Minireview

Tau aggregation into fibrillar polymers: taupathies

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Abstract Different neurological disorders, known as taupathies have been recently described. In these disorders it has been suggested that modifications in the microtubule-associated protein tau could cause neural degeneration in specific regions. Although these regions are different in the different taupathies, some common features appear to occur in all of them: abnormal hyperphosphorylation of tau and aberrant tau aggregation. These two features are commented upon in this review.

Key words: Tau protein; Assembly; Neurodegeneration; Alzheimer's disease

1. Introduction

In the last decade there has been an increase in the description of neurodegenerative diseases in which aberrant filamentous inclusions are present in selected damaged populations of nerve cells. These filamentous inclusions are assembled from proteins that, in non-pathological conditions, are in an unaggregated form [1]. Some of these neurological disorders have in common that the protein aberrantly present in an aggregated form is the microtubule-associated protein tau, a protein that is involved in microtubule stabilization [2,3]. Mice lacking the tau protein can develop in a way similar to that of wild-type mice [4] suggesting that its function may be substituted by other proteins.

The neural disorders or taupathies, in which tau is in an aggregated form, have in common the presence of these aberrant tau aggregates. However, these aggregates may be present in different types of neurons in each disorder. Among the taupathies, the most studied is Alzheimer's disease (AD), a senile dementia, and the analyses of other types of dementia with tau pathology (such as progressive supranuclear palsy (PSP), Pick's disease (PiD), corticobasal degeneration or frontotemporal dementias (FTD)), have usually been performed by comparison with AD.

In AD, tau pathology (lack of binding to microtubules and the formation of aberrant aggregates, neurofibrillary tangles (NFT)) has been correlated with the level of dementia [5]. In addition, the development of filamentous tau pathology in specific neural cells has been described. It starts in transentorhinal and entorhinal regions moving, later, to the hippocampus and cortical regions [6,7]. It has been suggested that the defects in a single cell, start with a modification of tau by phosphorylation, giving place to a 'pre-tangle' stage [8]. After this stage, filamentous polymers (paired helical filaments, PHF) are assembled and the aberrant aggregation of these PHF results in the formation of cytoplasmic (intracellular) NFT. As a consequence of this, it has been suggested that neurons degenerate and die, thus leaving NFT in the extracellular space [9,10]. The purpose of this review is mainly to discuss the possible mechanisms involving the aberrant polymerization of tau into PHF and the formation of NFT.

2. Tau modifications

Several abnormal modifications have been described for tau proteins present in the brain of AD patients. These modifications include hyperphosphorylation [11,12], glycation [13,14], ubiquitination [15], oxidation [16,17] and truncation [18]. Aberrant tau phosphorylation appears to be mainly involved in the regulation of its binding to microtubules, decreasing it [12], but not in facilitating tau assembly. Several kinases have been involved in the anomalous hyperphosphorylation of tau protein. These kinases have been divided into two groups: proline- and non-proline-directed kinases [19]. Within the first group, two kinases, first defined as tau kinases I and II [20], appear to play an important role. Tau kinase I corresponds to GSK3 whereas tau kinase II is cdk5. GSK3 phosphorylation of tau has been studied by different groups (i.e. [21,22]). This kinase also interacts with other proteins, like presenilin-1, that are important in the onset of AD pathology [23]. Cdk5 also modifies tau protein and this kind of phosphorylation could be deregulated in a neurodegenerative disorder like AD due to proteolytic cleavage of the regulatory subunit, p35, of the kinase [24]. Additionally, it has been suggested that another kinase, cdc2, that is mainly present in proliferating cells, is abnormally upregulated in AD [25] and that it could phosphorylate tau protein. The consequences of this phosphorylation could be a conformational change that prevents the binding of phosphotau to microtubules. Binding has been shown to be restored in the presence of a chaperone-like molecule, Pin-1 [26]. It is unknown if the conformational change regulated by Pin-1 could also affect tau aggregation.

Proline-directed phosphorylation mainly occurs at residues located around the tubulin-binding region of the tau molecule (see Fig. 1A). However, there are other non-proline-directed kinases that phosphorylate tau at its tubulin-binding region. These kinases are PKA, a novel MAPR kinase, and PKC [12,27–29]. However, this type of phosphorylation appears to play a role in AD but not in other taupathies like PiD.

Regarding the other modifications, ubiquitination does not appear to play a role in tau aggregation, the possible role of

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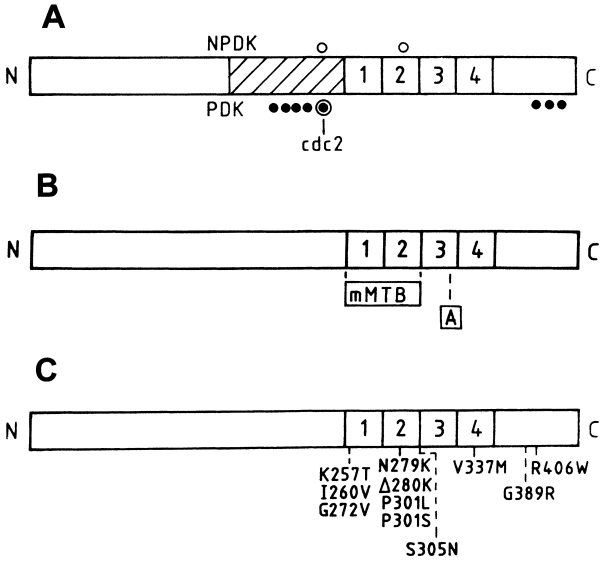

Fig. 1. A: Phosphorylation sites on tau molecule. The tau molecule contains a proline-rich region (hatched) located adjacent to the tubulin-binding region of the tau molecule. This tubulin-binding region is composed of four similar repeated sequences (numbers 1 to 4). Phosphorylation could take place by proline-directed (PDK) and non-proline-directed kinases (NPDK) leading to hyperphosphorylation in AD. The major phosphorylation sites for PDK (●) and NPDK (○) are indicated. Also shown is a phosphorylation site for cdc2 kinase involved in the binding to Pin-1 (encircled ●). B: Tau regions mainly involved in microtubule binding and self-assembly. The regions mainly involved in microtubule binding (mMTB) comprising the first and second tubulin-binding motifs and that mainly involved in self-assembly (A) comprising part of the third tubulin motif, are indicated. C: Location of tau mutations. The localization in the tau molecule of different exonic mutations found in FTDP-17 are indicated.

oxidation is discussed, truncation implicates the action of a yet unknown protease and glycation is probably involved in the aggregation of PHF into NFT but not in the formation of filaments.

3. Molecules that favor tau assembly into filaments polymers

Unmodified tau is able to self-aggregate in vitro in the absence of other molecules [30–32], however, this requires a very high concentration. To study if there are any molecules that could facilitate tau assembly, some of the molecules that are normally present in NFT were tested. Among these molecules were the sulfo-glycosaminoglycans (sGAG) [33]. In vitro assembly of tau in the presence of sGAG, indicates that the glycans facilitate tau polymerization [34,35], but only those in sulfated form [35,36]. Thus, it appears that the anionic nature of sGAG is essential for their function. Similarly other polyanions also favor tau aggregation [37,38]. Although sGAG are present in intracellular NFT [33], it is not known how they can be present in free form (not covalently linked to a protein to form a proteoglycan) in the cytoplasm. Although the presence of free glycans in the cytosol of some cells has been reported [39], this probably does not occur in a neuron in non-pathological conditions. Thus, it has been suggested that in pathological conditions, like AD, sGAG could be present in the cytosol as a result of a leakage from membrane compartments where sGAG and proteoglycans are normally present [10], since proteoglycans are delivered to the extracellular space into vesicles and are internalized from the extracellular space by endocytosis by following the endosome–lysosomal pathway. Possible abnormalities in any of these subcellular structures could result in membrane damage or in a dysfunction, and it was proposed that in AD several lysosomal alterations could occur [40]. Moreover, the injury of lysosome membranes in AD, probably by lipid peroxidation, has been reported [41,42]. These changes could be related to the oxidative stress that may occur in AD, as proposed by Smith et al. [43], since a possible deficiency of antioxidants in AD could induce lysosomal disorders and result in free radical formation. Nevertheless, more work should be done to determine how sGAG interacts with tau protein in the cytosol. On the other hand, it has been analyzed if changes in the amount of sGAG, present in the extracellular matrix, could have any correlation with the susceptibility of the surrounding neurons to form NFT. In a recent report it was concluded that there is a lower probability of forming NFT in those neurons with a high proportion of sGAG, like chondroitin sulfate, in their extracellular microenvironment [44]. Thus, it could be suggested that those neurons with less sGAG in their extracellular matrix have a higher risk for tau pathology. Interestingly, it should be noted that the interaction of factors like fibroblast growth factor 2 or the amyloid (Aβ) protein with their cell receptors are regulated by the amount of sGAG in the extracellular matrix and that a decrease in this amount could result in an increase in the availability of these factors. Both of these factors upregulate

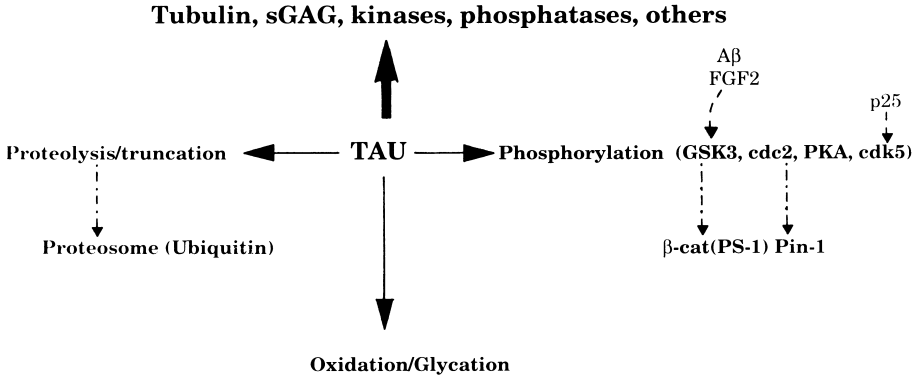

Fig. 2. Tau interactions and modifications. The tau protein may interact with different molecules (wide arrows) or may be modified in different ways (normal arrows) that can be modulated by different proteins (interrupted arrows).

GSK3 kinase activity [45,46]. Thus, these aspects on the amount of sGAG in the extracellular matrix of neurons susceptible to forming NFT, should also be further analyzed.

In some taupathies like PSP, sGAG are not present in the aberrant tau aggregates [47]. In these cases it has been suggested that other molecules, involved in redox reactions, could play a role in facilitating tau aggregation [47]. In any case, the search for other molecules (or proteins) that could regulate tau aggregation should be considered.

4. Tau mutations and tau polymerization

In one of the studied taupathies, the familial frontotemporal dementia associated with a mutation in chromosome 17 where tau is present (FTDP-17), pathogenic tau gene mutations have been observed, indicating that defects in the tau gene are sufficient to form aggregates and to cause a neurodegenerative disorder [48].

In vitro tau polymerization, in the presence of sGAGs, has been studied using different tau isoforms or fragments of the tau molecule. These studies indicate that 'big tau', the isoform that is mainly present in the peripheral nervous system, has a lower capacity to polymerize than those tau isoforms present in the central nervous system (our unpublished result). Additionally, it was observed that the minimal sequence of tau protein that could form filaments is that containing residues 317 to 335, corresponding to the third tau repeat present in the tubulin-binding region of the molecule (see Fig. 1B). Changes in this sequence have indicated that residues 326 and 331 appear to be important for the polymerization of the peptide. On the other hand the regions related to this peptide (the other tau repeats present in the molecule) show a much lower or no capacity to polymerize into filaments [49].

Tau mutations (see Fig. 1C) present in FTDP-17 have been located mainly in the different tau repeats, except in the peptide containing the minimal sequence needed for polymerization [50–53], and it has been found that some of these mutations favor tau polymerization in vitro [49,54,55]. However, many of these mutations, like those present in the first and second repeats, result in a decrease in the interaction of tau with microtubules [56,57]. The P301L mutation is probably the best example of the increase of tau polymerization in vitro and those mutations located at the C-terminus may be involved in altered tau phosphorylation (R406W). One yet unstudied mutation (G389R) is very close to the possible truncation site in the tau molecule [18] offering a mechanism, that could affect tau aggregation [18].

5. Concluding remarks

Tau is a microtubule-associated protein that is involved in microtubule stabilization, although mutants in this protein develop in a normal way [4] probably because its function can be replaced by other proteins. However, upon its aberrant modification by phosphorylation, the modified tau could also sequester some of those proteins [58] producing the breakdown of the microtubule network [59]. Additionally, abnormal tau aggregation is found in taupathies like AD. Thus, two main features are observed in tau pathology: microtubule destabilization and tau polymerization. For the first feature, the abnormal phosphorylation of tau could play a direct role, whereas for tau aggregation it does not appear to influence it in a direct way, whereas other factors like the presence of other molecules or the mutation of the tau gene could facilitate tau aggregation. However, the combination of some of these factors could facilitate a common conformational change of tau protein that could affect both tau microtubule binding and tau aggregation. The binding of tau to microtubules is mainly through the region comprising residues 241 to 304, whereas the minimal region needed for tau aggregation contains the residues 317 to 335 (the indicated residues are those of the longest central nervous system tau isoform [60]). Thus, two different sequences are involved in the two different features of tau pathology. This could be taken into account for possible therapeutical approaches.

Finally, Fig. 2 shows the interaction of tau with different molecules that could determine its localization (bound to microtubules), capacity of self-aggregation (sGAGs) or other features that can result in its modification by phosphorylation, proteolysis, oxidation or glycation.

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