

Tau protein in neurodegenerative diseases – a review

DENISA FLORIANA VASILICA PÎRȘCOVEANU¹⁾, IONICA PIRICI²⁾, VALERICA TUDORICĂ¹⁾,
 TUDOR-ADRIAN BĂLȘEANU³⁾, VALERIA-CARMEN ALBU¹⁾, SIMONA BONDARI⁴⁾, ANA-MARIA BUMBEA⁵⁾,
 MIRCEA PÎRȘCOVEANU⁶⁾

¹⁾Department of Neurology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

²⁾Department of Human Anatomy, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

³⁾Department of Physiology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

⁴⁾Department of Radiology and Medical Imaging, Faculty of Nursing, University of Medicine and Pharmacy of Craiova, Romania

⁵⁾Department of Medical Rehabilitation, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

⁶⁾Department of Surgical Semiology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

Abstract

The study of rare, inherited forms of different diseases resulted in the discovery of gene defects that cause inherited variants of the respective diseases. The defective genes were found to encode major molecular players leading to the neuropathological lesions or factors that characterize these diseases. The exact role of the tau protein in the neurodegenerative process is still under debate. It is very important to understand the normal biological roles of tau and the specific events that induce tau to become neurotoxic. Tau is the major microtubule-associated protein (MAP) of a mature neuron. The other neuronal MAPs are MAP1 and MAP2. These three MAPs perform similar function, promoting assembly and stability of microtubules. Tau protein was isolated as a microtubule-associated factor in the porcine brain. It was isolated as a protein that co-purified with tubulin and had the ability to promote microtubule assembly *in vitro*. Normal adult human brain tau contains 2–3 moles phosphate/mole of tau protein. Hyperphosphorylation of tau depress this biological activity of tau. Almost 80 diseases caused by missense mutations and intronic mutations in the tau gene have been found in familial cases of frontotemporal dementia (FTD). In Alzheimer's disease (AD), there are intraneuronal neurofibrillary tangles composed of the microtubule-associated protein tau (MAPT). In other neurodegenerative diseases, there are similar deposits of tau, in the absence of extracellular deposits (progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, etc.). Tau pathology is also often seen in some forms of Parkinson's disease (PD) and prion diseases. In genetic forms of FTD, mutations in tau implicate abnormal tau as the initiation of neurodegeneration. In FTD, there are deposits especially in temporal and frontal lobes, regions that are very important for behavior and executive function. It is critical to understand how tau becomes pathogenic, in order to consider developing any strategies for treatment.

Keywords: tau protein, hyperphosphorylation, neurofibrillary tangles, tauopathies, mutations.

Introduction

The process of cytoskeleton protein aggregation causes neurons to become unstable. These structural changes interfere with the anterograde and retrograde transport of biomolecules along their axons. Protein aggregation can block axons, and neurons can degenerate starting to the lesion point, back to the perikarya.

Tau belongs to the microtubule-associated proteins (MAPs) family, being identified in 1975, by Weingarten *et al.*, as a heat stable protein essential for microtubule assembly [1]. Its role is very important for the stabilization of microtubules, which are important cytoskeleton scaffolds for the cells and support cellular trafficking [1, 2]. They are supporting kinesin and dynein-based anterograde and retrograde transport, thus they enable the movement of cargo packages towards and from the perikarya to the axon/dendrites. Synapses are affected if the axonal transport is affected. It has been discovered in recent years that different forms of tau appear to be related to mitochondrial function [3]. Also, tau is related to deficiencies in oxidative phosphorylation or apoptotic activity [3, 4]. A consequence of these deficiencies is

the appearance of mitochondrial fragmentation, this being an important implication in neurodegeneration. As a result of loss of balance of mitochondrial dynamics, there is a large consequent production of reactive oxygen species, and this may lead to post-translational modifications of proteins throughout the cell.

It is known that normal tau is found in axons. In diseases that affect tau structure and function, the protein can also be translocated in the cell body and dendrites. The abnormal deposition of modified tau proteins in the neurons is a common aspect of many neurodegenerative disease called “tauopathies” [5, 6].

In these diseases, the aggregates of tau take the form of neurofibrillary tangles (NFTs) [6]. There are morphological differences in tau lesions associated with each of the tauopathies, but research data showed that the mechanisms of these accumulations in tauopathies share common features [6]. Many studies and transgenic animal models are currently trying to elucidate how the aggregation of tau into fibrillary inclusions causes neuronal death, and what is the connection with the accumulation of amyloid beta (A β) peptide in Alzheimer's disease [7, 8]. Tau deposits are found in many neurodegenerative

diseases, such as Pick's disease, corticobasal degeneration, progressive supranuclear palsy, frontotemporal lobar dementia, amyotrophic lateral sclerosis, dementia pugilistica. In addition, the patients with Parkinson's disease may have tau deposits.

Neuronal death occurs even in the absence of tangle formation. It seems that the toxicity appears following more subtle changes, such as glycosylation or truncation [6].

☐ Structure and function of normal brain tau

In humans, tau is encoded by the 16 exons-comprising microtubule-associated protein tau (MAPT) gene on chromosome 17q21 [9]. Because of the alternative splicing of exons 2, 3, and 10, six major tau isoforms are expressed in the human brain [10]. Exons 2 and 3 encode for amino-terminal inserts, whereas exon 10 encodes for a microtubule-binding (MTB) repeat. Hence, the six human isoforms are 352 to 441 amino acids long and contain either no, one or two amino-terminal inserts (0N, 1N, or 2N), and either three or four MTB repeats (3R or 4R). The ratio of 3R and 4R isoforms is approximately of 1:1 and changes to this ratio have been found in different diseases. Tau comprises an amino-terminal projection domain, followed by MTB repeats, and a short carboxyl-terminal tail sequence [11].

Tau proteins are present in many species, as *Caenorhabditis elegans*, *Drosophila*, fish, rodents, goats, monkeys and humans. In humans, they are mainly found in neurons, although non-neuronal cells also do present small but detectable quantities of these proteins. For

example, tau proteins might be expressed in the glial cells, especially in pathological conditions, and it is possible that the final transcripts and their mRNAs to be detected in some peripheral tissues such as the heart, kidney, lung, muscle, pancreas, and there especially in the fibroblasts [12]. The tau gene was identified later on, in 1986, as being localized on chromosome 17q21, with a homologous region on the chromosome 6p21; it was the same year in which the MAP2 protein was localized on chromosome 2q34-35 [13]. The primary transcript of tau mRNA contains 16 exons. Three of these (exons 4A, 6 and 8) are not present in any mRNA from the human brain. They are specific for tau peripheral proteins. Exon 4A is found in cattle and has a high degree of homology in peripheral tissues in humans and rodents. In humans have not been described mRNA with exons 6 and 8. Some forms containing exon 8 and are found in the brain of cattle or *Rhesus* monkey. Exon -1 is part of the promoter and is transcript but not translated. Exons 1, 4, 5, 7, 9, 11, 12 and 13 are constitutive exons. Exon 14 is found in mRNA but is not translated into the final protein. Exons 2, 3 and 10 are alternately linked and specific to the adult brain. Exon 3 never occurs independently of exon 2. Thus, the alternative combination of these three exons allows the existence of six combinations (2-3-10-; 2 + 3-10-; 2 + 3 + 10; 2-3-10 + 2 + 3-10 +; 2 + 3 + 10 +). In the human brain, the primary transcript leads to the appearance of six types of mature mRNA chains. The mRNA encoding for tau protein is found abundantly in the axonal segment, its translation occurring in this region (Figure 1).

Human tau gene (17q21.22)

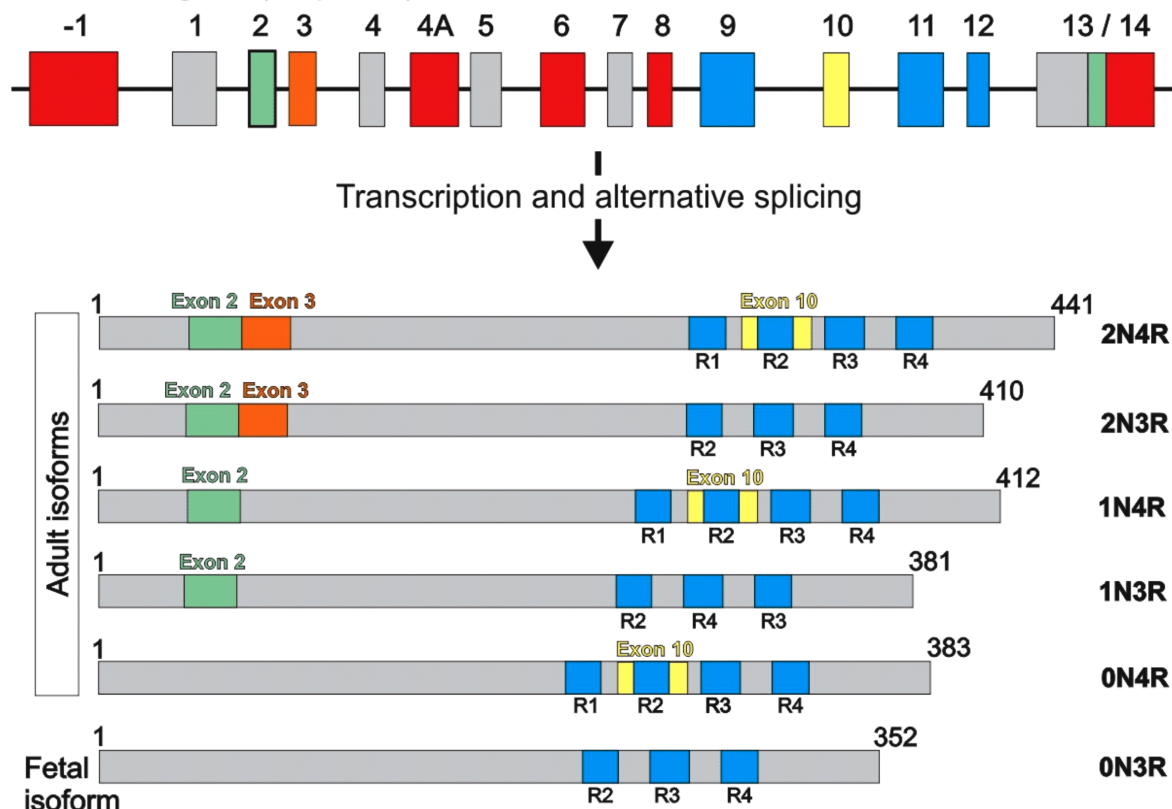


Figure 1 – Organization of the tau gene, and the resulting six isoforms of the protein. Exons 2 and 3 generate the inserts (N), and there can be four repeats (R) towards the COOH terminal end.

Tau isoforms from the human brain have a number of amino acids ranging between 352 to 441. Their molecular weight is between 45 and 65 kDa. These variants differ from each other by the presence of three or four imperfect repetitive regions of 31 or 32 amino acids (3R or 4R) in the carboxyl-terminal part of the molecule and the absence or presence of one or two insertions (with a length of 29 or 58 amino acids) at the amino-terminal side (0N, 1N, 2N) [13]. These two insertions are acidic and are followed by a proline-rich base region. The four repetitive regions at the COOH-terminal are the central component of the microtubule interaction unit. Interestingly, the most important component in the induction of microtubule polymerization is located between the repeating regions R1 and R2 at the KVQIINKK peptide in this sequence. This segment is specific for the adult 4R isoform and is responsible for a 40-fold increase in 4R isoform binding affinity.

The expression of the different tau isoforms in the brain is under developmental control, suggesting that the regulation of tau isoforms is important during formation of the brain [14]. Tau isoforms with three repeats (3R-tau) bind microtubules with a lower affinity than 4R-tau isoforms [11, 15]. Therefore, tau molecule is subdivided into an amino-terminal domain that projects from the microtubule surface and a carboxyl-terminal microtubule-binding domain [15]. The projection domain is proposed to determine the spacing between microtubules [16]. It may play a role in the interactions between tau and other cytoskeleton proteins, like neurofilament proteins [17]. In a normal mature neuron, tubulin is present in over 10-fold excess of tau. The neuronal concentration of tau is $\sim 2 \mu\text{M}$ [18, 19]. It binds to microtubules at a

dissociation constant (K_d) of $\sim 100 \text{ nM}$ [20]. Thus, all tau is likely to be microtubule bound in the cell [19].

Tau has been reported to interact with a number of other proteins besides tubulin/microtubules [21]. The biological relevance of many of these interactions is not clear. Recent findings shown that the interaction between tau and the protein kinase Fyn may be important for modulating neuronal cell signaling through Fyn [22]. The interaction tau–Fyn may have a role in process extension in oligodendrocytes [23].

One of tau's main functions is to modulate the stability of axonal microtubules. Tau is not present in dendrites and is active primarily in the distal portions of axons where it provides microtubule stabilization but also flexibility as needed. Tau generates a partially stable, but still dynamic, state in microtubules important for the dynamics of axonal growth cones and effective axonal transport. Some studies shown that tau can interact, either directly or indirectly, with actin and affect actin polymerization as well as the interaction of actin filaments with microtubules [24–26].

☞ Phosphorylation of tau in tauopathies

Although tau protein undergoes multiple posttranslational modifications, such as glycosylation, non-enzymatic glycosylation (glycation), phosphorylation represents the major posttranslational modification of tau protein. Tau is a phosphoprotein and its biological activity is regulated by the degree of its phosphorylation. Phosphorylation has been reported on approximately 30 of these sites in normal tau proteins (Figure 2) [27].

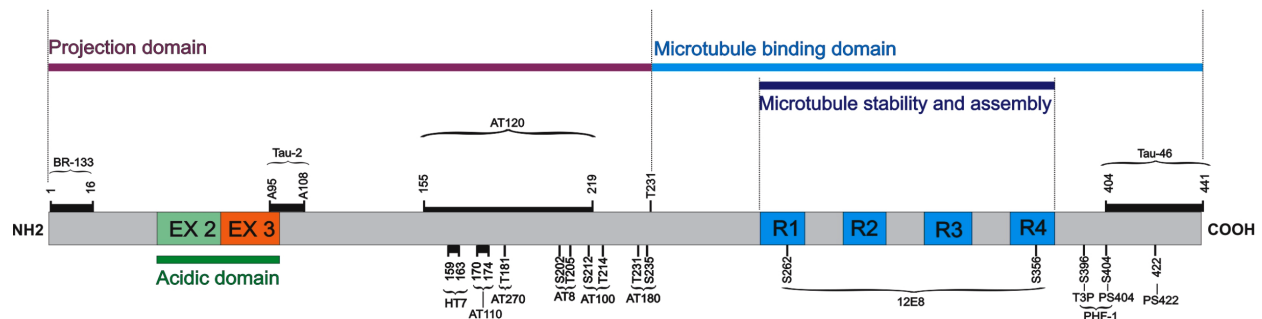


Figure 2 – The main phosphorylation sites of tau protein together with their placement in different functional domains.

Many of the phosphorylated sites are serine/threonine-proline, 17 of which are present in the longest human brain tau isoform [28]. These phosphorylations can control the normal biological functions of tau, such as its role in microtubule stability, as well as its pathological functions, such as its ability to self-assemble into neuronal filaments found in neurodegenerative diseases.

Physiologically, phosphorylation is regulated during development, fetal tau being more phosphorylated than the tau protein from the adult brain [29]. In the evolution of neurodegenerative diseases, initially intracellular storage occurs of aggregates composed of highly phosphorylated and glycosylated tau proteins that are twisted-like filaments (such as those found in Alzheimer's disease) or more straight (Pick's disease, progressive supranuclear palsy, corticobasal degeneration). In addition to the immunohistochemical detection of these aggregates, Western blot

analysis can detect two types of tau protein depending on its solubility in certain detergents. For example, the use of sarcosyl as a solubilizing medium leads to the detection of tau insoluble deposits in the hyperphosphorylated state and of the physiologically normal phosphorylated forms. Depending on the predominance of 4R or 3R isoforms, the insoluble fraction may be a characteristic pattern of different tauopathies. In the normal adult brain, there is a ratio of about 1:1 between 3R to 4R tau.

Mutations of tau gene lead to frontotemporal dementia (FTD) and parkinsonism linked to chromosome 17 (FTDP-17). Most patients with mutations in tau gene develop a dominant autosomal inherited syndrome with features of frontotemporal lobe degeneration. The analysis of tau mutations found in FTDP-17 provided new data on frontotemporal lobar degeneration (FTLD) pathogenesis. The mutations in tau gene that produce these clinical syndromes

are around exon 10; they alter either the microtubule binding affinity of translated proteins (missense mutations in exon 10) or tau 3R/4R ratio (mutation of the binding sites that fit exon 10) [30]. Changes in the expression of tau isoforms are the result of the formation of insoluble protein aggregates, leading to neuronal dysfunction and cell death. From a histopathological point of view, tau mutations may cause the formation of different types of insoluble protein aggregates, including Pick bodies, ballooned neurons and NFTs.

The biochemical analysis of tau protein from a brain with Pick's disease has suggested that usually Pick bodies are predominantly formed from 3R tau deposits. It is assumed that the ballooned neurons found in Pick's disease and corticobasal degeneration contain predominantly 4R tau, because they are tau deposits found in the brains of patients with progressive supranuclear paralysis. NFTs of Alzheimer's disease contain an equal ratio of 3R tau and 4R tau proteins. Other disorders such as post-encephalic parkinsonism [31], NFTs dementia [32] and Niemann–Pick type C disease [33] also produce insoluble protein aggregates that have an equal ratio of 3R/4R tau protein. FTLD and other primary neurodegenerative disorders with prominent pathology have been grouped under the name of “tauopathies” to distinguish them from other protein aggregates, such as Lewy and Parkinson's disease, which exhibit protein aggregates formed by α -synuclein [34]. A consensus has been reached on the pathological and clinical diagnosis of FTLD based on the composition of tau insoluble deposits found in the brain [35]. For example, it was suggested that if tau insoluble aggregates predominantly contained 3R tau, the diagnosis would most likely be Pick disease or FTDP-17. However, a study of isoform expression in sporadic Pick disease using tau specific antibodies for exon 10 revealed cases with predominance of 3R tau, 4R tau or an equal ratio of both [36].

Mitogen-activated protein (MAP) kinase, glycogen synthase kinase-3 (GSK-3), cyclin-dependent kinase-5 (Cdk5) phosphorylate tau *in vitro* [28, 37, 38]. Some studies found that GSK-3 is able to modulate the generation of A β [39]. They showed that GSK-3 can modify several sites of the tau protein into NFTs [39]. GSK-3 presents two isoforms: GSK-3 alpha and GSK-3 beta [40]. The non-cyclin regulatory proteins p39 and p35 activate Cdk5 in post-mitotic cells. Proteolysis of p39 and p35 by calpain to p29 and p25, respectively, leads to prolonged Cdk5 activity and an increase in tau phosphorylation [5].

Cyclic adenosine monophosphate (AMP)-dependent protein kinase A (PKA), protein kinase B (PKB) and microtubule-affinity regulating kinase (MARK) phosphorylate *in vitro* some sites in tau [41–43]. It is known that MARK selectively phosphorylates the KXGS motifs, particularly the one including Ser262. Tau phosphorylation at KXGS motifs induces its dissociation from microtubules and prevents its degradation [44]. The phosphorylation of tau by MARK/PAR-1 is very important for the action of kinases as GSK-3 β and Cdk5 [45].

There are also phosphorylation sites in tau located within the repeat region [46]. As a result of the phosphorylations at these sites, there is a decrease in tau affinity for microtubules [47]. Protein phosphatase 2A (PP2A) is the major phosphatase activity in brain toward tau phosphorylated by proline-directed and other kinases.

If a down-regulation of phosphatase activity occurs, increases in tau hyperphosphorylated occurs [48, 49].

Protein interacting with NIMA 1 (PIN1) regulates tau phosphorylation, too. It is a member of the peptidyl-prolyl *cis-trans* isomerase group of proteins involved in the assembly, folding and transport of cellular proteins [50]. The phosphorylation state of tau plays a very important role in interaction between tau and PIN1 [51]. PIN1 binds tau when phosphorylated at Thr231 and facilitates its dephosphorylation by PP2A [52]. In the hippocampus of the patients with Alzheimer's disease was found an important down-regulation and oxidation of PIN1 [53]. By deregulation of PIN1 expression and activity, there is a degradation of the phosphorylation-dephosphorylation balance of tau [6].

Tau hyperphosphorylation seems to precede tau filaments assembly. For sites that are phosphorylated in tau from normal brain, a higher proportion of tau molecules is phosphorylated in filamentous tau. Filamentous tau is phosphorylated at more serine and threonine residues than tau from normal adult brain. It was found that phosphorylation of S214 and S422 is specific for abnormal tau [54, 55].

☞ Tau in Alzheimer's disease

Alzheimer's disease (AD) is characterized at the tissue level by neuronal loss, amyloid plaques depositions and the formation of intraneuronal NFTs. In patients with AD, tau loses its ability to bind to microtubules and therefore its normal role of keeping the well-organized cytoskeleton is no longer effective [56]. It is well known that in patients with AD, tau is abnormally hyperphosphorylated but without ubiquitin reactivity. It is accumulated as intraneuronal tangles of paired helical filaments (PHFs), twisted ribbons or straight filaments with diameters between 2.1 and 15 nm [57].

The phenomenon of redistribution and aggregation of tau modified protein reserves occurs both with somatodendritic localization and isolated processes of affected neurons [56]. In tauopathies as progressive supranuclear palsy, corticobasal degeneration and Pick disease were found tau-positive inclusions in glial cells [58].

In experimental models, it was observed that a high percentage of tau is needed to promote tau fibrilization, and that is why it is assumed that the enhanced ability of tau to form filamentous inclusions in the cytoplasm of neurons and glia in human tauopathies may be due to pathological conditions that increase the pool of tau available for aggregation [6].

Abnormal hyperphosphorylation has an important role in the formation of NFTs. This aspect seems to be a leading cause of neuronal death in AD. In the brain of patients with AD has been discovered that phosphorylation level of tau is 3- to 4-folds higher than that of normal human brains [59].

It was found that approximately 40% of the abnormally hyperphosphorylated tau in AD brain is present in the cytosol [60, 61]. These patients present cytosolic hyperphosphorylated tau containing 5 to 9 moles of phosphate per mole of the protein. It sequesters normal tau, MAP1 and MAP2, and inhibits assembly and depolymerizes microtubules [61].

In the order of their appearance, it has been showed that NFT tend to appear first in the neurons of the entorhinal cortex, while amyloid plaques seem to appear afterwards in the dentate gyrus of the hippocampus proper. Since subicular neurons send their axons through the perforant pathway into the dentate granular cells, this sequence was explained to some extent by the fact that hyperphosphorylated tau that occurs during NFT formation also impairs axonal flow of the amyloid precursor protein (APP) leading to its deposition around the terminal buttons of the affected axons. In neurons without tangles were observed abnormally phosphorylated tau deposits, but not normal tau [62]. Thus, it can be concluded that the abnormal hyperphosphorylation of tau precedes its accumulation into NFT [63]. There are differences in the mix of tau repeats at the level of AD fibrils (3R and 4R tau) compared with other tauopathies (1R tau) [64]. Tau filaments have width between 8 and 20 nm, and a spacing between crossovers of about 80 nm [64]. There is a dynamic regulation of tau kinases and tau phosphates resulting in the phosphorylation process. Patients with AD present an imbalance between kinases and phosphatases resulting in tau protein to become detached from microtubules and aggregate [65].

Cdk5 is one of tau kinase having an important role in AD. It is upregulated in AD patients [66]. Among tau phosphatases, PP2A is very important in these patients [49, 59]. They present decreased activity and the expression of PP2A [49]. Two endogenous PP2A inhibitors have shown a deregulation: I1PP2A and I2PP2A [59]. Inhibition of PP2A activity results in a decrease in dephosphorylating activity. This leads to an abnormal hyperphosphorylation of tau. It is possible in this pathological process to play an important role up-regulation of the activities of calcium, calmodulin-dependent protein kinase II (CaM-KII), PKA, and several members of the mitogen-activated protein kinase (MAPK) family [67–69]. By combining PKA and CaM-KII with GSK-3 β or Cdk5, or Cdk5 plus GSK-3 β , can occur Alzheimer neurofibrillary degeneration [70].

Among kinases, p70 S6 kinase seems to be very important in AD as it up-regulates the translation of tau resulting increased tau level in AD brain [71]. β -Tubulin, β -catenin and MAP1B are also some of the neuronal protein hyperphosphorylated in AD [59, 72]. Besides phosphorylation, there is an important process called O-GlcNAcylation. This process involves the existence of tau residues serine/threonine that are modified by β -N-acetylglucosamine (GlcNAc) via a glycosidic bond [73, 74]. AD patients show an increase in phosphorylation while the O-GlcNAcylation process is decreasing [74]. Truncation is another post-translational modification of that has been investigated lately. Truncated tau is present from early to late stages of tau aggregation [75]. The truncation process occurs at the carboxy and also amino termini. These truncations influence the conformation into which the molecule folds, and hence the ability of tau to polymerize into fibrils [75]. In patients with AD are found truncations at Glu391 and Ser421 [76, 77].

☞ **Tau in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)**

FTLD represents a pathological group of disorders,

with up to 40% of the cases presenting with a family history of dementia and/or movement disorders [78]. The first mutations associated with FTLD were found in the MAP tau gene in families, thus they called “familial frontotemporal degeneration and parkinsonism” (FTDP-17) form of disease [79, 80]. The onset of neurological symptoms occurs between the ages of 30 and 50 years [81]. The alteration of personality and behavior appears from the incipient stages. These alterations include a loss of inhibition, inappropriate emotional responses, neglect of personal hygiene, and a general loss of interest in activities [82]. These patients develop dementia presenting an impairment of judgment, planning, and concentration [82]. They develop features of parkinsonism, such as tremors, rigidity, and bradykinesia. A vertical gaze palsy and rapid abnormal movements of both eyes may also occur in patients with FTDP-17 [83].

The altered proportion of tau isoforms and the ability of tau to bind microtubules play an important role in pathogenesis of FTDP-17 [84]. A very important neuropathological aspect of these patients is that the filamentous inclusions contain hyperphosphorylated tau protein but no β -amyloid plaques [84]. In patients with FTD are finding the following common pathological changes: atrophy brain region presenting neuronal loss, spongy change and gliosis in cortices of atrophied frontal and temporal lobes [84].

Several other kindred with FTDP had been linked to chromosome 17, but they had ubiquitin-positive inclusions rather than tauopathy pathology [85]. Many of these FTDP-17 families had, however, no tau mutation, and on pathology showed intraneuronal ubiquitin-positive tau-negative inclusions rather than the classical tau-positive bodies. Intense gene mapping and protein isolation studies identified in 2006 mutations in the progranulin gene linked to a similar region on chromosome 17, as the second cause of FTDP-17, and most of the families linked to chromosome 17 but without tau mutations proved to bear progranulin mutations [86]. At the tissue level, patients with progranulin mutations show FTLD with ubiquitinated transactive response (TAR) DNA 43-immunopositive inclusions [87]. To date, more than 40 mutations in the tau gene have been found in over 100 families diagnosed with this disease worldwide [87]. The phenotype of FTDP-17 may varies even between families carrying the same mutations [81].

Mutations in tau gene associated with FTDP-17 are predicted both to increase the proportion of tau that is unbound to microtubules and available for aggregation and also to increase directly the tendency of the unbound tau to form filaments [82, 88].

The mutations in non-coding regions affecting the splicing of exon 10 are most common [88]. Mutations in tau that result in increased splicing of exon 10 are important because they lead to the formation of wide twisted ribbon-like filaments consist of 4R tau isoforms [89]. These patients exhibit tau pathology in both neurons and glial cells [90]. The mutations found in exon 10 are N279K, L284L, S305N, S305S, Δ N296, N296N and N296H [90–96]. These patients present an increase in the 4R/3R ratio of their tau isoforms [90–92]. One of these mutation is deletion of the lysine codon at the position 280 (Δ K280) that inhibits the incorporation of exon 10 and consequently reduces the 4R/3R ratio [97, 98]. This finding suggests that neurotoxicity results rather from the

imbalance in 3R and 4R isoforms than from the increase in 4R [97, 98]. Mutations P301L and P301S in exon 10 leads to the formation of narrow twisted ribbons that contain four-repeat tau isoforms [30, 99]. They lead to a reduced ability of tau to promote microtubule assembly [100, 101]. In cases where the P301L mutation is present, perinuclear deposits of hyperphosphorylated tau were found, consisting of thin twisted filaments with a width of 15 nm as straight filaments [99]. These deposits were found in neurons, glial cells and the neuropil of frontal and temporal cortex, hippocampal formation and substantia nigra [99].

Patients presenting mutations located outside exon 10 have especially neuronal damage, glia damage being less significant. Tau deposits in both neuronal component and glial component have been found for mutations R5H and R5L in exon 1, I260V and L266V in exon 9 and L315R and K317M in exon 11 [101–105].

Mutations V337M in exon 12 and R406W in exon 13 lead to the formation of PHFs containing all six tau isoforms [106]. These filaments are similar to the filaments in the brains of AD patients [32, 106]. Tau proteins of patients with these two mutations are much faster phosphorylated than the wild-type tau [32]. This tau also self-assembles at lower levels of phosphorylation than the wild-type protein [32]. The R406W mutation is located downstream of the repeats and it seems that the effect of this mutation is weaker than the effect of the V337M mutation [107].

Intronic mutations have been discovered at positions +3, +12, +13, +14, +16 and +33 of the intron following exon 10, with the first nucleotide of the splice-donor site taken as +1 [101]. The consequence of this mutation is to increase production of exon 10-containing transcripts and to increase levels of the three tau isoforms with four microtubule-binding repeats [83]. Due to the fact that excess of four-repeat tau isoforms is found in these patients, an excess of tau over available binding sites on microtubules may occur. Because of this phenomenon, wide twisted ribbons are formed by assembling of four repeat tau isoforms [108].

☞ Tau in the sporadic tauopathies

In this category of diseases are included: progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and Pick's disease (PiD).

For the majority of cases of PSP, their cause is still unclear. The patients display difficulty in balance, abrupt falls, visual and ocular disturbances, dysphagia. In about 15% of cases, there is a familial history of a neurodegenerative disease [109]. In few cases, mutations have been found in the MAPT gene [109]. The +16 intronic mutation, R5L, N279K, G303V, S305S, and Δ N296 are the mutations that have been found in patients with PSP [98, 107, 110, 111–114].

CBD is also one of the sporadic tauopathies. Its clinical aspects consist of abnormalities in posture and motor function with relatively intact mental faculties [115]. The most important neuropathological aspect of this disease is represented by an important atrophy of parasagittal cortex particularly in peri-Rolandic regions [116]. A depigmentation of the substantia nigra was also found in the brain of these patients [117]. Neuropathological

research has found neuronal loss, gliosis, and prominent glial and neuronal intracytoplasmic filamentous tau-immunoreactive deposits [58]. An important aspect to be mentioned with regard to the glial damage is the presence of astrocytic plaques as well as numerous tau-immunoreactive inclusions in gray and white matter in astrocytes and oligodendrocytes [12]. The composition of filamentous inclusions in CBD consists of abnormally phosphorylated tau similar to other tauopathies such as AD, PSP and PiD [118]. Recently was found that CBD can be replicated at the phenotype level by some tau mutations: N296N, P301S and K317M [119–121].

AGD is also considered to be one of the tauopathies. This disease was first reported by Braak & Braak as an adult-onset dementia [122, 123]. Characteristic of this disease is the fact that spindle- or comma-shaped argyrophilic grains in the neuropil of the entorhinal cortex, hippocampus and amygdala are found [113]. Argyrophilic grains are aggregates of straight filaments or smooth tubules [123]. They are located mainly in dendrites of neurons [123, 124]. The clinical picture of this disease is not fully understood so far. It seems that dementia is characteristic for AGD [125]. Also, the personality change and emotional imbalance preceding memory impairment are found in these patients [125, 126]. The frequency of AGD increases with age [125]. The argyrophilic grains contain hyperphosphorylated tau, but the isoform composition of grains is not yet well known [125].

Pick's disease is one of the tauopathies that causes a progressive and irreversible dementia [127]. The frontal and temporal lobes are affected [127]. The clinical features that occur early in this disease consist in behavior and personality changes. For the pathology of PiD, characteristic are Pick bodies and ballooned neurons or Pick cells, presenting hyperphosphorylated tau protein [128]. It is not clear how tau hyperphosphorylation occurs in this disease. Also, the distribution of abnormal tau in affected neurons is not yet well known [129]. Two major components (Tau 55, 64 kDa) and a minor 69 kDa were found in phosphorylated tau from Pick bodies [129].

Tau proteins in PiD and AD share similar phosphorylated residues [128]. There is only one exception of Serine262, which appears to be phosphorylated in Alzheimer's NFT but not in Pick bodies or Pick cells [128]. Moreover, mutations have been uncovered that give rise to a neuropathological phenotype reminiscent of PiD (K257T, L266V, G272V, S305N, L315R, S320F, Q336R, E342V, K369I, G389R) [100, 108, 130, 131–138].

☞ Conclusions

As research shows, tau role is very important in the pathogenesis of various neurodegenerative diseases, called altogether tauopathies. It is known that misfolded and/or aggregated tau protein is responsible for the tauopathies. It is not yet well known the exact nature of the pathogenic form. In patients with AD, the progression of dementia is correlated with the fibrillary aggregation of tau. The abnormal posttranslational modifications such as hyperphosphorylation, acetylation, glycation, truncation, seems to be responsible for altered tau structure in these patients. The balance between tau kinase and phosphatase activities is very important in regulating tau phosphorylation because an altered balance seems to be at the origin of abnormal

tau phosphorylation and may have an important role in tau aggregation. It is hoped that in the future will be made more analyses of animal models in order to obtain more answers at the fundamental questions regarding tauopathies.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Denisa Floriana Vasilica Pîrșcoveanu and Ionica Pirici equally contributed to the manuscript.

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Corresponding author

Ana-Maria Bumbea, Teaching Assistant, MD, PhD, Department of Medical Rehabilitation, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Romania; Phone +40741–123 729, Fax +40251–593 077, e-mail: anamariabumbea@yahoo.com