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Chapter 12

Accumulation of Abnormally Processed Tau Protein in Neuronal Cells as a Biomarker for Dementia

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1. Introduction

Among neurodegenerative diseases, dementias are an heterogeneous group in terms of their symptoms and pathological findings. One of the main risk factors for developing neurodegenerative disease is aging. Currently there is no cure for these diseases, mainly due to the lack of knowledge of the causes and mechanisms of the accumulation of abnormal protein aggregates within the cellular or extracellular body. This is a common characteristic pathological feature in several neurodegenerative diseases. Pathological protein accumulations not only define the characteristics of a particular neurodegenerative disease, but also are associated with clinical progression, including cognitive impairment or motor disorders [1].

Research in this field had been focused on finding potential highly specific biomarkers that correlates with the disease and can be detected at early stages of the pathology. In medicine, a biomarker is defined as a featured specific somatic or measurable biological change related to a health condition or disease [2]. A biomarker can be measured and objectively evaluated as an indicator of normal biological processes or disease, as well as the pharmacological response to treatment. In general, we can say that a biomarker can be used to diagnose the disease, or to establish its severity and allow monitoring its progression and response [1, 3, 4]. A biomarker must adhere to the following statements: 1) detect a fundamental feature of the neuropathology of the disease, 2) must be validated in cases confirmed by neuropathological examination, 3) have a high sensitivity and specificity, above 80% for discriminating the

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neuropathology in question, 4) must be reliable. [3] In clinical studies, the biochemical analyse of cerebrospinal fluid, plasma and urine, constitute the preferred samples to search for biomarkers [5]. On the other hand neuroimaging studies and detection of genetic markers are also useful for tracking the progression of the disease [6-8]. However, these studies remain in an experimental phase and need to be further investigated. The challenge is to find the correlation between the biomarker expression, the cognitive decline and the onset of the neuropsychiatric symptoms. It is also important to emphasize that the diagnosis of neurodegenerative diseases is mainly clinical and in most of the cases it is done when the dementia syndrome has already been established. To this day, the more accurate confirmation of the diagnosis is the post-mortem pathological study. This greatly limits the early therapeutic interventions. Optimally, it is expected that biomarker studies will focus at four levels: 1) biomarkers of risk, which will help identify risk populations with mutations or changes in gene sequence, 2) diagnostic biomarkers in the early differential diagnosis would be useful to confirming the occurrence of the neurodegenerative disease, and thus allow the possibility of an early therapeutic intervention. An example of this type of biomarker approach are the neuroimaging studies, associated with the positron emission tomography, taking into consideration the measurement of the degree of atrophy of the cortex, the amplitude of the ventricles, as well as of hippocampus, 3) biomarkers of progression, these markers could predict the evolution of the disease. Finally, 4) neuropathological-molecular biomarkers are the abnormal neuropathological lesions that constitute the features of the disease. For example, the abnormal processing and deposits of hallmark proteins (such as of tau protein, amyloid-β peptide and α-synuclein) of neurodegenerative diseases.

In this chapter we will focus on the description and abnormal processing of tau protein, amyloid β peptide and α-synuclein, and its implication as specific biomarkers of neurodegeneration. First we will talk about abnormal processing and pathological aggregates of tau protein. The group of diseases characterized by abnormal tau processing and deposits, are known as tauopathies. Tauopathies include fronto temporal dementia (FTD), progressive supranuclear palsy (PSP), neurofibrillary tangle-predominant dementia (NFTD) and Alzheimer's disease (AD); these neurodegenerative diseases are characterized by the presence of neurofibrillary tangles (NFTs), consisting of paired helical filaments (PHFs). These filaments are mainly comprised of tau protein, and constitute specific markers of this kind of neurodegeneration. Better understanding the process that lead to protein aggregations and its abnormal processing in pathological conditions, could improve the differential diagnosis and would allow tracking the progression of the neurodegenerative disease.

2. Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia in older adults. Characterized for a severe cerebral atrophy that is associated to the presence of two types of structures, the neuritic plaques (NPs) and neurofibrillary tangles (NFTs). The density of these structures correlates with the clinical state of dementia and their presence offers a definitive diagnosis of AD at post mortem.

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2.1. Neuritic plaques

NPs, that could be found in normal aging brain, but in lower amount (approximately 1000 times less that in AD), are composed of a core of β amyloid fibrils (Aβ) closely associated with dystrophic neuritis distributed to the periphery of the amyloid core (Fig 1A). The biological Aβ peptide is a product of Amyloid precursor protein (APP) processed by several proteases (Fig 2).

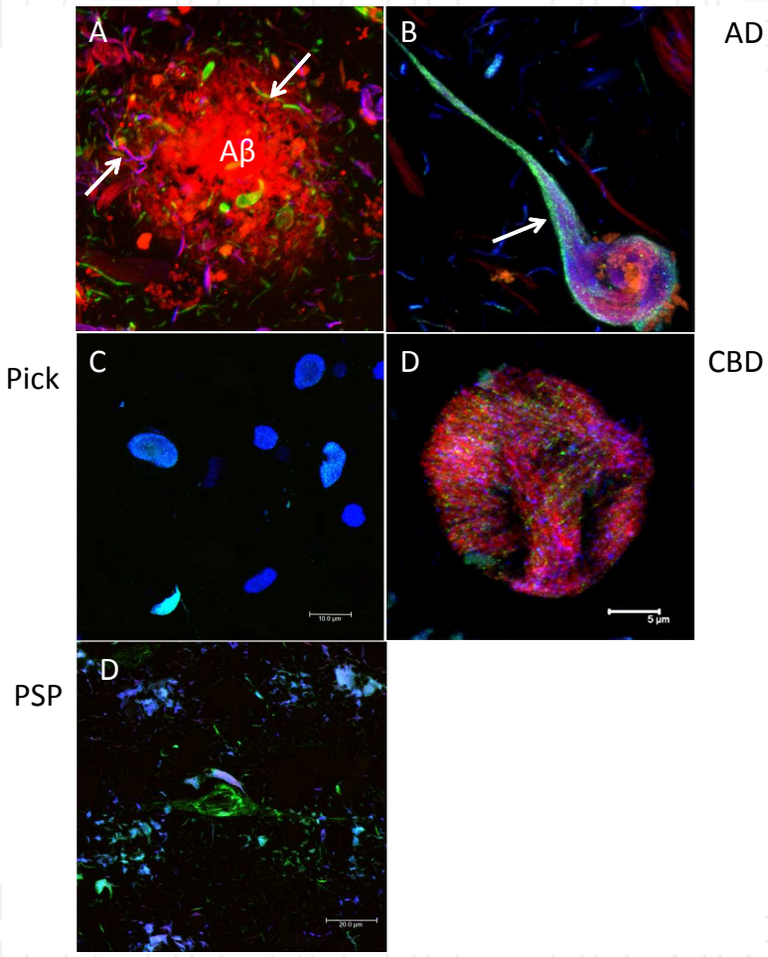


Figure 1. Histopathological lesions of human brain with dementia. A, B) Alzheimer´s disease, C) Pick's dementia, C) corticobasal degeneration D) progressive supranuclear palsy neurodegeneration. Triple inmunolabelling with antibodies raised against phosphorylated tau protein. A) neuritic plaque, amyloid beta peptide is evidenced by thiazine red dye, this dye recognized extracellular deposits of Aβ fibrillar. The dystrophic neurites are evidenced by antibodies raised against phosphorylated tau protein. B) Neurofibrillary tangles, evidenced by antibodies raised against phosphorylated tau protein at Thr231 (green channel) thiazine red (red channel) and phosphorylated tau at Ser396 (Blue channel). C) Pick Bodies in neuronal cells (Molecular layer of hippocampus) are detected by antibodies against phosphorylated tau protein at Thr231 (green) and phosphorylated tau at Ser396 (blue), thiazine red did not have affinity to this accumulation of tau protein. C) Ballooned neurons. Immunoreactivity to antibodies raised against phosphorylated tau at Thr231 (red channel), and tau pSer396 (blue channel). The expression of truncated tau protein at Asp423 (detected by antibody TauC3) showed a weak staining in a doted patter in the NFTs (green Channel). D) Immunureactivity of oligodendroglial coiled bodies and tufted astrocyes to phosphorylated tau protein at Ser202 and Ser205 (AT8 antibody, green channel) and phosphorylated tau at Ser396 (blue channel). Thiazine red showed a strong affinity for accumulations of tau protein in astrocytes and microglia.

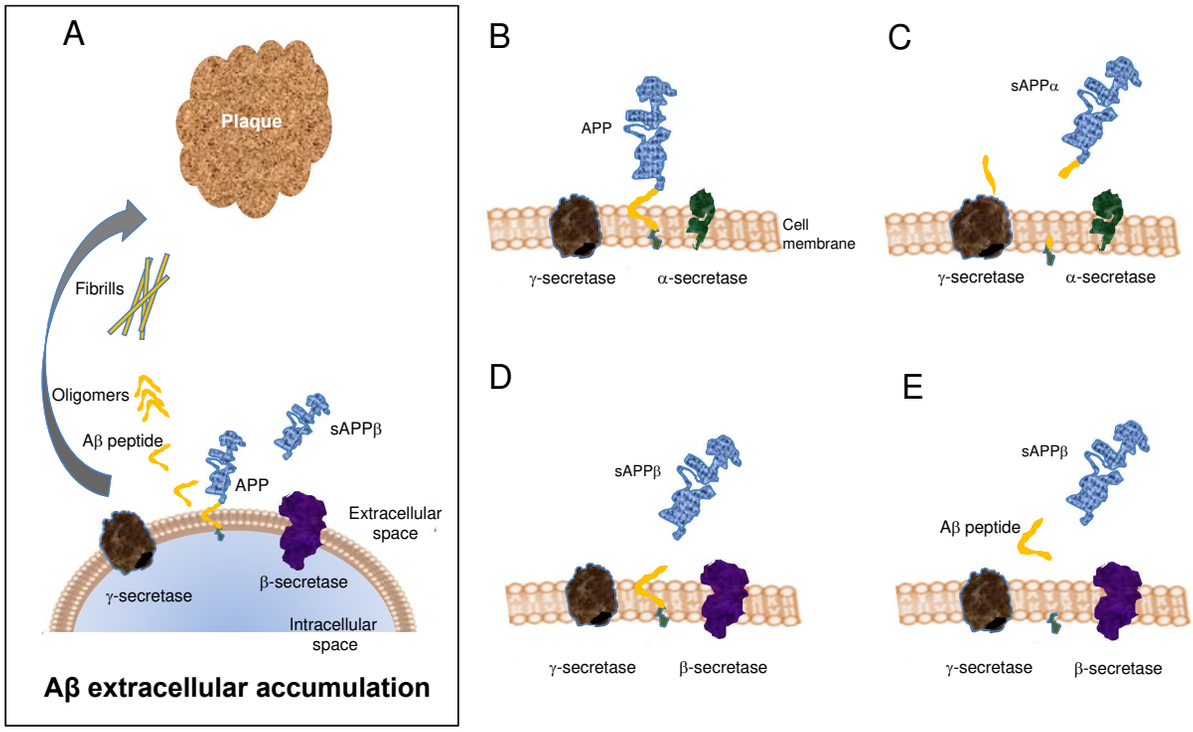


Figure 2. Processing of amyloid precursor protein. A) APP processing is the starting point of the formation of amyloid plaques. APP is a transmembranal protein that is processed by a series of proteolytical enzymes, releasing several fragments among themis the Aβ fragment that is released into the extracellular space which accumulates and forms amyloid-β plaques. B, C) APP processing to generate sAPPa fragment. C) non-amyloidogenic pathway of APP processing by α-secretase, generating a fragment called sPPAα, which is secreted into the extracellular space, subsequently proteolyzed by γ-secretase fragment remains in the membrane, leading to a small fragment called p3. D-E) amyloidogenic pathway. Alternative processing of APP, which generates the amyloid-β peptide, initiated by β-secretase, releasing a fragment called sPPAβ, being liberated into the extracellular space, the γ-secretase subsequently proteolyzed a fragment that is enclosed within the cell membrane releasing amyloid-β fragment into the extracellular space, that later could form amyloid-β plaques.

3. Amyloid precursor protein

The amyloid precursor protein (APP) is a type I transmembrane glycoprotein of approximately 120 kDa. APP has several isoforms derived from differential splicing, where the predominant variants are APP695, APP770 APP751(the numbers correspond to the number of amino acids (aa.) in each isoform). These three isoforms have in common the transmembrane region and the intracellular domain, however, in the brain, APP695 is the predominant APP specie present in neurons, while APP770 and APP751 and are primarily expressed in glial cells [9].

The human gene encoding APP, is located on chromosome 21, and was first identified in 1987 [10]. More than 76 mutations have been identified in APP, that cause the inherited form of AD and a related condition hereditary known as cerebral amyloid angiopathy. These mutations consist in amino acid substitutions within or adjacent the Aβ domain. However, even though

APP mutations are found only in rare cases of AD, they are important because they provide evidence that Aβ and APP play a central role in the pathogenesis of AD.

The APP is mainly located in the cell membrane, but has also been localized in the trans-Golgi, endoplasmic reticulum (ER) and endosomal and lysosomal membranes [11]. Aβ peptide release occurs where the secretase complex is precent and, therefore, is likely to be produced in various cell compartments. Most tissues and cells has the enzymatic machinery necessary to produce and degrade Aβ. This suggests that the production of Aβ from APP has a normal biological function. Since the discovery of the APP, a number of physiological functions have been attributed to this molecule, some of them unique to certain isoforms, but their actual functions remain unclear. It is important to mention that a number of functional domains have been assigned to the extracellular and intracellular APP regions. Most of these domains are binding sites for metals (copper and zinc), extracellular matrix components (heparin, collagen and laminin), neurotrophins and adhesion molecules, and protease inhibition domain (the protease inhibitor domain Kunitz present in the isoforms APP751 and APP770) [12].

APP processing by the complex of secretase enzymes, occurs thru two pathways: The non-amyloidogenic (Fig. 2 B, C) and amyloidogenic (Fig. 2 D, E). In the non-amyloidogenic pathway, APP is cleaved by the α-secretase, a membrane-associated zinc metalloprotease that belongs to the ADAM family (an enzyme in the family of metalloproteases and disintegrins such as ADAM9, ADAM10 and ADAM17). The cleavage by α-secretase occurs at amino acid position 83, counting from the carboxyl terminal domain of APP, where is a large ectodomain called sPPAα which is secreted into the extracellular milieu [13]. The resulting fragment of 83 amino acids, known as C83, is retained in the membrane and subsequently cut by the γ-secretase, resulting in a shorter fragment called p3, which is considered non-amyloidogenic although it is deposited in diffuse plaques [14]. The γ-secretase has been identified as an enzyme complex comprised of presenilin 1 or 2 (PS1 and PS2), nicastrin, APH-1 (anterior pharynx defective 1) and PEN-2 (presenilin enhancer 2). Importantly, the cleavage made by α-secretase occurs within Aβ sequence, between residues 16 and 17, which excludes the formation of this peptide (Fig. 2 B, C).

The amyloidogenic pathway is an alternative processing for APP resulting in the generation of Aβ. Initial proteolysis is mediated by β-secretase, the enzyme known as BACE1 (β-site APP-cleaving enzyme), at aminoacid position 99, counting from the C-terminus. This cut results in the release of a fragment called sPPAβ to the extracellular space and leaves the fragment C99 within the membrane, and generates the amino terminus for Aβ[15]. Subsequently, γ-secretase cuts at different points of the carboxyl terminus of the Aß, between amino acid residues 38 and 43, finally releasing the Aβ peptides [16]. (Fig. 2 D and E).

4. B-amyloid peptide

Most of the secreted Aβ peptide consist of 40 amino acid residues (Aβ40), while a small proportion, about 10%, comprise 42 amino acid residues (Aβ42) [11]. Because Aβ42 is more hydrophobic, aggregates rapidly and is more prone to form fibrils, which explains why this

isoform is predominantly found in brain plaques of AD patients. Historically, Aβ (1-40 aa.) and Aβ (1-42aa.) are the the main focus of research in the neurodegeneration field, because they are the most frequently found in NPs of AD brains. However, it is well established that Aβ truncated or modified forms at the N-and C-terminus are also present in AD brains. The Aβ C-terminus truncation may be due to the action of different γ-secretases. Furthermore, it has been confirmed a greater heterogeneity of species of Aβ truncated at the amino terminus in the core of the NPs [17].

5. N-terminal truncated species of amyloid β

The loss of the hydrophilic part located at Aβ amino terminus increases the hydrophobicity of this peptide, which favors their propensity to aggregate and deposit. It has been proposed that Aβ species truncated at the N-terminus play an important role in the pathogenesis of AD. In this respect, with mass spectrometry it has been identified in NPs, besides isoforms 40 and 42, two other peptideswith truncations at the amino terminus, one in the amino acid 3 of Aβ (3-42 aa.) and another at amino acid residue 11 of Aβ (11-42 aa.), with relative molecular masses of 4.2 kDa and 3.5 kDa, respectively [17]. Other in vitro studies have shown that a small increase in the physiological production of these species may be sufficient to trigger the formation of neuronal processes which induce changes in cytoskeletal proteins, moreover, It has been proposed that these amino-terminus truncated Aβ peptides might act as a center of aggregation of other Aβ neurotoxic species, that predominate in the core of the NPs [18]. Truncated species may be generated from APP through alternative processing by the BACE enzyme or produced from the full-length Aβ peptide (1-42 aa.) by extracellular amino peptidases. It is known that two isoforms of BACE are involved in the production of Aβ: BACE1 and BACE2, however it is established that the main neuronal protease BACE1 is required to cut an APP in sites 1 and 11 of the Aβ peptide. BACE1 is a transmembranal glycoprotein type I, that exhibits all the Properties of β-secretase. For example, the optimum pH is slightly acidic, is located in cell compartments where Aβ is generated, and cleaves APP in the β cleavage site with a high affinity for the swedish APP (swAPP), which is a mutated APP, associated with familial AD, known to increase the production of Aβ. Finally, BACE1 is present in the secretory cells (i.e. microglia) of Aβ and is highly expressed in neurons.

6. Aggregation of amyloid β

A common feature among several neurodegenerative diseases is that some mutations associated to them, lead to the expression of protein variants with an increased tendency to aggregate. Thus, conformational changes and aggregation of Aβ peptide are central features in AD.

Currently, there is evidence that Aβ monomers are not toxic to the cells and have a protective effects on neurons against oxidative stress [19]. However, there are many reports that indicate that the oligomers of Aβ, also known as soluble oligomeric ligands of amyloid-β peptide

(ADDLs) could be even more toxic than Aβ fibrils. The ADDLs mediated toxicity was described by Klein and colleagues, which found that the oligomers cause neuronal death in hippocampal slices at nanomolar concentrations [20].

The polymerization of Aβ monomers in the extracellular space of the brain appears to correlate with the presence of metals [21]. These same metals may generate reactive oxygen species (ROS), oxidative stress-producing agents. Iron, for example, is in the NPs. This could indicate that this metal has a toxic effect due to the promotion of ROS, but could also promote Aβ assembly [18]. It is known that transition metals produce oxidative stress through the generation of reactive oxygen species (ROS) and recently was noted that the presence of these metals may be related to the polymerization of the monomers of Aβ in the brain neuropil space [21]. Thus iron in NPs, seems to have toxic effects because it promotes the formation of ROS as it enhances Aβ assembly [18].

7. Tau protein – AD brains

7.1. Normal tau

The interaction between the microtubule motor proteins and microtubules is regulated by tau protein, which operates and controls the movement of axonal organelles such as mitochondria and vesicles favoring the function and viability of neuronal cells [22] (Fig 3A). Proline-rich region at the N-terminus, interact with proteins containing an SH3 domain and with FYN tyrosine kinase. FYN interaction is highly relevant for routing toward the postsynaptic region, since this kinase phosphorylates the NMDA receptor 2B subunit [23]. This phosphorylation enables interaction of NMDA receptor with the postsynaptic density protein 95 (PSD95) and this interaction is required for the excitotoxic signaling[24].

Two main regions characterize the tau molecule, the N-terminal portion that accounts for two-thirds of the molecule, and the proline-rich region. The N-terminus region is subdivided into two subregions: one acidic, which has been proposed as a possible binding site for metals [25]. The other region is the proline-rich region. This site has a high amount of amino acids potentially susceptible to phosphorylation and appears to be important for the binding of tau to microtubules [26]. Other important regions in tau protein are: the microtubule binding domains including the repeats 3 or 4 with 31 or 32 aa's. and theC-terminal region, that also contains a proline rich region and an acidic region (Fig 3).

tau is encoded by a single gene located on chromosome 17q21. The gene has 16 exons, in which through alternative splicing 6 isoforms are generated in the Central Nervous System (CNS). These isoforms vary in length by including exons 2, 3 and 10, with a maximum length of 441 amino acids in the largest protein isoform. In sporadic AD, no mutations of the tau protein have been reported.

The tau protein is susceptible to posttranslational modifications that have direct effects on their function (Fig. 3B). The most important modification is the phosphorylation of certain residues that regulate microtubule binding. The coordinated activity of kinases and phosphatases

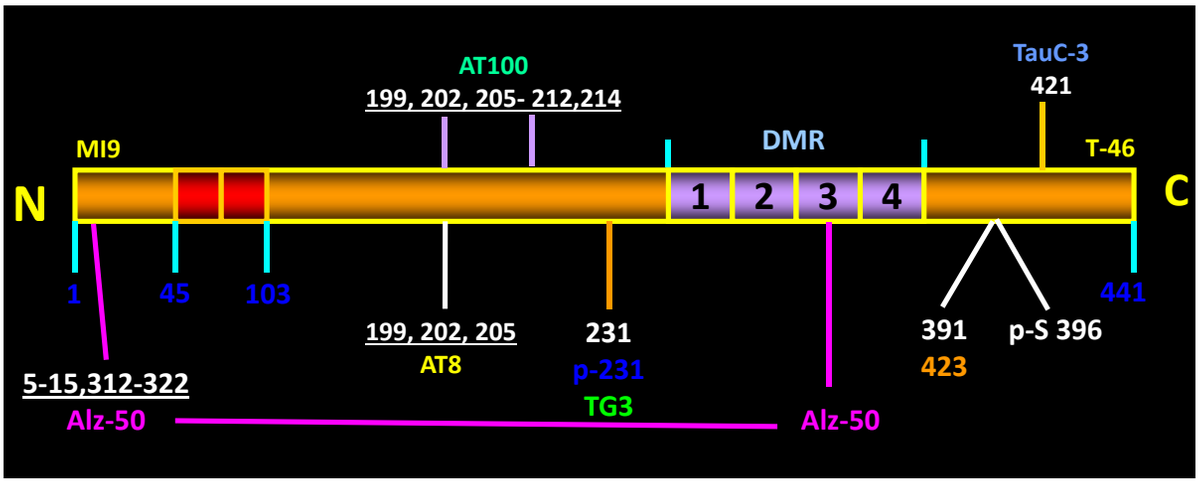


Figure 3. Schematic representation of the functional domains of the longest tau isoform. The projection domain, including an acidic and a proline-rich region, interacts with cytoskeletal elements between microtubules in axons. The N-terminal region is also involved in signal transduction pathways by interacting with proteins as PLC-γ and Src-kinases. The C-terminus part, referred to as microtubules binding domain, regulates the rate of microtubules polymerization. In this schematic diagram it is depicted the site were some tau antibodies specifically recognize tau protein epitopes.

regulate the phosphorylated state of the protein, which decreases when the level of phosphorylation promotes microtubule binding. Otherwise, the increased phosphorylation of the protein in these residues facilitates disassembly of the microtubule. tau protein has 85 potential phosphorylation sites, of which a large amount is not involved in the normal regulation of its association with microtubules [27].

tau protein may undergo other posttranslational modifications such as glycosylation, nitration, poliamination, ubiquitination and SUMOlyzation [28], which role is not well understood. These changes seem to be more involved in the deregulation of the normal function of the tau protein favouring other effects such as loss of function and promotion of abnormal aggregation characteristic of the large group of diseases with tau alterations (tauopathies), including AD.

7.2. Abnormal post-translational modification of tau

Several studies have confirmed the importance of tau abnormalities as a mechanism that alters its microtubule binding capability, and promotes abnormal aggregation [29, 30]. Phosphorylation is a major post-translational modification of tau that regulates microtubule binding and release. Tau protein is equipped with 85 phosphorylation sites, 45 serines, 35 threonines, and 5 tyrosines [28]. Increased phosphorylation reduces its affinity for microtubules, resulting in disruption of the cytoskeleton, particularly phosphorylation at threonine 231 and serine 293, 324 and 356. It has been described 30 phosphorylation sites related to AD. *In vivo*, the kinases that are more associated with tau phosphorylation are glycogen synthase kinase-3β (GSK3β), cyclin-dependent kinase 5 (CDK5) and the microtubule-affinity regulating kinase (MARK) [28, 31].

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Kinases that contribute mainly in the abnormal phosphorylation of tau protein are: GSK3β, CDK5 and MARK. In AD and other tauopathies an alteration in the expression or in the activity of these kinases has been reported [32, 33].

Moreover, tau protein is a substrate for various proteases such as calpain, caspase 6 and caspase-3, shown by *in vitro* experiments [34, 35]. However, this effect has not been recognized as a normal mechanism and it has been proposed that endogenous proteolysis contributes tau aggregation process and abnormal toxicity. The most relevant truncations in AD are those occurring in the Asp421 and Glu391 of tau C-terminus [34, 36-38]. There is controversy about the genesis of these truncations, and it has even been postulated that they are mutually exclusive, but occur in a continuous process along AD porogression [39-41] and contribute to the formation of NFTs [40]. Moreover, it has also been proposed that such truncations occur very early in the disease and do not necessarily participate in tau assembled, thus these truncations can be observed in the unassembled amorphous aggregates of tau protein [42]. Notwithstanding these studies it has been found that there is a pathological effect of these truncations, reflected in an increased cytotoxicity when they are overexpressed in cultured neuronal cells *in vitro*. Finally, the accumulation of these truncated forms in brain tissue of subjects with AD, seems to correlate with AD clinical diagnosis and progression [40], which makes the truncation of tau protein an important biomarker in the diagnosis AD.

The truncated form of tau protein in the Glu391, is characterized as a 12 kDa fragment, with a length of 92 to 95 amino acids corresponding to the region of the microtubule binding domain. This fragment is known as paired helical filament minimum core (PHFcore) [43]. tau PHFcore has high affinity for the intact tau protein. The association of tau full length with the PHF core, triggers a molecular mechanism of phosphorylation and subsequent truncations that could induce the formation of a new tau fragment truncated at Glu391 that would have affinity for more intact tau molecules, thus inducing phosphorylations and truncations of these intact full length tau molecules, self-propagating this capture-breaking process generating more aggregated PHFcores that forms stable insoluble filaments [36]. The PHFcore fragment is recognized by antibody 423 [44]. So far the PHFcore seems to be the only peptide whose cytotoxicity has been demonstrated by Fasulo et al [45], in COS cells co-transfected with the cDNA of full length tau protein and the sequence for the PHFcore, reporting that these cells died by apoptosis. This showed the high toxicity of tau truncated at Glu391. This finding in a cell model, together with molecular neuropathology studies, which showed that tau truncation at Glu391 correlates with AD pathology and other tauopathies, suggests that this PHF core could be used as an accurate marker for this type of neurodegenerative disease. This type of propagation of the pathological tau specie (PHFcore), resembles prions disease “infectious process”, thus modified tau could induce pathological changes in normal tau, which in turn would modify more normal tau molecules. This new approach to understanding AD pathology in terms of protein seeding had been proposed by several groups [46-48], however, since 1993, the group of Novak [43], had already called the PHFcore as "tauon", considering its prion like behaviour.

Glycation is a non-enzymatic glycosylation observed during aging, and its modified products cannot be degraded or eliminated by the normal clearance mechanisms. These products also contribute to the generation of free radicals. tau is a substrate of glycation and this modification increases the capability of tau to form aggregates and stabilize the formation of polymers of this protein [49]. O-GlcNAcylation may regulate phosphorylation of tau in a site-specific manner. Moreover O-GlcNAcylation at Ser356 greatly slows down the aggregation speed of tau and also reduces its phosphorylation by GSK3β and CDK5 [50].

Other dementias known as tauopathies, such as Pick's disease, hereditary frontotemporal dementia with Parkinsonism linked to chromosome 17, sporadic corticobasal degeneration and progressive supranuclear palsy, are also associated with post-translational modifications of tau protein. In these neurological disorders, it has been described that tau protein is aggregated in characteristic lesions that include pick bodies (Fig 1D), the NFTs, granulo-vacuolar degenerations, the threads of neuropil, and dystrophic neurites. In most of these lesions, it has been reported that tau protein undergoes the same posttranslational modifications that occur in AD, mainly hyperphosphorylation at various domains [51]. However, in other diseases characterized by the presence of filamentous tau protein, known as tauopathies, several mutations of this gene occur, mainly the P301L mutation, which is associated with the frontotemporal degeneration with parkinsonism linked to chromosome 17 (FTLD17). This mutation is the most widely studied in various *in vivo* models [52]. Apart from mutations, there are truncations in tau protein that are associated to this disease, such as endogenous truncation and mainly the C-terminus truncation at the Asp421 [51].

8. α-synuclein and Parkinson's disease

In elder adults, Parkinson's disease (PD) is a major cause of movement disorders. This disease is characterized by loss of dopaminergic neurons of the compact substantia nigra, which results in lowering of dopamine in the striatum. PD belongs to a group of neurodegenerative disorders called Lewy bodies diseases (ECL) [53] (Fig 1 C). The major components of Lewy bodies are aggregates of filamentous α-synuclein (αS) protein (Fig 5C). The human α-S is a 140 amino acid protein. This protein consists of three regions: an amphipathic N-terminal (amino acids residues 1-60), non-β-amyloid component (NAC) hydrophobic central region (amino acids residues 61-95) and an acidic C-terminal region (amino acids 96-140) [54].

αS belongs to the family of Synuclein included beta-synuclein (β-S), and γ-synuclein (γ-S) [54]. The Synuclein genes are highly conserved between species. Synuclein family was found in vertebrates and has never been observed in unicellular organisms. In invertebrates it has been observed an homologous to the synuclein protein.

With regard to the normal function of the αS, little is known. However, it is reported that αS is expressed at high levels in the brain, specifically associated to neurons, and also has been observed expression in other tissues such as hematopoietic cells. αS can be associated to lipids, in neurons it has been observed associated with synaptic vesicles modulating its activity, suggesting that under normal conditions αS could be involved in various functions associated

with neurotransmission and synaptic plasticity [55]. Also, it was shown that αS participates in synaptic plasticity during development and learning [54] and in the regulation of synaptic vesicle mobilization in nerve terminals [56].

Immunostaining with antibodies recognizing αS in normal human brain, shown a diffuse pattern in the neuropil-like synaptic region. However, in PD brains, αS immunoreactivity is also strong in some of the Lewy bodies and neuronal processes [57]. Currently, ubiquitin immunostaining and eosin staining, are the most widely used technique to demonstrate Lewy bodies in PD brains. Biochemical studies have shown that αS is the most abundant protein in Lewy bodies and it is located in the fibrous material contained in this structure. αS pathological deposits are less soluble than the normal synuclein. This is possibly due to posttranslational modifications such as truncations, nitrations, and phosphorylations, ubiquitination. αS undergoes pathological modifications in PD. It should be emphasized that although αS is a neuropathological marker of PD as well as dementia with Lewy bodies (DLB), there is no evidence that αS is related to the cause of these disease.

In vitro studies suggest that the hydrophobic region of αS NAC is essential for the aggregation and toxicity of the molecule [58]. This region is partially absent in β-Synuclein (βS), which may explain why the βS has a low ability to auto-aggregate and form oligomers and fibrils [59, 60]. Hashimoto et al (2001), demonstrated, that βS interacts with αS and it is capable of preventing αS aggregation *in vitro* and *in vivo* [59]. *In vitro* studies have shown that βS by itself tends to associate strongly with αS to form aggregates [61][58]. Studies suggest that the aggregates are formed from intermediate forms (with unchanged conformation) partially folded structures, which would give rise to the fibrils. Previous structures of these fibrils are oligomers and annular protofibrils forming pore-like structures [62]. However, the mechanisms by which they form oligomers and then fibrils are not yet understood.

Some changes in αS protein are posttranslational, which have been associated with a role as mediators of the cytotoxicity of this protein.

Furthermore, the pathological αS is characterized by phosphorylation at Ser129 which is detected by immunohistochemistry in Lewy bodies in PD human brain. The Kinase responsible for this phosphorylation is casein kinase II and GRK2/5, which phosphorylates αS *in vitro*. Originally, the Ser129 phosphorylation was found in a Drosophila model, which generated a pseudophosphorilation (S129A) from the regular αS. This modification resulted in a tendency to intracellular accumulation of this protein (αS), compared with wildtype organisms. This change was not associated with any toxicity, olthough this still is controversial and it is need to clarify the role of phosphorylation at Ser129 αS in the molecular pathology of PD.

The truncation of αS has been associated with its high capacity of aggregation. Ttransgenic mice expressing truncated αS have substantial cell loss especially in the brain. Truncated species of αS were found in the lysosome suggesting its proteolysis in these organelles, nonetheless α-synuclein is also a substrate for cytoplasmic calpains [57].

In the pathogenesis of diseases with Lewy Bodies, interactions between β-amyloid protein and αS are crucial. For example, Aβ worsens associated deficit coused by αS accumu-

lation and also promotes oligomerization of αS [63]. It has also been demonstrated that in pathological conditions both aggregates of αS and Aβ, are membrane-associated. It is suggested that lipid rafts can be a suitable site for abnormal interactions between the aggregated forms of α-S and Aβ. These aggregated forms are also described in various intracellular membranous structures [59].

To elucidate how the interactions between αS and Aβ influence its aggregation properties, *in vitro* studies were done. Evidence, demonstrated that β-amyloid promotes αS aggregation *in vivo*, on the other hand, in APP transgenic mice, it was observed an accumulation of αS. Therefore, It was hypothesized that β-amyloid, αS, and tau protein promote the accumulation of each other [64], in recent years, there have been a number of studies that support this hypothesis.

The αS has become one of the key proteins in the aetiology and pathogenesis of some of the most common neurodegenerative diseases, such asPD.

It is suggested that the Lewy bodies (LB) constitute an histpopathological marker that correlates with the onset of symptoms of dementia. In 10-20% of the cases of dementia with LB it is observed also the presence of NFTs and NPs at Braak stages V and VI, suggesting that this type of neurodegeneration could share pathologic features with AD. The molecular analysis of LB in PD and dementia associated with Parkinson's disease are indistinguishable, however the difference is based on the localization of these lesions. Using double immunostaining it is possible to observed the presence of epitopes of phosphorylated and non-phosphorylated tau protein, in the periphery of the LB or colocalizing with these structure and with αS aggregates. *in vitro* studies had shown that alpha synuclein preformed fibrils may promote the formation of fibrils of phosphorylated recombinant tau protein, that is insoluble and thioflavin-S positive.

9. Taupathies

The Tauopathies are classified according to the predominant species of tau that accumulates: tau proteins containing 3 (3R) or 4 repeats (4R) of microtubule binding domain. In Pick's disease (PiD), 3R tau predominates, whereas 4R tau is characteristic of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) [65].

PiD is the least common FTLD-tau characterized by neuronal Pick bodies in a stereotypic neuroanatomical distribution. PSP and CBD are more common than PiD and have extensive clinical and pathologic overlap, with no distinctive clinical syndrome or biomarker that permits their differentiation. The hallmark’s to diagnosis rests upon postmortem analysis of the human brain and demonstration of the presence of tangles, oligodendroglial coiled bodies and tufted astrocytes in PSP or threads, pretangles and astrocytic plaques in CBD. The anatomical distribution of tau pathology determines the clinical presentation of PSP and CBD, as well as PiD

10. Pick´s disease

In Pick's disease the first symptoms occur in emotional and social functioning. It is the mood changes, often biased towards euphoria, disinhibition and deterioration in social skills that are so noticeable. Pick's disease generally occurs between the ages of forty and sixty years of age. In PiD brain tissue changes and neuronal loss occurs in focal areas rather than the generalized damage of Alzheimer's. Pick's disease affects the frontal and temporal lobes of the brain. Marked shrinkage, called atrophy, of the frontal lobes of the brain occurs that can be seen on brain scans. Pick's disease is marked by the presence of abnormalities in brain cells called Pick's bodies. These are found in the affected areas as well as elsewhere in the brain. Pick's bodies are fibres that look very different from the neurofibrillary tangles found in Alzheimer's disease. Pick's bodies are straight rather than paired and helical. Pick bodies, are characterized by the presence of distinct argyrophilic (silver staining) spherical inclusions called Pick bodies and globose neurons. Pick bodies are composed of tau protein enriched in 3R tau, which can be evidenced with biochemical studies [66] or more recently with antibodies specific to tau isoforms. Mondragon-Rodriguez et al (2008) [51], conducted an immunohistochemical study and confocal microscopy analysis of brains section of Pick body dementia, and showed phosphorylation epitopes and conformational changes of tau protein that are described in AD.

11. Cortico basal degeneration

CBD is a progressive neurological disorder characterized by neuronal cell loss and *atrophy* (shrinkage) of multiple areas of the brain including the cerebral cortex and the basal ganglia. CBD progresses gradually. Initial symptoms, which typically begin at or around age 60, may first appear on one side of the body (unilateral), but eventually affect both sides as the disease progresses. Symptoms are similar to those found in Parkinson disease, such as poor coordination, *akinesia* (an absence of movements), *rigidity* (a resistance to imposed movement), *disequilibrium* (impaired balance); and limb *dystonia* (abnormal muscle postures). Other symptoms such as cognitive and visual-spatial impairments, apraxia (loss of the ability to make familiar, purposeful movements), hesitant and halting speech, *myoclonus* (muscular jerks), and *dysphagia* (difficulty swallowing) may also occur. An individual with CBD eventually becomes unable to walk.

CBD is a sporadic neurodegenerative process related to abnormal aggregation of hyperphosphorylated tau protein. This disease is associated with abnormal insoluble tau isoforms with four conserved repeat sequences (4R tau). Neuropathological criteria for CBD emphasize the histopathological findings of tau-immunoreactive lesions in addition to ballooned neurons, cortical atrophy, and nigral degeneration. The ballooned achromatic neurons, were once emphasized as a major component of the histopathology and gave the disorder its original name. Abnormal tau immunoreactivity is found in both the neurons and the glia. In neurons, tau immunohistochemistry reveals diffuse or granular cytoplas-

mic staining, pre-tangles, and small neurofibrillary tangles. These probably account for the corticobasal inclusions found in subcortical gray matter regions including the substantia nigra. tau immunoreactive threads in both neurons and glia are numerous in gray and white matter. CBD pathology includes astrocytic plaques with tau deposition largely in the distal processes of astrocytes. These astrocytic plaques are distinct from tufted astrocytes found in PSP, where tau is deposited more proximally to the cell body as well as in distal processes. Both CBD and PSP had in common oligodendroglial inclusions, coiled bodies, and threads, although the astrocytic changes can distinguish between the two disease (CBD or PSD). In addition, while threads are numerous and diffuse in CBD, they are rarely seen in the cerebral cortices in PSP, although they may be dense in other areas. A recent neuropathological study has discovered the presence of TAR-DNA-binding protein 43 (TDP-43) in a subset of patients with CBD pathology. There was no clear clinical correlation with the presence of TDP-43 inclusions in CBD [67].

12. Progressive supranuclear palsy

Progressive supranuclear palsy affects men and women equally and in most cases it appears as a atypical parkinsonism with axial rigidity, postural instability and unexplained falls, with most patients also developing progressive vertical gaze palsy (for which the disorder is named), dysarthria and dysphagia [68] PSP has asymmetric cortical atrophy and can clinically mimic CBS. The pathologic diagnosis is made by the microscopic findings of globose neurofibrillary tangles and variable neuron loss with gliosis of the globus pallidus, subthalamic nucleus, periaqueductal grey matter of pons, and substantia nigra. Mutant tau protein is present in inclusions [69, 70].

Whereas 4R tau is characteristic of corticobasal degeneration (CBD) and progressive supranuclear palsy. Diagnosis rests upon postmortem examination of the brain and demonstration of globose tangles, oligodendroglial coiled bodies and tufted astrocytes. The core neuroanatomical regions affected in all cases of PSP include the basal ganglia, subthalamic nucleus and the substantia nigra. Cortical involvement is greatest in motor and premotor cortices. Pathology of the cerebellar dentate nucleus and the cerebellar outflow pathway (dentato-rubrothalamic pathway) is usually severe and associated with profound atrophy of the superior cerebellar peduncle.

13. Conclusion

This review, gives a neuropathological approach towards finding biomarkers for dementia. However, finding the optimal biomarker for each neurodegenerative disease is still in an experimental face. In the case of AD, it is required far deeper molecular and immunohistochemical studies of abnormal tau posttranslational modifications (i.e. phosphorylation and

truncation) and better understanding of its contribution to the development of dementia, particularly, it is important to understand the role of the paired helical filaments, that accumulate in the neuronal soma, promoting degeneration and cell death. Of relevance is to consider that in other dementias such as tauopathies, tau protein processing resembles the initial steps in AD, although there is no well-defined neuropathological impact of tau aggregation in lesions such as Pick bodies, Lewy bodies, as well as the presence of tau in NFTs and glial cells in CBD and PSP. Therefore, all efforts should be focused on determining reliable biomarkers for each of the dementias with the aim of generating new improved diagnostic approaches for early detection of these neurodegenerative diseases.

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