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# 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

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## 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.

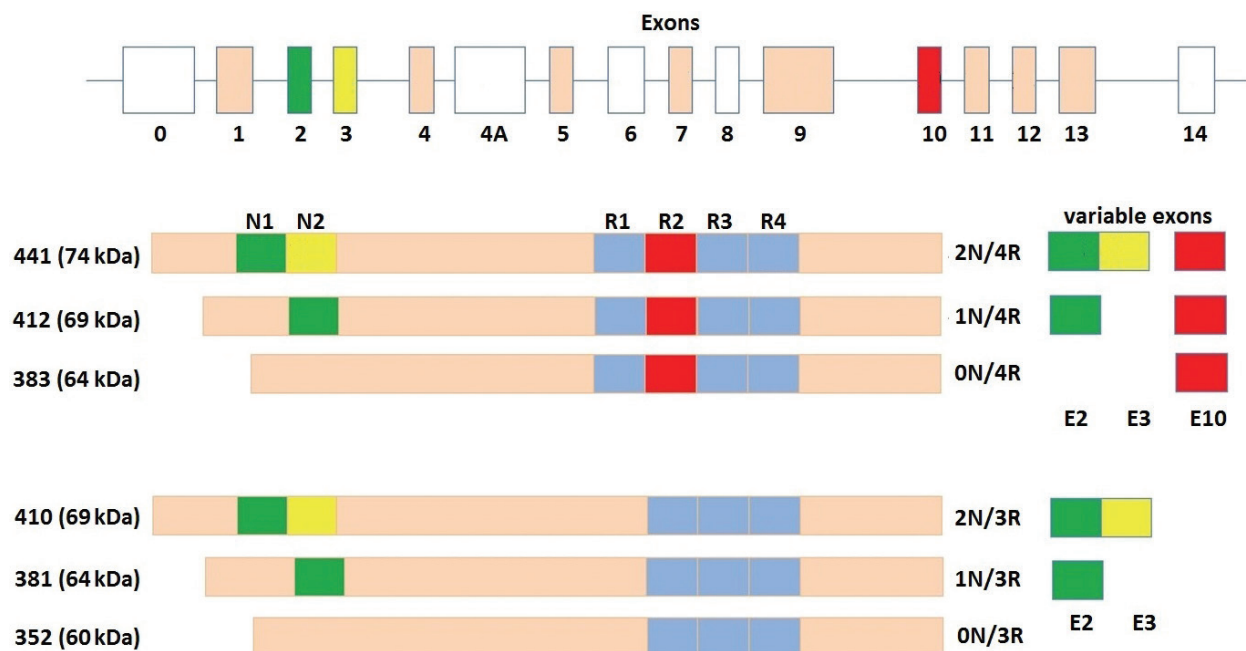
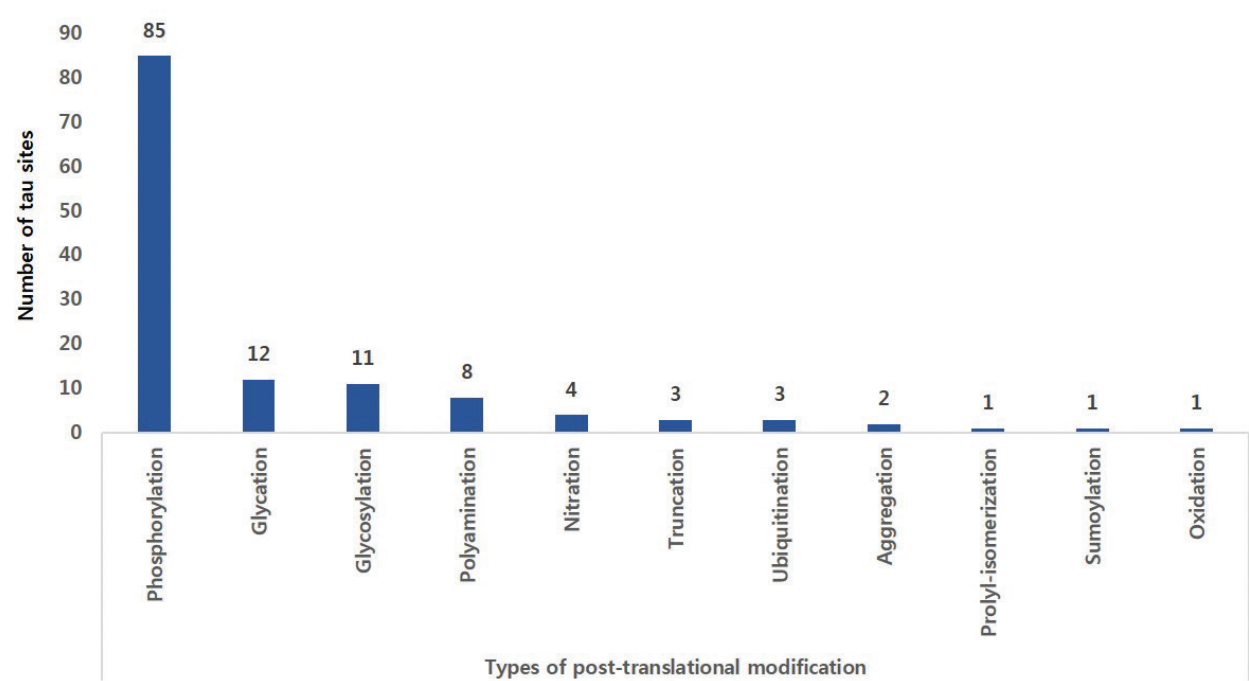


Figure 1. Graphic representation of human tau gene.

### 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 A $\beta$ -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 prickly-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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