Joachim C, Selkoe D, Forman A, Pendlebury WW, et al. Adult onset Hallervorden-Spatz disease with neurofibrillary pathology. A discrete clinico-pathological entity. Brain. 1987;**110**(Pt 4):993-1013

[108] Zarranz JJ, Gomez-Esteban JC, Atares B, Lezcano E, Forcadas M. Tau-predominant-associated pathology in a sporadic late-onset Hallervorden-Spatz syndrome. Movement Disorders: Official Journal of the Movement Disorder Society. 2006;**21**(1):107-111

[109] Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). Journal of the Neurological Sciences. 1989;**94**(1-3):79-100

[110] Nagaishi M, Yokoo H, Nakazato Y. Tau-positive glial cytoplasmic granules in multiple system atrophy. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2011;**31**(3):299-305

[111] Auer IA, Schmidt ML, Lee VM, Curry B, Suzuki K, Shin RW, et al. Paired helical filament tau (PHFtau) in Niemann-Pick type C disease is similar to PHFtau in Alzheimer's disease. Acta Neuropathologica. 1995;**90**(6):547-551

[112] Love S, Bridges LR, Case CP. Neurofibrillary tangles in Niemann-Pick disease type C. Brain. 1995;**118**(Pt 1):119-129

[113] Suzuki K, Parker CC, Pentchev PG, Katz D, Ghetti B, D'Agostino AN, et al. Neurofibrillary tangles in Niemann-Pick disease type C. Acta Neuropathologica. 1995;**89**(3):227-238

[114] Goedert M, Spillantini MG, Crowther RA, Chen SG, Parchi P, Tabaton M, et al. Tau gene mutation in familial progressive subcortical gliosis. Nature Medicine. 1999;**5**(4):454-457

[115] Caillet-Boudin ML, Fernandez-Gomez FJ, Tran H, Dhaenens CM, Buee L, Sergeant N. Brain pathology in myotonic dystrophy: When tauopathy meets spliceopathy and RNAopathy. Frontiers in Molecular Neuroscience. 2014;**6**:57

[116] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica. 1991;**82**(4):239-259

[117] Braak H, Braak E, Grundke-Iqbal I, Iqbal K. Occurrence of neuropil threads in the senile human brain and in Alzheimer's disease: A third location of paired helical filaments outside of neurofibrillary tangles and neuritic plaques. Neuroscience Letters. 1986;**65**(3):351-355

[118] Meyer MR, Tschanz JT, Norton MC, Welsh-Bohmer KA, Steffens DC, Wyse BW, et al. APOE genotype predicts when—Not whether—One is predisposed to develop Alzheimer disease. Nature Genetics. 1998;**19**(4):321-322

[119] Borroni B, Agosti C, Magnani E, Di Luca M, Padovani A. Genetic bases of progressive Supranuclear palsy: The MAPT tau disease. Current Medicinal Chemistry. 2011;**18**(17):2655-2660

[120] Pittman AM, Myers AJ, Abou-Sleiman P, Fung HC, Kaleem M, Marlowe L, et al. Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration. Journal of Medical Genetics. 2005;**42**(11):837-846

[121] Williams DR. Tauopathies: Classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. Internal Medicine Journal. 2006;**36**(10):652-660

[122] Pickering-Brown S, Baker M, Yen SH, Liu WK, Hasegawa M, Cairns N, et al. Pick's disease is associated with mutations in the tau gene. Annals of Neurology. 2000;**48**(6):859-867

[123] Goedert M, Jakes R. Mutations causing neurodegenerative tauopathies. Biochimica et Biophysica Acta. 2005;**1739**(2-3):240-250

[124] Rebeiz JJ, Kolodny EH, Richardson EP Jr. Corticodentatonigral degeneration with neuronal achromasia: A progressive disorder of late adult life. Transactions of the American Neurological Association. 1967;**92**:23-26

[125] Forman MS, Zhukareva V, Bergeron C, Chin SS, Grossman M, Clark C, et al. Signature tau neuropathology in gray and white matter of corticobasal degeneration. The American Journal of Pathology. 2002;**160**(6):2045-2053

[126] Gu YJ, Oyama F, Ihara Y. Tau is widely expressed in rat tissues. Journal of Neurochemistry. 1996;**67**(3):1235-1244

[127] Kenner L, Elshabrawi Y, Hutter H, Forstner M, Zatloukal K, Hoefler G, et al. Expression of 3-repeat and 4-repeat tau-isoforms in mouse-liver. Hepatology. 1994;**20**(4):1086-1089

[128] Pusztai L, Jeong JH, Gong Y, Ross JS, Kim C, Paik S, et al. Evaluation of microtubule-associated protein-tau expression as a prognostic and predictive marker in the NSABP-B 28 randomized clinical trial. Journal of Clinical Oncology. 2009;**27**(26):4287-4292

[129] Matsuno A, Takekoshi S, Sanno N, Utsunomiya H, Ohsugi Y, Saito N, et al. Modulation of protein kinases and microtubule-associated proteins and changes in ultrastructure in female rat pituitary cells: Effects of estrogen and bromocriptine. The Journal of Histochemistry and Cytochemistry. 1997;**45**(6):805-813

[130] Matrone MA, Whipple RA, Thompson K, Cho EH, Vitolo MI, Balzer EM, et al. Metastatic breast tumors express increased tau, which promotes microtentacle formation and the reattachment of detached breast tumor cells. Oncogene. 2010;**29**(22):3217-3227

[131] Dickey CA, Kamal A, Lundgren K, Klosak N, Bailey RM, Dunmore J, et al. The high-affinity HSP90-CHIP complex recognizes and selectively degrades phosphorylated tau client proteins. The Journal of Clinical Investigation. 2007;**117**(3):648-658

[132] Zhang H, Burrows F. Targeting multiple signal transduction pathways through inhibition of Hsp90. Journal of Molecular Medicine. 2004;**82**(8):488-499

[133] Dickey CA, Dunmore J, Lu B, Wang JW, Lee WC, Kamal A, et al. HSP induction mediates selective clearance of tau phosphorylated at proline-directed Ser/Thr sites but not KXGS (MARK) sites. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2006;**20**(6):753-755

[134] Luo W, Dou F, Rodina A, Chip S, Kim J, Zhao Q, et al. Roles of heat-shock protein 90 in maintaining and facilitating the neurodegenerative phenotype in tauopathies. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(22):9511-9516

[135] Lim J, Lu KP. Pinning down phosphorylated tau and tauopathies. Biochimica et Biophysica Acta. 2005;**1739**(2-3):311-322

[136] Ryo A, Nakamura M, Wulf G, Liou YC, Lu KP. Pin1 regulates turnover and subcellular localization of beta-catenin by inhibiting its interaction with APC. Nature Cell Biology. 2001;**3**(9):793-801

[137] Ayala G, Wang D, Wulf G, Frolov A, Li R, Sowadski J, et al. The prolyl isomerase Pin1 is a novel prognostic marker in human prostate cancer. Cancer Research. 2003;**63**(19):6244-6251

[138] Yeh ES, Means AR. PIN1, the cell cycle and cancer. Nature Reviews Cancer. 2007;**7**(5): 381-388

[139] Lu KP, Hanes SD, Hunter T. A human peptidyl-prolyl isomerase essential for regulation of mitosis. Nature. 1996;**380**(6574):544-547

[140] Ryo A, Liou YC, Wulf G, Nakamura M, Lee SW, Lu KP. PIN1 is an E2F target gene essential for Neu/Ras-induced transformation of mammary epithelial cells. Molecular and Cellular Biology. 2002;**22**(15):5281-5295

[141] Rippmann JF, Hobbie S, Daiber C, Guilliard B, Bauer M, Birk J, et al. Phosphorylation-dependent proline isomerization catalyzed by Pin1 is essential for tumor cell survival and entry into mitosis. Cell Growth & Differentiation: The Molecular Biology Journal of the American Association for Cancer Research. 2000;**11**(7):409-416

[142] Driver JA, Lu KP. Pin1: A new genetic link between Alzheimer's disease, cancer and aging. Current Aging Science. 2010;**3**(3):158-165

[143] Goedert M, Satumtira S, Jakes R, Smith MJ, Kamibayashi C, White CL 3rd, et al. Reduced binding of protein phosphatase 2A to tau protein with frontotemporal dementia and parkinsonism linked to chromosome 17 mutations. Journal of Neurochemistry. 2000;**75**(5):2155-2162

[144] Davis PK, Johnson GV. The microtubule binding of tau and high molecular weight tau in apoptotic PC12 cells is impaired because of altered phosphorylation. The Journal of Biological Chemistry. 1999;**274**(50):35686-35692

[145] Biernat J, Mandelkow EM, Schroter C, Lichtenberg-Kraag B, Steiner B, Berling B, et al. The switch of tau protein to an Alzheimer-like state includes the phosphorylation of two serine-proline motifs upstream of the microtubule binding region. The EMBO Journal. 1992;**11**(4):1593-1597

[146] Aizawa H, Kawasaki H, Murofushi H, Kotani S, Suzuki K, Sakai H. Microtubule-binding domain of tau proteins. The Journal of Biological Chemistry. 1988;**263**(16):7703-7707

[147] Cheadle C, Ivashchenko Y, South V, Searfoss GH, French S, Howk R, et al. Identification of a Src SH3 domain binding motif by screening a random phage display library. The Journal of Biological Chemistry. 1994;**269**(39):24034-24039

[148] Lee G, Newman ST, Gard DL, Band H, Panchamoorthy G. Tau interacts with src-family non-receptor tyrosine kinases. Journal of Cell Science. 1998;**111**(Pt 21):3167-3177

[149] Bhaskar K, Yen SH, Lee G. Disease-related modifications in tau affect the interaction between Fyn and Tau. The Journal of Biological Chemistry. 2005;**280**(42):35119-35125

[150] Sharma VM, Litersky JM, Bhaskar K, Lee G. Tau impacts on growth-factor-stimulated actin remodeling. Journal of Cell Science. 2007;**120**(Pt 5):748-757

[151] Kim H, Strong TV, Anderson SJ. Evidence for tau expression in cells of monocyte lineage and its in vitro phosphorylation by v-fms kinase. Oncogene. 1991;**6**(6):1085-1087

[152] Vanier MT, Neuville P, Michalik L, Launay JF. Expression of specific tau exons in normal and tumoral pancreatic acinar cells. Journal of Cell Science. 1998;**111**:1419-1432

[153] Cross DC, Munoz JP, Hernandez P, Maccioni RB. Nuclear and cytoplasmic tau proteins from human nonneuronal cells share common structural and functional features with brain tau. Journal of Cellular Biochemistry. 2000;**78**(2):305-317

[154] Stearns ME, Tew KD. Antimicrotubule effects of estramustine, an antiprostatic tumor drug. Cancer Research. 1985;**45**(8):3891-3897

[155] Husseman JW, Nochlin D, Vincent I. Mitotic activation: A convergent mechanism for a cohort of neurodegenerative diseases. Neurobiology of Aging. 2000;**21**(6):815-828

[156] McShea A, Lee HG, Petersen RB, Casadesus G, Vincent I, Linford NJ, et al. Neuronal cell cycle re-entry mediates Alzheimer disease-type changes. Biochimica et Biophysica Acta-Molecular Basis of Disease. 2007;**1772**(4):467-472

[157] Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P. Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. The Journal of Neuroscience. 2005;**25**(22):5446-5454

[158] Khurana V, Lu YR, Steinhilb ML, Oldham S, Shulman JM, Feany MB. TOR-mediated cell-cycle activation causes neurodegeneration in a Drosophila tauopathy model. Current Biology. 2006;**16**(3):230-241

[159] Lu PJ, Wulf G, Zhou XZ, Davies P, Lu KP. The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein. Nature. 1999;**399**(6738):784-788

[160] Liou YC, Sun A, Ryo A, Zhou XZ, Yu ZX, Huang HK, et al. Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. Nature. 2003;**424**(6948): 556-561

[161] Mantovani F, Piazza S, Gostissa M, Strano S, Zacchi P, Mantovani R, et al. Pin1 links the activities of c-Abl and p300 in regulating p73 function. Molecular Cell. 2004;**14**(5):625-636

[162] Wetzel MK, Naska S, Laliberte CL, Rymar VV, Fujitani M, Biernaskie JA, et al. p73 regulates neurodegeneration and phospho-tau accumulation during aging and Alzheimer's disease. Neuron. 2008;**59**(5):708-721

[163] Ibanez K, Boullosa C, Tabares-Seisdedos R, Baudot A, Valencia A. Molecular evidence for the inverse comorbidity between central nervous system disorders and cancers detected by transcriptomic meta-analyses. PLoS Genetics. 2014;**10**(2):e1004173

[164] Yang M, Moon C. Neurotoxicity of cancer chemotherapy. Neural Regeneration Research. 2013;**8**(17):1606-1614

[165] Wu H, Huang M, Lu M, Zhu W, Shu Y, Cao P, et al. Regulation of microtubule-associated protein tau (MAPT) by miR-34c-5p determines the chemosensitivity of gastric cancer to paclitaxel. Cancer Chemotherapy and Pharmacology. 2013;**71**(5):1159-1171

[166] Wosnitzer MS, Domingo-Domenech J, Castillo-Martin M, Ritch C, Mansukhani M, Petrylack DP, et al. Predictive value of microtubule associated proteins tau and stathmin in patients with nonmuscle invasive bladder cancer receiving adjuvant intravesical taxane therapy. The Journal of Urology. 2011;**186**(5):2094-2100

[167] Wang K, Deng QT, Liao N, Zhang GC, Liu YH, Xu FP, et al. Tau expression correlated with breast cancer sensitivity to taxanes-based neoadjuvant chemotherapy. Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine. 2013;**34**(1):33-38

[168] Nishioka H, Tooi N, Isobe T, Nakatsuji N, Aiba K. BMS-708163 and Nilotinib restore synaptic dysfunction in human embryonic stem cell-derived Alzheimer's disease models. Scientific Reports. 2016;**6**:33427

[169] Pagan F, Hebron M, Valadez EH, Torres-Yaghi Y, Huang X, Mills RR, et al. Nilotinib effects in Parkinson's disease and dementia with Lewy bodies. Journal of Parkinson's Disease. 2016;**6**(3):503-517