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Review

March separate, strike together — Role of phosphorylated TAU in mitochondrial dysfunction in Alzheimer's disease☆

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ABSTRACT

The energy demand and calcium buffering requirements of the brain are met by the high number of mitochondria in neurons and in these, especially at the synapses. Mitochondria are the major producer of reactive oxygen species (ROS); at the same time, they are damaged by ROS that are induced by abnormal protein aggregates that characterize human neurodegenerative diseases such as Alzheimer's disease (AD). Because synaptic mitochondria are long-lived, any damage exerted by these aggregates impacts severely on neuronal function. Here we review how increased TAU, a defining feature of AD and related tauopathies, impairs mitochondrial function by following the principle: 'March separate, strike together!' In the presence of amyloid-β, TAU's toxicity is augmented suggesting synergistic pathomechanisms. In order to restore mitochondrial functions in neurodegeneration as a means of therapeutic intervention it will be important to integrate the various aspects of dysfunction and get a handle on targeting distinct cell types and subcellular compartments. This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction, and Neurodegenerative Diseases.

1. Introduction

The family of microtubule-associated proteins (MAPs) comprises three major classes of polypeptides: MAP1 (>250 kDa), MAP2 (~200 kDa), and TAU (50–70 kDa) [1,2]. MAP2 and TAU are expressed in most neurons, where they localize to separate subcellular compartments. While MAP2 is largely found in dendrites, TAU is concentrated in axons [3]. In the roundworm *Caenorhabditis elegans*, protein with TAU-like repeats (PTL-1) is the sole MAP homolog [4,5], allowing for studies into shared functions of TAU and MAP2 [6]. In the human brain, TAU exists as six isoforms that have either three or four microtubule-binding domains. In the adult mouse brain, there are only isoforms with four microtubule-binding domains expressed. TAU has been localized to cell-types other than neurons such as astrocytes and oligodendrocytes although under physiological conditions expression levels are relatively low [7]. When TAU was discovered in 1975 [8], the subsequent years focused mainly on its tissue distribution and the role TAU has in microtubule assembly and stabilization. With the identification of aggregates of TAU in the Alzheimer's disease (AD) brain, the focus shifted to addressing pathological functions. Histopathologically, AD is characterized by reduced synaptic density, neuronal loss in selected brain areas, as well as amyloid-β (Aβ)-containing plaques and neurofibrillary tangles (NFTs). It is the filamentous core of NFTs that is composed of highly phosphorylated forms of TAU [9,10].

1.1. TAU phosphorylation

What is the role of TAU phosphorylation in disease? TAU is a remarkable protein inasmuch as it contains 80 serine and threonine residues and 5 tyrosine residues that can be potentially phosphorylated [11]. In the normal brain there are 2–3 mol of phosphate per mole of TAU. In the AD brain, TAU is hyperphosphorylated to a stoichiometry of at least three-fold greater than normal supporting the notion that phosphorylation is a critical step in the aggregation process [12]. Whether phosphorylation at distinct sites is required or whether a generally elevated level of phosphorylation is sufficient is not known although the latter possibility is suggested by work in *Drosophila* [13]. With the entering of a formulation of the TAU dye methylene blue (Rember) into clinical trials a discussion has been initiated whether this putative drug is truly an aggregation inhibitor [14] and more specifically whether TAU in NFTs is massively phosphorylated (http://www.alzforum.org/new/detail.asp?id=3410).

While one study claims that the filaments in the NFTs are entirely composed of hyperphosphorylated TAU [15], another claims that hyperphosphorylated TAU accounts for less than 10% of total TAU that is moreover localized to the proteolytically susceptible fuzzy outer coat of the filaments, and not to their structural core [16,17].

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1.2. MAPT mutations and TAU transgenic mice

The TAU field has received a major boost with the identification of pathogenic mutations in the *MAPT* gene that encodes TAU in familial cases (FTDP-17, frontotemporal dementia with Parkinsonism linked to chromosome 17) of frontotemporal lobar degeneration (FTLD-TAU), a disease that shares with AD the aggregation of TAU and NFT formation, but lacks an overt Aβ pathology [18–20]. This enabled us and others to express FTLD mutant forms of TAU in mice and thereby reproduce TAU aggregation and NFT formation, and also to achieve a concomitant behavioural impairment in transgenic mouse models [21]. One such mouse strain generated in our laboratory is pR5 that expresses P301L mutant TAU and because of the pattern of TAU aggregation in the brain, displays amygdala- and hippocampus-dependent memory impairments [22,23]. This and other mouse models were instrumental in determining that manipulating phosphorylation by either inhibiting kinases or activating phosphatases causes an amelioration of the TAU pathology, including a restoration of behavioural impairments and prevention of neuronal cell loss [24–26]. When TAU mutant pR5 mice that progressively develop NFTs were crossed with phosphatase (PP2A)-impaired mice, this caused 7-fold increased numbers of hippocampal neurons that specifically phosphorylated the pathological Ser422 epitope of TAU, and 8-fold increased numbers of NFTs [27]. Another mouse strain generated by us expresses K369I mutant TAU and because of a unique expression pattern that includes the substantia nigra it is characterized by Parkinsonism [28]. Again, in these mice, TAU is highly phosphorylated; however, different from the pR5 strain, the 12E8 phospho-epitope Ser262/Ser356 is spared. Together this underscores the importance of phosphorylation in disease. Importantly and relevant to the topic of this article, TAU transgenic mouse models have proven instrumental in highlighting mitochondrial dysfunction as a central mechanism in neurodegeneration.

2. Mitochondrial dysfunction — cause or consequence

Mitochondria play a pivotal role in cell survival and death by regulating both energy metabolism and apoptotic pathways. They contribute to many cellular processes including intracellular calcium homeostasis and synaptic plasticity [29]. Maternally inherited, mitochondria are compartmentalized organelles consisting of a matrix and two membranes, an outer and an inner membrane with folded cristae, separated by an intermembrane space. These organelles are the powerhouses of all nucleated cells. They produce adenosine triphosphate (ATP) via the combined efforts of the tricarboxylic cycle (TCA) and the oxidative phosphorylation (OxPhos) system of the electron transport chain (ETC). The respiratory chain comprises four biochemically linked multi-subunit complexes I, II, III and IV, as well as two electron carriers, ubiquinone/coenzyme Q and cytochrome C, that are localized at the inner mitochondrial membrane (Fig. 1). By using the energy that is stored in nutritional sources the respiratory chain generates a proton gradient across the inner membrane to drive ATP synthesis via ATP synthase (complex V), while at the same time transferring electrons to oxygen and producing water [30]. Mitochondria are the major producer of reactive oxygen species (ROS) and at the same time a target of ROS toxicity [31]. The organelle has at its disposal a powerful quality control system to deal with these challenges: firstly intra-mitochondrial proteases and molecular chaperones that maintain mitochondrial proteostasis; secondly a dynamic network maintained by membrane fission and fusion, a process termed mitochondrial dynamics, by which damaged or defective mitochondrial components are isolated and targeted for autophagy (mitophagy) [32]. Mitochondrial dynamics cannot be discussed in isolation, as mitochondrial fission (i.e. biogenesis), fusion, motility/transport and turnover (by mitophagy) are highly inter-dependent processes [33]. This is especially critical for highly polarized cells such as neurons. The role of mitochondria in ageing and in pathophysiological processes such as AD is constantly being unravelled. Concomitant to ROS production an inefficient mitochondrial base excision repair (BER) machinery has been postulated, with oxidative damage to mitochondrial DNA (mtDNA) being a determining event that occurs during ageing [34].

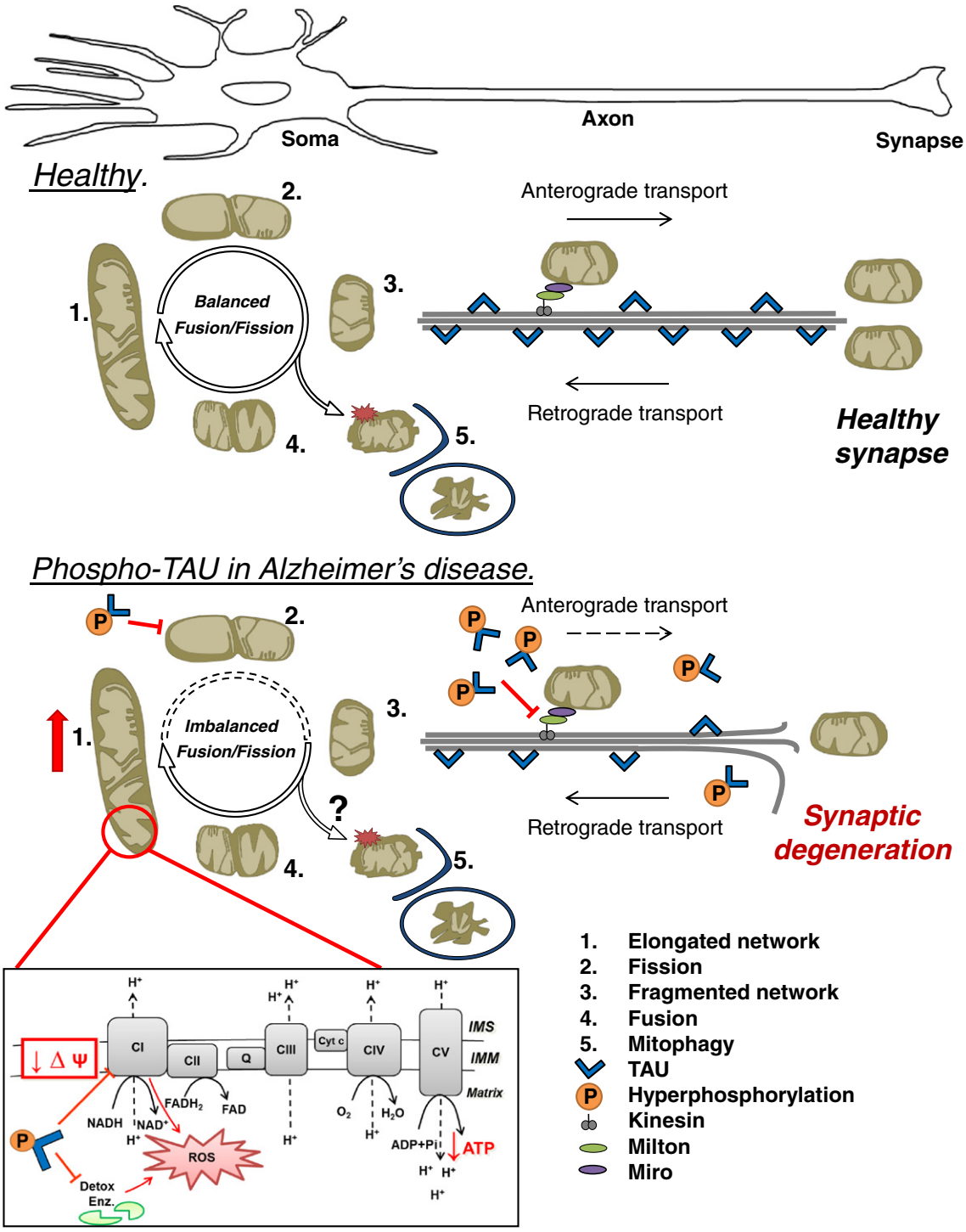
2.1. Manipulating fission and fusion genes

The question arises whether any form of chronic oxidative stress-associated event would at an early stage contribute to the synaptic abnormalities and, ultimately, selective neuronal degeneration that characterizes AD, as a growing body of evidence would suggest [35]. The bulk of AD cases are sporadic, and only a small fraction is caused by autosomal dominant mutations. Regarding the role of mitochondrial dysfunction in AD one can envisage several scenarios. Firstly, oxidative stress could be a down-stream consequence of another pathogenic event; secondly, it could be the cause of neurodegeneration; thirdly, it might accelerate and/or augment the damage elicited by TAU and/or Aβ [31]. By manipulating mitochondrial in vivo genes with a role in fusion and fission, a process discussed in more detail below, neither an AD-like TAU nor an Aβ pathology has been encountered [36–41], which would place mitochondrial dysfunction down-stream of TAU and Aβ toxicity. However, as most mouse strains that lack fission or fusion genes show early lethality it has not been possible to study consequences for TAU and Aβ and in particular the role ageing has in such an impairment.

2.2. Senescence-accelerated mice

In studying mitochondrial functions and age-related mitochondrial decline, senescence-accelerated mouse strains such as SAMP8 (senescence accelerated prone 8) are useful, as the mice display many features known to occur early in the pathogenesis of AD, such as increased oxidative stress and memory impairment [42]. Together with a series of related senescence-accelerated mice, the SAMP8 strain was established in the mid 1970s by conventional inbreeding of AKR/J-derived mice that displayed features of accelerated ageing such as hair loss, reduced activity, shortened life expectancy, lordokyphosis (increased curvature of the spine), and periophthalmic (around the eye) problems [43]. Littermates that did not show a senescence-associated phenotype were also inbred and senescence-resistant, longer-lived SAMR strains were obtained such as SAMR1 (senescence accelerated mouse resistant 1). To better delineate the role of specific single nucleotide variants (SNVs) of these multigenic strains with distinct phenotypes, two recent independent studies used whole exome sequencing to make the strains more useful for studies into ageing and neurodegeneration [44,45].

In SAMP8 mice learning and memory deficits were already evident at 6 months of age and became more pronounced with advanced age [46]. TAU was found to be hyperphosphorylated using a small set of phosphorylation site-specific antibodies, but filament and NFT formation has not been reported indicating that the SAMP8 mice present with an early rather than a more advanced TAU pathology [47]. Staining with Aβ-specific antibodies suggested Aβ deposition [48,49], although, because the murine protein differs from the human Aβ-precursor protein (APP) and lacks the amino acids that are required to generate Aβ, these deposits have been termed 'Aβ-like' [48]. Compared with SAMR1 mice, age-related changes in cerebral energy production were found in SAMP8 at 2 months followed by a decrease in mitochondrial function [50,51]. More recent studies extended this finding by revealing decreases in cytochrome C oxidase (COX) activity, mitochondrial ATP content, and mitochondrial glutathione (GSH) levels in young SAMP8 compared with SAMR1 mice [52,53]. Ageing is accompanied not only by increased mitochondrial ROS production due to ETC impairment but also by an imbalance of the protective mitochondrial antioxidant machinery. For instance, age-related changes in levels of antioxidant enzymes, such as copper/zinc superoxide dismutase (Cu/Zn-SOD) and manganese SOD (Mn-SOD) were found in the liver and cortex of



IMS, inter-membrane space; IMM, inner mitochondrial membrane; ROS, reactive oxygen species; ΔΨ; mitochondrial membrane potential; CI, complex I; CII, complex II; CIII, complex III; CIV, complex IV; CV, complex V.

Fig. 1. The mitochondrion under physiological and pathological conditions. Under healthy conditions, fusion and fission are balanced, and damaged mitochondria are removed by a process termed mitophagy. Both antero- and retrograde axonal transports are unimpaired providing the synapses with sufficient numbers of functional mitochondria to meet the special energy requirement and calcium buffering of this cellular compartment. Under conditions of elevated TAU, the delicate balance of fission and fusion is deregulated. Fission is impaired and an elongated mitochondrial network results. This may or may not affect mitophagy. Phosphorylated TAU also impairs anterograde transport of distinct cargoes, which include mitochondria. As a consequence, less mitochondria are provisioned to the synapses, which leads to synaptic degeneration. In the scheme, key molecules with roles in mitochondrial transport are indicated, with kinesin being the actual motor and Miro and Milton being adaptor proteins. Inset: Elevated levels of phosphorylated TAU selectively impair complex I of the electron transfer chain, ultimately resulting in reduced levels of ATP and hence, energy deprivation of affected neurons. Hyperphosphorylated forms of TAU also cause an increased production of reactive oxygen species (ROS) and reduced activities of detoxifying enzymes (detox. enz.) including superoxide dismutase (SOD).

SAMP8 mice compared with age-matched SAMR1 mice [54–56]. Increased lipid peroxidation and carbonyl damage is present as early as two months of age [57]. Furthermore, SAMP8 mice reveal age-dependent reductions of various receptors including the NMDA receptor that has a role in excitotoxicity as discussed below [58]. Whereas SAMP mice are certainly a better model for accelerated ageing rather than neurodegeneration, they nonetheless support increased oxidative stress as a key mechanism in the ageing process. Crossing TAU transgenic mice

with mitochondrial impairment onto a SAMP8 genetic background might establish a more advanced model of neurodegeneration compared to one where the TAU transgene is expressed on a conventional inbred background such as C57Bl/6.

2.3. The Harlequin model

Another, although less frequently, employed strain with mitochondrial dysfunction and oxidative stress is the Harlequin (Hq) mutant mouse strain. Hq mice show an 80–90% depletion of the mitochondrial apoptosis-inducing factor (AIF) resulting in reduced levels of complex I of the ETC and increased oxidative stress [59]. Interestingly, although AIF is reduced throughout the brain, neuronal loss is largely restricted to distinct brain regions (cerebellum and retina), indicating selective vulnerability. Because a mitochondrial dysfunction specifically of complex I characterizes the P301L TAU transgenic pR5 mice, the two strains were crossed. This caused an increased TAU pathology (higher degree of phosphorylation and more NFTs) and age-dependent cerebellar neurodegeneration that was preceded by decreased activities of the ETC and depletion of ATP levels [60]. Interestingly, low levels of TAU in the cerebellar granule cell layer significantly increased cerebellar apoptosis and led to an aggravation of motor deficits even though only a very small number of cerebellar granule neurons were positive for TAU phospho-epitopes. This implies that in particularly vulnerable neuronal populations such as the Hq cerebellar granule cells, even low levels of non-hyperphosphorylated TAU may be sufficient to induce apoptosis and cause functional neurological impairment [60]. Analysis of the activities of complexes I–V revealed a complex picture: In the TAU/Hq mice an additive effect of the two mutations was observed, i.e. both a reduced complex I protein content caused by the Hq mouse mutation and a functional reduction of the remaining complex I activity caused by additional TAU expression. For complex III, for example, early decreases in activity were observed in 1-month-old TAU transgenic and TAU/Hq mice. However, while TAU single mutant mice were able to compensate for this deficiency, complex III activity remained reduced in the TAU/Hq double mutant mice at 7 months. Together this study demonstrates a mutual reinforcement of the TAU pathology and mitochondrial dysfunction in vivo, proposing TAU/Hq double mutant mice as a valuable model to study TAU-related neurodegenerative changes in a setting of impaired mitochondrial function.

3. TAU specifically impairs complex I and Aβ complex IV

3.1. Proteomic and functional studies in P301L TAU transgenic mice

An unbiased approach to address TAU-mediated impairment in model systems is by functional genomics that generally generates long lists of deregulated transcripts and proteins, which can then be grouped by category analysis [61]. P301L TAU expressing pR5 mice reveal a significant aggregation of TAU at an early age, with NFTs developing around the age of 6 months, and hence they represent a model suited for the proteomic investigation of TAU-related changes in AD [62,63]. A mass spectrometric analysis of fractionated brain proteins derived from these mice revealed mainly a deregulation of mitochondrial respiratory chain complex components (including complex V), antioxidant enzymes, and synaptic proteins [64]. The reduction in mitochondrial complex V levels in the pR5 mice that was revealed using proteomics was also confirmed as decreased in brains from human carriers of the P301L FTDP-17 mutation. The functional analysis demonstrated age-related mitochondrial dysfunction, together with reduced NADH ubiquinone oxidoreductase (complex I) activity as well as age-related impaired mitochondrial respiration and ATP synthesis in the pR5 mouse model. Mitochondrial dysfunction was further associated with higher ROS levels in aged transgenic mice, concomitant with the upregulation of antioxidant enzymes in response to oxidative stress (Fig. 1). Increased TAU pathology resulted also in lipid peroxidation [64]. Because prior studies had shown that Aβ mainly impairs complex IV [65,66], the finding that TAU mainly impairs complex I of the ETC demonstrated for the first time that TAU pathology also leads to metabolic impairment and oxidative stress, by mechanisms that are distinct from those exerted by Aβ. How TAU affects complex activities is not understood and TAU may well do so indirectly. For Aβ, interaction with and binding to mitochondrial proteins (such as Aβ-binding alcohol dehydrogenase, ABAD; or the voltage-dependent anion channel 1 protein, VDAC) has been postulated [67,68]. Intracellular localization of Aβ has been questioned by a recent study, however, which highlights the use of antibodies in these studies that bind not only to Aβ but also to its precursor protein, APP [69]. Because VDAC was found to interact with phosphorylated TAU it has been proposed that phosphorylated TAU may block mitochondrial pores and that one of TAU's functions is to maintain normal mitochondrial pore opening and closure [68].

3.2. P301L TAU transgenic mice crossed with Aβ-forming mice

While the focus of this review article is on TAU and not on Aβ, it is still worthwhile looking into models that combine both pathologies. When the triple transgenic ^{triple}AD mouse model (pR5/APP^{sw}/PS2 N141I) was subjected to quantitative proteomics, this revealed that one-third of the proteins had functions in mitochondria, specifically complexes I and IV. Therefore, mitochondrial functions were assessed [70]. Again, deregulation of the activity of complex I was found to be TAU-dependent, and deregulation of complex IV Aβ-dependent, when analyzing 10-month-old ^{triple}AD mice. The convergent effects of Aβ and TAU led to a depolarization of the mitochondrial membrane potential in ^{triple}AD mice already at the age of 8 months. Additionally, we found that age-related oxidative stress played a significant part in the deleterious vicious cycle by exaggerating Aβ- and TAU-induced disturbances in the respiratory system and ATP synthesis, finally leading to synaptic failure. Furthermore, synergistic effects of TAU and Aβ on mitochondrial impairment were revealed.

These data complement those obtained in another triple transgenic mouse model, 3xTg-AD (P301Ltau/APPSw/PS1 M146L) [71]. Mitochondrial dysfunction was evidenced by an age-related decrease in the activity of regulatory enzymes of the oxidative phosphorylation system such as COX, or of the TCA cycle such as pyruvate dehydrogenase, analyzing 3xTg-AD mice between 3 and 12 months of age [72]. In addition, these mice also exhibited increased oxidative stress and lipid peroxidation. Most of the effects on mitochondria were seen at the age of 9 months, whereas mitochondrial respiration was significantly decreased at 12 months of age. Importantly, mitochondrial bioenergetic deficits were found to precede the development of AD pathology in these mice. In a follow-up study, the 3xTg-AD mice were analyzed by 2D-DIGE, a quantitative proteomic profiling method [73]. Proteins that were dysregulated in 3xTg-AD cortices functioned in a wide variety of metabolic pathways, including the TCA cycle, oxidative phosphorylation, pyruvate metabolism, glycolysis, oxidative stress, fatty acid oxidation, ketone body metabolism, ion transport, apoptosis, and mitochondrial protein synthesis. These alterations in the mitochondrial proteome of the cerebral cortices of 3xTg-AD mice occurred well before the development of significant Aβ plaques and NFTs, supporting the notion that mitochondrial dysregulation is an early event in AD pathogenesis.

4. TAU impairs mitochondrial transport

Mitochondria can move in both anterograde and retrograde directions in one axon [74]. Early studies in wild-type TAU overexpressing mice using pulse-chase experiments had already revealed that TAU mediates impaired anterograde transport [75]. In K369I mutant TAU transgenic K3 mice, it was then demonstrated that elevated TAU impairs transport of distinct cargoes including mitochondria, both in the nigrostriatal pathway and in the sciatic nerve [28]. More specifically, by ligating the sciatic nerve proteins whose transport was impaired

could be discriminated from those, whose was not, indicating selectively impaired axonal transport. It was found that complex V accumulated proximally and distally of the ligation in wild-type nerves, representing bidirectional transport of mitochondria. In ligated transgenic nerves, however, complex V accumulated only in the distal part, suggesting impaired anterograde and unaffected retrograde transports of mitochondria in K3 mice (Fig. 1). As an underlying pathomechanism, trapping of the kinesin adaptor molecule JIP1 by phosphorylated forms of TAU in the soma was identified. This trapping prevented JIP1 from loading distinct cargoes (including mitochondria) onto the kinesin machinery for transport down the axon. Relocalization of JIP1 from the axon to the soma was also found in the AD brain underscoring the validity of the finding in the transgenic model [76]. Another pathomechanism was identified in the squid axon, where filamentous, but not soluble, forms of wild-type TAU were found to inhibit anterograde transport by activating axonal protein phosphatase 1 (PP1) and glycogen synthase kinase 3 (GSK3), independent of microtubule binding [77]. In a related study, increased expression of GSK3β and the p25 activator of cyclin dependent kinase 5 (cdk5) in neurons was shown to cause an increased pausing of mitochondria rather than changes to their velocities [78]. Competition for binding to kinesin has been suggested by co-immunoprecipitation experiments: The data indicate that TAU being a cargo of kinesin itself may displace other kinesin-based cargo, including cytoskeletal proteins and organelles such as mitochondria [79]. Also in *C. elegans*, perturbed axonal transport of mitochondria was reported when so-called pro-aggregant tau was expressed which causes TAU aggregation [80].

While TAU is often treated as if it were one protein, it is in fact several proteins. Differential effects of three-repeat (3R) and four-repeat (4R) TAU on mitochondrial axonal transport have been reported [81]. As 3R TAU is believed to be less tightly associated with microtubules than 4R TAU [82,83], it was postulated that 4R TAU may lead to greater alterations of organelle transport than 3R TAU. Indeed, while both 3R and 4R TAU changed the normal mitochondrial distribution within the cell body and reduced mitochondrial localization to axons, the effects of 4R TAU were more pronounced. Furthermore, 3R and 4R TAU caused different alterations in retrograde and anterograde transport dynamics; however, 3R TAU had a slightly stronger effect on axon transport dynamics. TAU over-expression in general increased the net movement of axonal mitochondria towards the neuronal cell body [81]. Multiple studies have shown that Aβ, the second key player in AD, impairs mitochondrial transport [84], while a recent study using oligomeric Aβ did not find changes to mitochondrial motility [85]. However, reducing TAU levels prevents Aβ toxicity as discussed below, and more specifically the defects in axonal transport induced by Aβ in APP mutant mice [86].

More recently, RNAi-mediated knockdown of *Milton* or *Miro*, which encodes adaptor proteins essential for axonal transport of mitochondria, in human TAU transgenic flies was found to enhance the TAU-induced neurodegeneration [87] (Fig. 1). Phosphorylation of TAU at the 12E8 phospho-epitope Ser262 was increased when Milton or Miro was reduced. Partitioning defective-1 (PAR-1), the *Drosophila* homolog of mammalian microtubule affinity-regulating kinase (MARK) mediated this increase. Mutagenesis studies suggested that increased phosphorylation of the 12E8 epitope through PAR-1 contributes to TAU-mediated neurodegeneration in a pathological context when axonal mitochondria are depleted. Mitochondrial movement in the neuritic processes of PC12 cells was inhibited when another phospho-epitope of TAU, AT8 (comprised of three sites, Ser199, Ser202, and Thr205) was changed to phosphomimetic aspartates [88]. These mutations also caused an expansion of the space between microtubules in cultured cells when membrane tension was reduced by disrupting actin filaments. Thus, the authors concluded that TAU phosphorylation at the AT8 sites may affect mitochondrial movement by controlling microtubule spacing [88]. In human embryonic stem cell-derived neural stem cells the consequences of an overexpression of the longest human tau isoform, 2N4R tau versus pseudohyperphosphorylated tau (p-tau) was studied. Interestingly, p-tau, but not 2N4R tau, readily leads to TAU aggregation and impaired mitochondrial transport in human neurons. Although these alterations did not induce cell death, p-tau-expressing neurons cultured under non-redox-protected conditions underwent a pronounced degeneration with the formation of axonal varicosities sequestering transported proteins and progressive neuronal cell death [89]. That tau can impair axonal transport of mitochondria in the absence of hyperphosphorylation has been shown in P301L tau knock-in mice that did not develop a TAU pathology. In fact, the overall phosphorylation of tau in these mice was reduced (e.g., at epitopes PHF-1 or AT270), perhaps due to a reduced microtubule binding [90]. The impact of impaired transport on TAU pathology has also been studied. In mice lacking the kinesin light chain 1 (KLC1) subunit of the anterograde motor kinesin-1, this caused an axonopathy, with dystrophic axons exhibiting abnormal tau hyperphosphorylation and accumulation [91]. Together these studies illustrate that phosphorylated forms of TAU alter mitochondrial transport.

5. TAU impairs mitochondrial dynamics

Mitochondria differ remarkably from each other in size depending on cell-type and subcellular compartment [92,93]. Because axons and dendrites have differential energy demands, the mitochondrial network is generally more elongated in the cell body and dendrites of a neuron, and more fragmented in the axon [94,95] (Fig. 1). Moreover, a distinction is made between nonsynaptic and synaptic mitochondria [96–98]. To meet the specific subcellular demands, the mitochondrial network is shaped by a set of proteins that regulates fusion and fission [99]. In mammalian cells three large GTPases govern fusion: Mitofusins 1 and 2 (MFN1 and MFN2) dimerize on the outer membranes of adjacent mitochondria to induce outer membrane fusion. This is followed by fusion of the inner membranes, a process mediated by OPA1 (optic atrophy 1) that resides in the intermembrane space [100,101]. Fission is under control of yet another GTPase, DRP1 (dynamin-related protein 1, also known as DLP1 and DNM1) [102]. A set of additional proteins, including FIS1, mitochondrial fission factor (MFF), and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51), have a role in recruiting and assembling DRP1 at the outer membrane [103]. Fission and fusion need to be balanced. For example, knockdown of *Drp1* leads to mitochondrial elongation, respiratory dysfunction and, ultimately, apoptosis [104], whereas elevated mitochondrial fusion is also a stress response in certain situations, enhancing ATP production and resistance to apoptosis [105], as reviewed recently [99].

Not surprisingly, an impaired balance of fission and fusion has been reported in AD, both at the transcript and protein levels [106,107]. Reduced levels of DRP1 and increased mitochondrial length were found in one study [108], whereas another revealed reduced cytoplasmic levels but (although not statistically significant) increased mitochondrial levels of DRP1, indicative of increased fission [106,109]. This and other recent studies suggest some degree of variability in the regulation of mitochondrial dynamics. For a conclusive picture it will be crucial to analyze the subcellular localization and post-translational modifications of DRP1, rather than global changes.

Mitochondrial dynamics has also been studied in mouse models of AD. Here, a significant body of data is available for the role of Aβ, which overall suggests that its net effect is towards increased fragmentation [106,108,110,111]. However, as discussed above, in addition to Aβ, TAU also forms aggregates in the AD brain and it would not be surprising if the observed differences in the impairment of complex activities would also extend to differences in the rates of fission and fusion. While hyperphosphorylation of TAU is believed to be a precipitating event in disease, recent data suggest that carboxy-terminal cleavage of TAU, which impairs mitochondrial function may also be critical [112,113]. Full-length TAU induced an increase in mitochondrial size, whereas truncated TAU induced mitochondrial fragmentation [114]. In neuroblastoma cells, P301L TAU impaired mitochondrial motility, together with a down-regulation of both fission and fusion [115]. When

combined with Aβ, truncated TAU impaired mitochondrial transport, enhanced oxidative stress, and caused a depletion of the mitochondrial membrane potential in cortical neurons. These effects were either modest or absent when Aβ was combined with full-length TAU, suggesting a specific synergistic cooperation of cleaved TAU with Aβ in disrupting mitochondria [112,113]. An altered distribution of mitochondria, without a change in size, was found in transgenic mice with high levels of P301L mutant TAU expression [116]. In these mice, mitochondrial distribution was progressively disrupted with age, particularly in somata and neurites that contained TAU aggregates. Apparently, the effects of TAU on mitochondria, both independently and in cooperation with Aβ, vary widely between TAU species, although the reasons for these divergent effects remain to be determined.

New light on TAU's role in mitochondrial dynamics was shed by a complementary study in TAU transgenic worms and flies. It has previously been found that TAU induces the stabilization and bundling of filamentous (F)-actin [117]. Because localization of the fission protein DRP1 to mitochondria is an actin-dependent process, whereby DRP1 and mitochondria (via myosin II) must interact with filamentous (F)-actin prior to their colocalization, increased F-actin in human TAU transgenic mice and flies disrupts the physical association of mitochondria and DRP1, leading to mitochondrial elongation [118,119] (Fig. 1). This causes neurotoxicity that can be rescued by reducing mitochondrial fusion, enhancing fission, or reversing actin stabilization. The study further found that elongation is not a secondary effect of impaired axonal transport [118]. Despite those new highlights on the role of TAU in the impairment of mitochondrial dynamics, there is no clear evidence of its role in mitochondrial turnover. In fact, as mentioned above, fusion/fission activity plays an important role in mitochondrial quality control. It allows the exchange of materials such as lipids, proteins, metabolites and mtDNA throughout the mitochondrial network, avoiding energetic deficiencies. However, when mitochondria are extensively damaged, they exit the fusion/fission cycle and are selectively eliminated by mitophagy (Fig. 1). This process occurs when mitochondria are in a fragmented state and when the mitochondrial membrane is depolarized after stress [120]. Mitochondria are degraded by engulfment into autophagosomes, which fuse with lysosomes and break down the organelles. In the case where the process of mitophagy is disturbed, a decreased cellular respiration has been observed, parallel to an accumulation of oxidized proteins [33]. Nothing seems to be known about the effect of TAU on mitochondrial turn-over but since new evidence shows that TAU may lead to mitochondrial elongation (fused state), we can speculate that it might decrease the elimination of damaged mitochondria via the process of mitophagy (which requires mitochondrial fragmentation). However, because AD is characterized by both TAU and Aβ pathology, future studies into mitochondrial dynamics/mitophagy need to take both molecules into consideration. More specifically, it will be necessary to firstly analyze synaptosomal as well as total mitochondria, and secondly, human tissue that represents the full spectrum of TAU and/or Aβ pathology, to dissect effects of Aβ on mitochondria dynamics from those of TAU.

6. TAU mediates excitotoxicity

TAU affects mitochondrial dysfunction also because of its crucial role in mediating excitotoxicity, a pathomechanism that has been implicated in AD [121]. Under basal conditions, mild activation of the NMDA receptor (NMDAR) results in physiological ROS production, while under neurodegenerative conditions triggered by Aβ, over-activation of NMDARs causes excessive calcium influx, nitric oxide (NO) activation, mitochondrial depolarization and superoxide formation that result in neuronal damage and death [122–124]. Aβ is believed to exert excitotoxicity either directly or indirectly, by over-activating the NMDAR [125]. NO exerts the majority of its effects by reacting with a cysteine thiol on target proteins, a process termed S-nitrosylation. This modifies enzymes with a role in glycolysis, gluconeogenesis and oxidative phosphorylation, indicating that this type of posttranslational modification may regulate metabolism and mitochondrial bioenergetics [126]. In a recent study, inhibition of Drp1 was found to prevent excitotoxic cell death in a hippocampal cell culture system [127]. Calcium influx also stimulates kinases, causing TAU to detach from microtubules and relocalize to the somatodendritic domain, where it aberrantly interacts with proteins including JIP1, thereby impairing mitochondrial transport [28].

Is there a more direct role for TAU in excitotoxicity? In a pathocascade, Aβ has been placed upstream of TAU [128]. This concept has been proven in P301L mutant TAU transgenic mice that develop an increased number of NFTs, either by crossing them with Aβ plaque-forming transgenic mice [129], or by intracerebral injections of Aβ [130]. While Aβ causes TAU aggregation, its toxicity is also dependent on TAU as has been first shown in vitro [131] and subsequently in vivo [132]. Removing TAU largely abrogates the pathological features that characterize Aβ plaque-forming mice, namely premature mortality, high susceptibility to experimentally induced excitotoxic seizures and memory deficits [132]. Mechanistically, this protection appeared to be conferred by a reduced susceptibility to excitotoxicity either when TAU was absent or when its levels were reduced [132,133]. Even under physiological conditions, TAU was found to be present in the dendrite (although at low quantities compared with the axon), where it is critically involved in postsynaptic NMDAR downstream signalling by localizing the SRC kinase FYN to the dendrite. FYN phosphorylates the NMDAR that then recruits the postsynaptic scaffolding protein PSD-95 to form a complex [133]. The TAU axis hypothesis claims that as TAU accumulates in a phosphorylated form in the dendrite, it mediates the toxic effects of Aβ by causing increased concentrations of FYN which is then available to phosphorylate the excitotoxic NMDAR signalling complex [134]. Aβ, Fyn and TAU therefore seem to orchestrate neuronal damage [133,135,136]. It has been shown that synaptic NMDAR signalling and extrasynaptic NMDAR signalling have opposite effects on cell survival and that differentially located NMDARs are coupled to different intracellular cascades. A recent study found that Aβ induces dendritic spine loss via a pathway involving synaptic NR2A-containing NMDARs whereas activation of extrasynaptic NR2B-containing NMDARs is required for neurodegeneration that is TAU-dependent [137]. Together this suggests that manipulating components of the NMDAR or the interaction of TAU and FYN may be therapeutically beneficial. In fact, disrupting the complex between NMDAR and PSD-95 pharmacologically was found to protect Aβ plaque-forming mice from premature death, memory impairment and the susceptibility to excitotoxic seizures [133]. In conclusion, TAU affects mitochondrial dysfunction also because of its crucial role in mediating excitotoxicity, a pathomechanism that has been implicated in AD.

7. Integration — mitochondria are key targets of Aβ and TAU toxicity in AD

Mitochondria are key targets of Aβ and TAU toxicity in AD (Fig. 1). A picture is emerging whereby these two molecules damage mitochondria in multiple ways, by marching separately and striking together. While the causes of sporadic AD are not known it is evident that Aβ and TAU levels are elevated at an early stage. An impaired homeostasis because of increased Aβ production and decreased clearance causes increased levels, which acts on mitochondria by impairing complex IV function, and by facilitating the fragmentation of mitochondria. Both insults cause increases in ROS levels, decreased activities of detoxifying enzymes such as superoxide dismutase (SOD), and an impaired mitochondrial membrane potential that results in reduced ATP levels. Elevated Aβ levels also result in the overexcitation of neurons, which leads to an influx of calcium ions, with the consequence of increased COX levels, which then damages mitochondria. When Aβ levels are increased this also activates distinct TAU kinases and/or inactivates TAU phosphatases resulting in a massive hyperphosphorylation of TAU. Hyperphosphorylated TAU specifically impairs complex I of the

mitochondrial respiratory chain, again leading to increased ROS levels, lipid peroxidation, decreased activities of detoxifying enzymes such as superoxide dismutase (SOD), and an impaired mitochondrial membrane potential. It also impairs anterograde transport of mitochondria and other cargoes by trapping the kinesin adaptor molecule JIP1 in the neuronal cell body, preventing it from executing its normal function. In AD, hyperphosphorylated TAU not only accumulates in the axon, but also relocalizes and accumulates in the cell body and dendrites of affected neurons. In the dendritic compartment, it facilitates the toxic effects of Aβ that are mediated by the NMDAR. Elevated levels of TAU have also functional consequences on mitochondrial dynamics. TAU causes actin stress fibres to form. This blocks the proper execution of DRP1-mediated fission with a net result of mitochondrial elongation. This, similar to an augmented fragmentation caused by Aβ, causes increased ROS levels, decreased activities of detoxifying enzymes and an impaired mitochondrial membrane potential. In light of the apparently opposing effects Aβ has on mitochondrial size it seems that either too little or too much fission/fusion is detrimental for neurons. Obviously, with TAU impairing axonal transport of mitochondria, the calcium buffering requirements at the synapse are undermined. Together, TAU and Aβ establish a vicious cycle of misregulated dynamics and transport of the mitochondria, which together with alterations in mitochondrial components such as complex proteins or mtDNA, causes mitochondrial impairment in AD.

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