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Review

Mutations causing neurodegenerative tauopathies

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Abstract

Tau is the major component of the intracellular filamentous deposits that define a number of neurodegenerative diseases. They include the largely sporadic Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal degeneration, Pick's disease and argyrophilic grain disease, as well as the inherited frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). For a long time, it was unclear whether the dysfunction of tau protein follows disease or whether disease follows tau dysfunction. This was resolved when mutations in *Tau* were found to cause FTDP-17. Currently, 32 different mutations have been identified in over 100 families. About half of the known mutations have their primary effect at the protein level. They reduce the ability of tau protein to interact with microtubules and increase its propensity to assemble into abnormal filaments. The other mutations have their primary effect at the RNA level and perturb the normal ratio of three-repeat to four-repeat tau isoforms. Where studied, this resulted in a relative overproduction of tau protein with four microtubule-binding domains in the brain. Individual *Tau* mutations give rise to diseases that resemble progressive supranuclear palsy, corticobasal degeneration or Pick's disease. Moreover, the H1 haplotype of *Tau* has been identified as a significant risk factor for progressive supranuclear palsy and corticobasal degeneration. At a practical level, the new work is leading to the production of experimental animal models that reproduce the essential molecular and cellular features of the human tauopathies, including the formation of abundant filaments made of hyperphosphorylated tau protein and nerve cell degeneration.
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Keywords: Tau protein isoform; Mutation; Tau filament; Frontotemporal dementia; Parkinsonism; Tauopathy

1. Introduction

Progress in understanding some of the most common neurodegenerative diseases was made possible by the coming together of two independent lines of research. First, the biochemical study of the neuropathological lesions that define these diseases led to the identification of their major components. Second, the study of rare, familial forms of disease led to the discovery of gene defects that cause inherited variants of the different diseases. Remarkably, in most cases, the defective genes were found to encode either the main components of the neuropathological lesions, or factors that increase their expression. It follows that the basis of the familial forms of these diseases is a toxic property conferred by mutations in the proteins that make up the filamentous lesions. A corollary of this insight is that a similar toxic property may also underlie the much more common sporadic forms of disease.

Alzheimer's disease (AD) is the most common neurodegenerative disease. Neuropathologically, it is defined by the presence of abundant extracellular neuritic plaques made largely of β-amyloid peptide and intraneuronal neurofibrillary lesions composed of microtubule-associated protein tau [1]. Similar tau lesions, in the absence of extracellular deposits, are also the defining characteristic of a number of other neurodegenerative diseases, including progressive supranuclear palsy, corticobasal degeneration (CBD), Pick's disease (PiD) and argyrophilic grain disease (AGD) [2]. For many years, there was no genetic evidence implicating tau protein in the neurodegenerative process. This changed with the discovery of tau gene mutations in a familial form of parkinsonism and dementia [3–5].

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2. Tau isoforms in human brain and their interactions with microtubules

Tau is a microtubule-binding protein that is believed to be important for the assembly and stabilization of microtubules. In nerve cells, tau is normally found in axons, but in the tauopathies it is redistributed to the cell body and dendrites. In normal adult human brain, there are six isoforms of tau, produced from a single gene by alternative mRNA splicing [6–9]. They differ from one another by the presence or absence of a 29- or 58-amino-acid insert in the amino-terminal half of the protein and by the inclusion, or not, of a 31-amino acid repeat, encoded by exon 10 of *Tau*, in the carboxy-terminal half of the protein. The exclusion of exon 10 leads to the production of three isoforms, each containing three repeats, and its inclusion leads to a further three isoforms, each containing four repeats. The repeats constitute the microtubule-binding region of tau protein. In normal adult human cerebral cortex, there are similar levels of three-repeat and four-repeat isoforms [10]. In developing human brain, only the shortest tau isoform (three repeats and no amino-terminal inserts) is expressed.

The tau molecule can be subdivided into an amino-terminal domain that projects from the microtubule surface and a carboxy-terminal microtubule-binding domain. Recent structural work has begun to shed light on the way that tau and microtubules interact [11,12]. Microtubules were assembled with tubulin and tau in the absence of taxol and in the presence of the natural osmolyte trimethylamine N-oxide. One of the repeats in tau had been labelled with nanogold and was localized by three-dimensional analysis of electron micrographs. The tau repeats were found to bind to the inner surface of the microtubule, in a region that overlapped with the taxol-binding site on β-tubulin. Taxol binds to a site in β-tubulin, where α-tubulin has a conserved loop of eight amino acids [TVVPGGDL]. Interestingly, part of the tau repeat motif [THVPGGN] resembles this sequence. Since tubulin cannot have evolved to bind taxol, these findings may answer the question of what natural substrate binds in this pocket of β-tubulin. In this model, part of the proline-rich region of tau must provide the link between the amino-terminal projection domain on the outside of the microtubule and the repeat motifs on the inside surface. It could thread through one of the holes between protofilaments. Another model has been derived from experiments in which gold-labelled tau was bound to pre-assembled, taxol-stabilized microtubules [13]. Tau was found to bind only to the outer surface of the microtubule, where it localized along the outer ridges of the protofilaments.

3. Tau filaments as nerve cell amyloid

In human diseases with tau pathology, the normally soluble tau protein is present in an abnormal filamentous form. It is also hyperphosphorylated. In AD, tau filaments consist primarily of paired helical filaments (PHFs), with straight filaments (SFs) being a minority species [14]. Electron micrographs of negatively stained isolated filaments show images in which the width of the filament varies between about 8 and 20 nm, with a spacing between crossovers of about 80 nm [15]. Although the filament morphologies and their tau isoform compositions vary between diseases, it is the repeat region that forms the core of the filament, with the amino- and carboxy-terminal regions forming a fuzzy coat around the filament [16]. During the course of the disease, the fuzzy coat is frequently proteolysed, such that filaments comprise only the repeat region of tau [17]. However, it is the full-length protein that assembles into filaments in the first place [18].

The discovery that incubation of bacterially expressed human tau with sulfated glycosaminoglycans leads to bulk assembly of full-length tau into filaments [19,20] made it possible to obtain structural information. Filaments assembled from either three- or four-repeat tau showed cross-β structure by selected area diffraction, X-ray diffraction from macroscopic fibres and Fourier transform infrared spectroscopy [21]. Similar conclusions were reached in two subsequent studies [22,23]. This work was extended to PHFs and SFs extracted from diseased human brain [21,22]. There had been controversy in the literature with regard to the internal molecular fine structure of these filaments. The difficulty had been to prepare from human brain pure preparations of filaments for analysis. This problem was circumvented by using selected area diffraction from small groups of filaments of defined morphology. Using this approach, PHFs and SFs had a clear cross-β structure [21], which is the defining feature of amyloid fibres. They share this structure with the extracellular deposits present in the systemic and organ-specific amyloid diseases. It is therefore appropriate to consider the tauopathies a form of brain amyloidosis.

4. Mutations in *Tau*

Frontotemporal dementias occur as familial forms and, more commonly, as sporadic diseases. They are characterized by a remarkably circumscribed atrophy of the frontal and temporal lobes of the cerebral cortex, often with additional, subcortical changes. In 1994, an autosomal-dominantly inherited form of frontotemporal dementia with parkinsonism was linked to chromosome 17q21.2 [24]. Subsequently, other forms of frontotemporal dementia were found to be linked to this region, resulting in the denomination “frontotemporal dementia and parkinsonism linked to chromosome 17” (FTDP-17) for this class of disease. All cases of FTDP-17 have so far shown a filamentous pathology made of hyperphosphorylated tau protein. In June 1998, the first mutations in *Tau* in FTDP-17 patients were reported [3–5]. Currently, 32 different

mutations have been described in over 100 families with FTDP-17. *Tau* mutations are either missense, deletion or silent mutations in the coding region, or intronic mutations located close to the splice-donor site of the intron following the alternatively spliced exon 10 (Fig. 1).

5. Functional effects of *Tau* mutations

Tau mutations fall into two largely non-overlapping categories—those that influence the alternative splicing of tau pre-mRNA and those whose primary effect is at the protein level. Several mutations in exon 10 of *Tau*, such as ΔK280, ΔN296 and N296H, have effects at both RNA and protein levels [25–28]. In accordance with their location in the microtubule-binding region of tau, most missense mutations reduce the ability of tau to interact with microtubules, as reflected by a reduction in the ability of mutant tau to promote microtubule assembly [29,30]. Mutations S305N and Q336R are exceptions, since they slightly increase the ability of tau to promote microtubule assembly [31,32], besides having additional effects that may be pathogenic. A reduction in microtubule function is observed when mutant tau is expressed in a number of cell types [33–36]. Expression of tau with a variety of mutations caused varying degrees of reduced microtubule binding and stability, as well as disorganized microtubule morphology. The same was true when *Xenopus* oocyte maturation was used as an indicator of microtubule function [37]. Following microinjection of wild-type or mutant human tau proteins, oocyte maturation was inhibited to variable degrees. A good correlation was observed between the effects of individual tau mutations in this system and in the in vitro experiments.

A number of mutations in *Tau* may cause FTDP-17, at least in part, by promoting the aggregation of tau protein [32,38–43]. Several studies have demonstrated that some of these mutations, including R5L, K257T, I260V, G272V, ΔK280, P301L, P301S, Q336R, V337M and R406W, promote heparin- or arachidonic acid-induced filament formation of tau in vitro relative to wild-type tau. This effect is particularly marked for mutations P301L and P301S. Furthermore, the assembly of mutant tau into filaments following its conditional expression in human neuroglioma cells has been reported [44]. Additional mechanisms may play a role in the case of some coding region mutations. For instance, protein phosphatase 2A is known to be the major tau phosphatase in brain and to bind to the tandem repeats in tau. Accordingly, several mutant tau proteins have shown reduced binding to protein phosphatase 2A [45]. Furthermore, one study has reported enhanced phosphorylation of tau in vitro as a result of the presence of FTDP-17 mutations [46].

The intronic mutations and most coding region mutations in exon 10 (N279K, L284L, ΔN296, N296N, N296H,

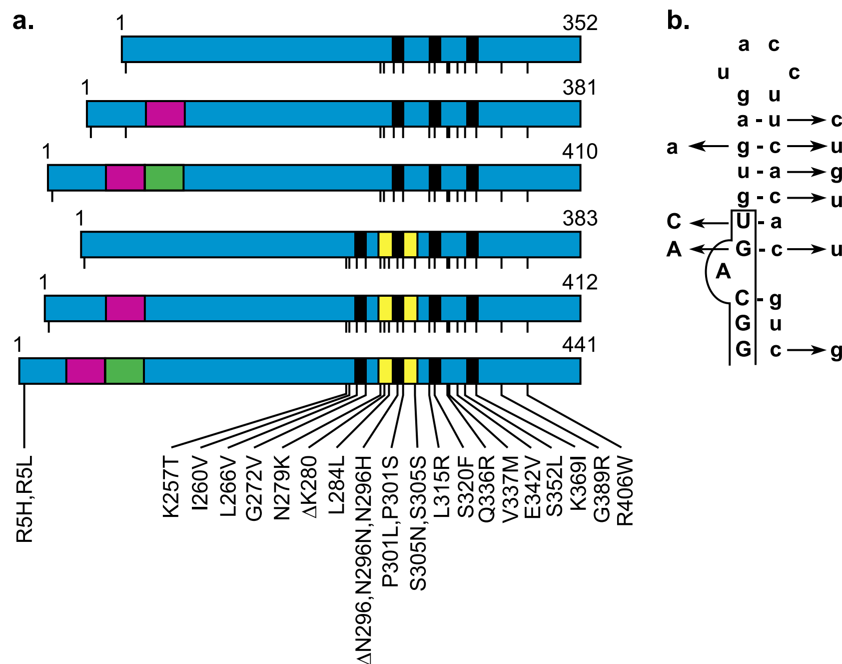

Fig. 1. Mutations in the tau gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Schematic diagram of the six tau isoforms (352 to 441 amino acids) that are expressed in the adult human brain, with mutations in the coding region indicated using the numbering of the 441-amino-acid isoform. Twenty missense mutations, two deletion mutations and three silent mutations are shown. The six tau isoforms are produced by alternative mRNA splicing from a single gene. They differ by the presence or absence of three inserts, shown in red (encoded by exon 2), green (encoded by exon 3) and yellow (encoded by exon 10), respectively. Stem-loop structure in the pre-mRNA at the boundary between exon 10 and the intron following exon 10. Nine mutations are shown, two of which (S305N and S305S) are located in exon 10. Exon sequences are boxed and shown in capital, with intron sequences being shown in lowercase letters.

S305N and S305S) increase the splicing of exon 10, thus changing the ratio between three- and four-repeat isoforms, resulting in the overproduction of four-repeat tau [4,5,25,27,28,31,47–50]. Mutation ΔK280 in exon 10 is an apparent exception, since it decreases the splicing of exon 10 in transfection experiments [25]. However, it remains to be seen whether this mutation leads to an overproduction of three-repeat tau in human brain. It is one of the few mutations with effects at both RNA and protein levels. Approximately half of the known *Tau* mutations have their primary effect at the RNA level. Thus, to a significant degree, FTDP-17 is a disease of the alternative mRNA splicing of exon 10 of the tau gene. It follows that a correct ratio of three-repeat to four-repeat tau isoforms is essential for preventing neurodegeneration and dementia in mid-life.

Accordingly, the regulation of the alternative splicing of exon 10 is an area of great current interest. It is known to involve multiple *cis*-acting regulatory elements that either enhance or inhibit utilization of the 5′-splice site of exon 10. These elements are located in exon 10 itself and in the intron following exon 10 [25,51–55]. Splicing regulatory elements within exon 10 include two exon splicing enhancers (ESEs) separated by an exon splicing silencer (ESS). Sequences located at the end of exon 10 and at the beginning of the intron following exon 10 inhibit the splicing of exon 10, probably because of the presence of a stem-loop structure that limits access of the splicing machinery to the 5′-splice site [4,5]. The determination of the three-dimensional structure of a 25-nucleotide-long RNA from the exon 10–5′-intron junction has shown that this sequence forms a stable, folded stem-loop structure (Fig. 1b) [56,57]. The stem consists of a single G–C base pair that is separated from a double helix of six base pairs by an unpaired adenine. As is often the case with single nucleotide purine bulges, the unpaired adenine at position −2 does not extrude into solution, but intercalates into the double helix. The apical loop consists of six nucleotides that adopt multiple conformations in rapid exchange. Downstream of this intron splicing silencer (ISS), an intron splicing modulator has been described [55]. It mitigates exon 10 expression by the ISS.

Pathogenic mutations in the tau gene may alter exon 10 splicing by affecting several of the regulatory elements described above. Thus, the intronic mutations (+3, +11, +12, +13, +14 and +16) destabilize the inhibitory stem-loop structure. The S305N mutation and the +3 intronic mutation may also enhance exon 10 splicing by increasing the strength of the 5′-splice site. However, the finding that the S305S mutation, which weakens the exon 10 5′-splice site, leads to a predominance of four-repeat tau [58] argues against this as the primary effect of these mutations. The N279K mutation may improve the function of the first ESE, thus enhancing exon 10 splicing. Mutation L284L, which enhances exon 10 splicing, may do so by disrupting a potential ESS or by lengthening the first ESE. The effects of the three mutations at codon 296 (ΔN296, N296N and N296H) are probably through disruption of the ESS.

In general, the high fidelity of splice-site selection is believed to result from the cooperative binding of trans-acting factors to *cis*-acting sequences [59]. The heterogeneous nuclear ribonucleoproteins (hnRNPs) and the serine–arginine rich (SR) proteins are involved in splice-site selection. The SR domain-containing proteins Tra2β, SF2/ASF and SRp30c have been found to interact with the first ESE in exon 10 and to function as activators of the alternative splicing of exon 10 [60,61]. In transfection experiments, several other SR proteins, such as SRp20, have been shown to promote the exclusion of exon 10 [53,62]. Moreover, phosphorylation of SR proteins by CDC2-like kinases has also been found to result in the skipping of exon 10 [63].

6. Neuropathology of FTDP-17

All cases with *Tau* mutations that have been examined so far have shown the presence of a filamentous pathology made of hyperphosphorylated tau protein [64,65]. To a significant degree, the morphologies of tau filaments and their isoform compositions are determined by whether *Tau* mutations affect mRNA splicing of exon 10, or whether they are missense mutations located inside or outside exon 10. The latter give rise to a number of different pathologies.

Mutations in *Tau* that result in the increased splicing of exon 10 lead to the formation of wide twisted ribbon-like filaments that consist only of four-repeat tau isoforms [66]. Where examined, the tau pathology was widespread and present in both nerve cells and glial cells. This has been shown for the intronic mutations [49,50,67–70] and for mutations N279K, L284L, S305N, S305S, ΔN296, N296H and N296N in exon 10 [25,47,58,71–73]. Mutations in exon 10 of *Tau* that do not affect alternative mRNA splicing lead to the formation of narrow twisted ribbons that contain four-repeat tau isoforms. This has been shown for the P301L mutation [30,74,75]. Using an antibody specific for mutant tau, biochemical studies have demonstrated that filaments extracted from the brains of patients with the P301L mutation contain predominantly mutant tau [75]. Tau pathology is widespread and present in both nerve cells and glial cells [74,75]. Compared with mutations that affect the splicing of exon 10, the glial component is less pronounced.

Most coding region mutations located outside exon 10 lead to a tau pathology that is neuronal, without a significant glial component. However, tau deposits in both nerve cells and glial cells have been described for mutations R5H and R5L in exon 1, I260V and L266V in exon 9 and L315R in exon 11 [43,76–79]. Two mutations, V337M in exon 12 and R406W in exon 13, lead to the formation of PHFs that contain all six tau isoforms, like the tau filaments of AD [80,81]. Using an antibody specific for tau protein with the R406W mutation, both wild-type and mutant proteins were detected in the abnormal filaments [82]. Mutations K257T,

L266V, G272V, L315R, S320F, Q336R, E342V, K369I and G389R lead to a tau pathology similar or identical to that of PiD [32,73,78,79,83–87]. These findings indicate that, depending on the positions of *Tau* mutations in exons 9–13 and the nature of these mutations, a filamentous tau pathology ensues which resembles that of either PSP, CBD, AD or PiD.

7. Pathogenesis of FTDP-17

The pathway leading from a mutation in *Tau* to neurodegeneration is unknown. The likely primary effect of most missense mutations is a change in conformation that results in a reduced ability of tau protein to interact with microtubules. It can be overcome by natural osmolytes, such as trimethylamine N-oxide, probably through the promotion of tubulin-induced folding of tau [88]. The primary effect of these mutations may be equivalent to a partial loss of function, with resultant microtubule destabilization and deleterious effects on cellular processes, such as rapid axonal transport. However, in the case of mutations whose primary effect is at the RNA level, this appears unlikely. The net effect of these mutations is a simple overproduction of tau with four repeats, which is known to interact more strongly with microtubules than tau with three repeats [10]. It is therefore possible that in cases of FTDP-17 with intronic mutations and those coding region mutations whose primary effect is at the RNA level, microtubules are more stable than in brain from control individuals. Moreover, some mutations, such as P301L and P301S in exon 10, will only affect 20–25% of tau molecules, with 75–80% of tau being wild-type, arguing against a simple loss of function of tau as a decisive mechanism. Mice without tau protein are largely normal and exhibit no signs of neurodegeneration [89].

A correct ratio of wild-type three-repeat to four-repeat tau may be essential for the normal function of tau in human brain. However, the fact that the tau isoform composition is not conserved between humans, rodents and chickens argues against this possibility [90,91]. An alternative hypothesis is that a partial loss of function of tau is necessary for setting in motion the “gain of toxic function” mechanism that will lead to neurodegeneration. This hypothesis requires that an overproduction of tau isoforms with four repeats results in an excess of tau over available binding sites on microtubules, thus resulting in the cytoplasmic accumulation of unbound four-repeat tau. It would probably necessitate the existence of different binding sites on microtubules for three-repeat and four-repeat tau. Validation of this hypothesis will require structural information at the atomic level.

From the above, a reduced ability of tau to interact with microtubules emerges as the most likely primary effect of the FTDP-17 mutations. It will lead to the accumulation of tau in the cytoplasm of brain cells and result in its hyperphosphorylation. Over time, hyperphosphorylated tau protein will assemble into abnormal filaments. It is at present unknown whether the filaments themselves cause nerve cell loss, or whether non-assembled, conformationally altered tau is toxic.

8. Relevance of *Tau* mutations for the sporadic tauopathies

The study of FTDP-17 has established that dysfunction of tau protein can cause neurodegeneration and dementia. It follows that tau dysfunction is most probably also of central importance for the pathogenesis of sporadic diseases with a filamentous tau pathology, such as AD, PSP, CBD, AGD and PiD. This is further underlined by the fact that the aforementioned diseases are partially or completely phenocopied by cases of FTDP-17 [2].

Nine missense mutations in *Tau* have been shown to give rise to a clinical and neuropathological phenotype reminiscent of PiD [32,73,78,79,83–87]. The finding that overproduction of four-repeat tau causes disease and leads to the assembly of tau with four repeats in nerve cells and glial cells may shed light on the pathogenesis of PSP, CBD and AGD. Neuropathologically, all three diseases are characterized by a neuronal and glial pathology, with the filaments comprising predominantly four-repeat tau [69,92–95]. PSP and CBD can be phenocopied by some *Tau* mutations. Thus, individuals with mutations R5L, N279K, ΔN296, S305S and the +16 intronic mutation have presented with a clinical picture similar to PSP [58,77,96–98], whereas some individuals with mutations N296N and P301S suffered from a disease resembling CBD [48,99].

An association between PSP and a dinucleotide repeat polymorphism in the intron between exons 9 and 10 of *Tau* was described in 1997 [100], even before the identification of *Tau* mutations in FTDP-17. The alleles at this locus carry 11–15 repeats. The A0 allele, with 11 repeats, has a frequency of over 90% in patients with PSP and about 70% in controls. Subsequently, two common *Tau* haplotypes, named H1 and H2, were identified [101]. They differ in nucleotide sequence and intron size, but are identical at the amino acid level. H2 is the ancestral haplotype, with H1 being human-specific [102,103]. The haplotype block extends beyond the tau gene, potentially involving additional genes as risk factors for neurodegenerative diseases [104]. Homozygosity of the H1 allele predisposes to PSP and CBD, but not to AD or PiD [101,104–108]. In addition, and more surprisingly, several groups have described a significant, but relatively weak, association between the H1 haplotype and idiopathic Parkinson’s disease, a disease without a significant tau pathology [109–112]. The functional consequences resulting from the presence of the H1 or the H2 haplotype are incompletely understood. It has been reported that H1 was more effective than H2 at driving expression of a reporter gene in transfected cells [113]. The intron between exons 9 and 10 of *Tau* also contains the putative intronless gene

Saitohin, which encodes a predicted protein of 128 amino acids that is poorly conserved [102,103,114]. It remains to be seen whether saitohin exists as a bona fide protein and, if so, what its physiological function may be.

9. Animal models of the tauopathies

The identification of mutations in *Tau* in FTDP-17 is rapidly leading to the production of transgenic mouse lines that reproduce the essential molecular and cellular features of the human tauopathies. They represent an improvement over earlier lines that expressed wild-type human tau in nerve cells and showed signs of axonopathy and amyotrophy [115–117], but failed to develop abundant tau filaments and nerve cell death.

Mouse lines expressing human tau with mutations P301L, G272V, V337M, R406W, P301S and the triple mutation G272V, P301L and V337M have been published [118–126]. Abundant tau filaments were found in the lines expressing four-repeat P301L or R406W human tau under the control of the murine prion protein promoter and four-repeat P301S human tau under the control of the murine Thy1 promoter [118,123,126]. Filamentous tau protein was hyperphosphorylated in a similar way to the human diseases and hyperphosphorylation at most sites appeared to precede the assembly of tau into filaments. Moreover, an increase in the phosphorylation of soluble tau resulted in increased filament formation, suggesting that phosphorylation can drive filament assembly [127]. In the lines transgenic for P301L and P301S tau, non-apoptotic nerve cell loss and a pronounced inflammatory reaction were detected in the spinal cord [123,128,129]. The mice suffered from a severe paraparesis and showed histological signs of neurogenic muscle atrophy.

In a mouse line expressing P301L tau in oligodendrocytes, co-expression of mutant human α-synuclein resulted in the appearance of thioflavin S-positive staining that was not observed in the single transgenic lines [130]. Moreover, in vitro experiments have shown that α-synuclein can induce the formation of tau filaments, giving a possible explanation for the co-occurrence of tau and α-synuclein in some neurodegenerative diseases. In mouse lines expressing P301L tau in nerve cells, co-expression of mutant human amyloid precursor protein (APP) or the intracerebral injection of β-amyloid fibrils resulted in an increase in the number of tangle-bearing cells [131,132]. In a mouse line triple transgenic for mutant APP, mutant presenilin-1 and P301L tau, the intracerebral injection of anti-Aβ antibodies or of a γ-secretase inhibitor resulted in the disappearance of somatodendritic tau staining in younger, but not in older, animals [133]. It thus appears that extracellular β-amyloid deposits can exacerbate the intraneuronal pathology caused by the expression of mutant human tau protein. However, one must bear in mind that these experiments are artificial to the extent that mutant APP and mutant tau have not been encountered together in human diseases. So far, β-amyloid deposition has not been found to induce wild-type tau pathology in transgenic mice.

In these mouse lines, tau filaments are made of mutant human tau protein. Filamentous deposits made of wild-type human tau were observed in a line expressing all six human brain tau isoforms in the absence of endogenous mouse tau [134]. The observed imbalance between levels of three- and four-repeat isoforms may have caused tau pathology in this line. Endogenous mouse tau has been reported to assemble into filaments in a neurodegenerative condition caused by inactivation of the gene encoding the prolyl isomerase Pin1 [135].

The existing mouse models of tauopathies indicate a connection between the development of tau filaments and nerve cell degeneration. This contrasts with *C. elegans* and *D. melanogaster*, where the overexpression of wild-type and mutant human tau resulted in nerve cell degeneration, in the apparent absence of tau filaments [136,137]. Phosphorylation of tau was more extensive in the fly than in the worm. In *Drosophila*, phosphorylation of S262 and S356 in tau by PAR-1 kinase, the fly homologue of MARK, appeared to be necessary for the subsequent phosphorylation at other sites, indicating the existence of a hierarchical and temporally ordered phosphorylation process [139]. Co-expression of human tau with the fly homologue of GSK3-β resulted in accelerated neurodegeneration and formation of tau-immunoreactive inclusions [138]. In contrast to what has been described in FTDP-17 and in mouse models of tauopathies, tau-induced neurodegeneration involved programmed cell death. Taken together, it appears that conformationally altered, non-filamentous human tau protein is neurotoxic in invertebrates.

10. Outlook

It is now well established that a pathway leading from soluble to insoluble filamentous tau protein is central to the neurodegenerative process in the human tauopathies. The availability of animal models that exhibit the essential molecular and cellular features of the human diseases has opened the way to a detailed understanding of the neurodegenerative process and the identification of genetic and pharmacological modifiers. In particular, it will be possible to test the relevance of the hyperphosphorylation of tau. Specific protein kinase inhibitors are widely believed to represent a major class of the drugs of the future. Such compounds may well constitute the first mechanism-based therapies for the human tauopathies.

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