Minireview

Tau phosphorylation and aggregation in Alzheimer's disease pathology

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Abstract In this article I shall review how tau phosphorylation and aggregation participates in Alzheimer's disease (AD) and other tauopathies. Tau, a microtubule associated protein, is the main component, in phosphorylated form, of the aberrant paired helical filaments found in AD. Tau is present in phosphorylated and aggregated form not only in AD, but in other pathologies (tauopathies). In this review, the phosphorylation of tau, its aggregation, and the possible relation between tau phosphorylation and aggregation is, briefly, described. Also, it is discussed the toxicity of modified tau. In addition, I propose a working model detailing the progression of tau pathologies.
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1. Introduction

Tau protein was first discovered as a microtubule associated protein that lowered the concentration at which tubulin polymerizes into microtubules in the brain [1]. Subsequently, two additional consequences of tau binding to neural microtubules were identified, a positive and a negative one. The positive effect of tau is to stabilize assembled microtubules permitting neurite extension and stabilization [2,3]. The negative effect is that tau competes with the motor protein kinesin for microtubule binding [4–6], leading to a decrease in axonal transport [4–6]. It is possible that an equilibrium between these two effects is necessary for correct axonal transport via stable microtubules. Nevertheless, proteins other than tau may also be involved in these processes since mice lacking tau do not display important differences with respect to wild type mice [7,8].

Some twenty years ago, additional interest in the tau protein arose when it was identified as a component of the paired helical filaments (PHFs) in 1986 [9]. PHFs contribute to neurofibrillary tangles (NFT), protein aggregates that along with senile plaques, are the aberrant structures found in the brains of patients with Alzheimer's disease (AD) [10]. At virtually the same time, it was further shown that tau was probably the main component of PHFs since it alone was able to form PHF-like structures [11]. The contribution of Tau to PHFs was further confirmed in elegant biochemical studies [12,13], and PHF-tau was demonstrated to exist in a hyperphosphorylated form [14]. Indeed, tau hyperphosphorylation was provoked a decrease in the binding of tau to microtubules [15].

Different isoforms of the tau protein can be expressed as the result of differential RNA splicing and each of these displays a different degree of phosphorylation [16,17]. All the isoforms are capable of polymerizing into fibrillar structures [18] such as those present in AD. Significantly, tau polymers can also be found in other neurodegenerative disorders characterized by the presence of phosphotau aggregates, the so-called tauopathies [19]. Thus, the pathologies associated with tau are related to its phosphorylation and its aggregation, the two points on which this review will be focused.

2. Tau phosphorylation

The serine/threonine phosphorylation of tau is a modification that can affect a total of 79 residues in the longest tau isoform in the central nervous system of 441 residues [20], and it is that which has been most studied. In AD, at least thirty serine/threonine residues are phosphorylated [21,22] by two different types of kinases: proline directed kinases, like GSK3, cdk5, p38 or JNK; and non-proline directed kinases, like PKA, PKC, CaMKII, MARK or CKII [22–31]. Moreover, it appears that this phosphorylation often regulates the binding of tau to microtubules [15]. Among the kinases identified above, GSK3 plays an important role in regulating tau phosphorylation under pathological conditions. Indeed, a link between tau phosphorylation, by GSK3, and the formation of aberrant tau aggregates has been established in certain mouse models [32,33]. There is also evidence that pseudohyperphosphorylated tau is toxic to cells and that is associated with the induction of apoptotic cell death [34]. Indeed, since phosphorylated tau appears to be more resistant to proteolysis by different proteases [35,36], this phosphotau could accumulate in neurons, thereby exerting its toxic influence on the cell.

3. Tau phosphorylation by GSK3 in FAD

A particular class of AD, familiar AD (FAD), is associated with mutations in the genes app, ps-1 and ps-2 [37], which are responsible for the expression of the proteins APP, PS-1 and PS-2. APP is the protein precursor for the main component

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PS-1
mutations

(lack or deletion
of PS-1)

γ secretase ▲
(gain of function)

binding cadherin ▼
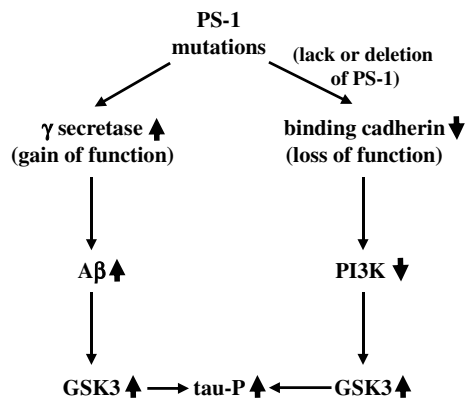(loss of function)

Aβ▲

PI3K ▼

GSK3 ▲ ⟶ tau-P ▲ ◀— GSK3 ▲

Fig. 1. Tau phosphorylation promoted by PS-1 mutations. PS-1 is a protein present in the γ-secretase complex that can also bind to cadherins and to the regulatory subunit of PI3K. Mutations in PS-1 could result in an increase of γ-secretase activity and may promote an increase in the amount of beta amyloid peptide and in GSK3 activity. As a consequence tau phosphorylation will increase. In contrast, other PS-1 mutations, or the lack of PS-1, may diminish PI3K activity, also resulting in an increase in GSK3 activity and in tau phosphorylation.

of senile plaques, the beta amyloid peptide (Aβ), whereas PS-1 and PS-2 are components of a protein complex that displays proteolytic activity and that is involved in the cleavage of APP to yield Aβ. The current hypothesis, the Aβ cascade hypothesis [38], proposes that the accumulation of Aβ may be augmented by mutations in APP that facilitate its cleavage to Aβ. Alternatively, it has been suggested that gain of function mutations might increase the activity of the protease complex in which PS-1 or PS-2 participates, thereby augmenting its activity towards APP and the production of the Aβ peptide. The accumulation of Aβ in turn facilitates tau phosphorylation by kinases like GSK3 [39].

However, the validity of this hypothesis has been recently been questioned, since pathological tau isoforms (phosphorylated tau) can accumulate in the absence of the Aβ peptide. Indeed, there is a neurological disorder that appears to be promoted by mutations in PS-1 [40,41], mutations that result in tau hyperphosphorylation in the absence of Aβ aggregates [42]. Thus, different mutations in FAD associated genes, such as PS-1, can produce either a gain or loss of function that facilitate tau phosphorylation (see Fig. 1), a main feature of AD and other tauopathies. Accordingly, tau is hyperphosphorylated in other tauopathies and in some of these disorders, like frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP) or corticobasal dementia (CBD), mutations in the tau protein itself appear to facilitate its phosphorylation, aggregation, and the onset of the disease [19].

4. How is tau phosphorylated in other tauopathies like FTDP-17

A familiar form of FTDP-17 has been related to alterations of chromosome 17, in the q 21.2 region [43]. This is the locus of the tau gene and mutations in this gene have been associated with FTDP-17 in some patients [19]. These mutations proved to be either missense, deletions, or silent mutations in exons or introns, and they might affect tau RNA splicing [44]. One consequence of these mutations may be a loss of the capacity

to bind PP2A, the protein phosphatase that is mainly responsible for the dephosphorylation of phosphotau [45]. This would result in the accumulation of this mutated and phosphorylated tau, since it will not be dephosphorylated. In other tauopathies linked to mutations in tau like PSP or CBD, an association has also been made between the phosphorylation of the protein and the onset of the disease [19,44].

5. Tau aggregation

5.1. In vitro

As indicated above, the assembly of the tau protein into fibrillar polymers resembling the PHF found in the brain of AD patients in vitro was first described in 1986 [11]. However, a large amount of tau was required to produce polymerization in vitro [7,11,46,47]. Nevertheless, the minimum tau concentration needed for its assembly could be lowered in the presence of inducers, an effect that has been attributed to sulfoglycosaminoglycans, like heparin, which facilitate tau polymerization in vitro [48,49]. Similarly, fatty acids like arachidonic acid (or its peroxidation products [50]) can induce tau polymerization in vitro [51] and more recently, quinones such as CoQ_0, have been shown to induce tau polymerization [52]. The minimum region required for tau self-assembly has been mapped to the third tubulin binding motif of the tau molecule [49,53] and within this motif, two peptides have been implicated in self-assembly. Specifically, these involve a peptide containing residues 306–301 (peptide 1) that is able to self-assemble in the absence of any added compound [53] and a peptide containing residues 317–335 (peptide 2) [49]. Characterization of tau variants lacking either of these peptides indicated that while peptide 1 facilitates tau assembly, it is not essential. In contrast, the presence of peptide 2 is a requisite for tau polymerization in the presence of quinones (Santa-Maria et al., to be published). A model to explain the influence of both peptides in promoting filament formation has recently been proposed [54]. In this model, it is suggested that tau will only assemble after these two peptides undergo a conformational change, P1 forming a β-sheet structure and P2 an α-helix [54].

5.2. In vivo

In mice, two approaches have been followed to mimic the AD [55] or FTDP17 (see for example [56,57]) tauopathies. In the first case, human tau was overexpressed in a mouse lacking the endogenous tau protein [55] while in the second model, human tau protein bearing some of the mutations found in FTDP17 patients was expressed in mice [56,57]. In both cases, hyperphosphorylated tau filaments were generated. In the mouse model of the AD tauopathy, human tau expression was driven by its own promoter, whereas in FTDP17 model, tau was expressed under different promoters that controlled the expression of tau (and the pathology) in neurons at different locations [58]. It has been suggested that the onset of distinct tauopathies in different localizations could be due to variations in environmental conditions, or related to different tau mutations. Indeed, in some cases, the presence of different tau variants could play a role in the formation of tau polymers in distinct types of neurons. Hence, Goedert suggested [44] that changes in the first tubulin binding motif of the tau molecule could be related to the onset of Pick's disease, whereas changes in the C-terminal domain of the tau molecule could be related

to the onset of AD. Similarly, changes in 4R/3R ratio could promote the appearance of CBD or PSP.

5.3. Are tau aggregates toxic?

The discovery of mutations in the tau gene that promote familiar FTDP-17, provided clear evidence that defects in tau alone are sufficient to cause neurodegenerative disorders [59–61]. As indicated above, tau pathologies can be reproduced in specific locations of the mouse brain by expressing human tau driven by different promoters. However, tau pathology in AD follows a clear and specific kinetic pathway that does not usually correspond to that found in animal models. Some time ago, the different stages of tau pathology in AD were described by Braak and Braak [62] and more recently, a similar description was made by Delacourte et al. [63]. Tau pathology starts in the entorhinal cortex (EC), from where it spreads to neighbouring regions, like the hippocampus (Fig. 2). Neurodegeneration was found in these regions and as a consequence, extracellular ghost tangles (eNFT) could be observed as described in the pioneer work of Alzheimer [10]. In the hippocampus, an inverse relation has been found between the number of eNFT and the number of surviving neurons [64–66]. Thus, this data would suggest that the neurons which degenerate previously develop tau aggregates. Recent experiments done in cultured cells, expressing tau protein fragments [67] support that view. That degeneration could be related to a possible sequestration, by the sticky tau aggregates, of different proteins important for cell function [68,69]. On the other hand, it is clear that the degeneration of neurons could also result in the appearance of extracellular unpolymerized tau, which could finally be found in the cerebrospinal fluid of AD patients [70]. Nevertheless, it has also been proposed that neurons bearing neurofibrillary lesions could survive for long periods of time, and it has been suggested that these aggregates may

not be toxic but rather that they could protect against degeneration in a similar way to the aggregates found in Huntington's disease [71]. Accordingly, it has been proposed that tau aggregates might protect against neurodegeneration by sequestering the toxic phosphotau that accumulates in a neuron under pathological conditions [72]. More recently, it was shown that the memory defects observed in a transgenic mouse model in which tau filaments accumulate were unrelated to the presence of those tau polymers [73], a result that agrees well with previous experimental data from Drosophila [74]. In contrast, it was suggested that intermediate tau aggregates, rather than PHF-like structures could be involved in neurodegeneration [75]. Native tau can be found in the form of small oligomers [76]. Furthermore, the fact that FTDP-17 patients suffer extensive neurodegeneration with a high level of tau phosphorylation but with few tangles, also supports the possible existence of toxic, modified tau in human tauopathies [77]. Our preliminary results (Gomez-Ramos et al., to be published), suggest that some tau proteins are toxic to cultured neuronal cells, and that such toxicity could change upon tau aggregation.

5.4. A working model

Taking into account all the data reviewed above, I propose a working model to explain the spreading of tau pathologies. This model is based on the fact that tau, when is not bound to microtubules, or is in modified form, is toxic to neuronal cells. In AD, the tau pathology starts in the entorhinal cortex. If the probability of neuron death in this region were similar to that in other regions, it might be possible to explain the onset of the tau pathology in the EC if the EC cells were to have a lower proportion of their tau bound to microtubules, or in modified form. Indeed, a lower affinity for tau to microtubules in entorhinal neurons has already been proposed [78]. Through
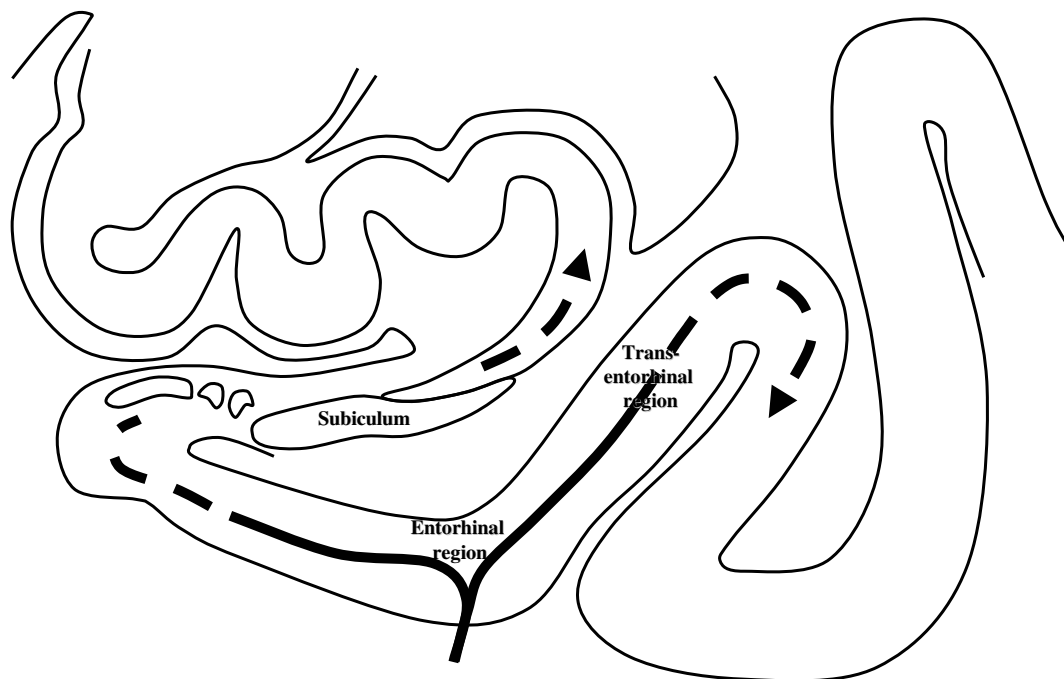

Fig. 2. Progress of tau pathology in AD. The scheme, first indicated by Braak and Braak [62], shows the initiation of the tau pathology in the entorhinal cortex and its spreading to neighbouring regions from that point.

the degeneration of these neurons, the proportion of tau, not bound to microtubules, or in modified form, that enters the extracellular space would augment, and that could in turn interact with and be taken up by other neurons. The ensuing degeneration of these neurons would again release the tau, and more extracellular tau will be available to exert a toxic effect on other neurons. This process could be repeated periodically, establishing a type of chain reaction that would result in the spread of the tau pathology.

In essence, this model involves two steps: the initiation of the pathology and its spreading. In AD, initiation may be due to the toxic effect of the beta amyloid peptide, particularly if we take into account the amyloid cascade hypothesis [38]. The distribution of beta amyloid aggregates varies widely across different brain regions [62] and the presence of such aggregates in the EC could promote local neurodegeneration in a region where also mutations of PS-1 would further enhance neuronal loss [79].

In the case of familiar FTDP-17, it is possible that an unknown factor could initiate the degeneration of neurons in any brain region. Since a higher proportion of tau is expressed in the frontotemporal region [80] and it is in a mutated (unbound to microtubules, or in modified form) form in familiar FTDP-17, the probability that the pathology will progress would be higher in that area.

In those tauopathies, a possible change in the interaction of tau (unbound to microtubules) to internal membranes [81,82], could not be excluded.

For the second step, the rate at which the tau pathology spreads will depend on the neural death promoted by the presence of extracellular tau protein, toxic to neurons. Thus, while our model suggests a pathological role for extracellular tau, there is still much work to be carried to fully understand how tau pathology initiates in AD.

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