



Pathological Impact of Tau Proteolytical Process on Neuronal and Mitochondrial Function: a Crucial Role in Alzheimer's Disease

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Abstract

Tau protein plays a pivotal role in the central nervous system (CNS), participating in microtubule stability, axonal transport, and synaptic communication. Research interest has focused on studying the role of post-translational tau modifications in mitochondrial failure, oxidative damage, and synaptic impairment in Alzheimer's disease (AD). Soluble tau forms produced by its pathological cleavage induced by caspases could lead to neuronal injury contributing to oxidative damage and cognitive decline in AD. For example, the presence of tau cleaved by caspase-3 has been suggested as a relevant factor in AD and is considered a previous event before neurofibrillary tangles (NFTs) formation.

Interestingly, we and others have shown that caspase-cleaved tau in N- or C- terminal sites induce mitochondrial bioenergetics defects, axonal transport impairment, neuronal injury, and cognitive decline in neuronal cells and murine models. All these abnormalities are considered relevant in the early neurodegenerative manifestations such as memory and cognitive failure reported in AD. Therefore, in this review, we will discuss for the first time the importance of truncated tau by caspases activation in the pathogenesis of AD and how its negative actions could impact neuronal function.

Keywords Tau · Alzheimer's disease · Caspase · Mitochondria · Neurodegeneration · Synaptic loss

Introduction

Tau protein is a microtubule-associated protein (MAP) that contributes to neuronal function by participating in microtubule dynamics and stability [1, 2]. Tau undergoes numerous post-translational modifications such as phosphorylation, glycosylation, nitration, methylation, and proteolytic cleavage, among others [reviewed in 3]. For a long time, tau hyperphosphorylation has been proposed as the main neurotoxic factor in AD [3–5]. This tau form promotes the formation of neurofibrillary tangles (NFTs) that accumulate in neuropil threads and neuritic plaques in AD [6]. However, nowadays has been proposed that proteolytic cleavage of tau by caspases could play a vital role in the genesis and progression of AD [7–9]. Furthermore, several studies have suggested that caspase-3-cleaved tau contributes to NFT

formation and neurodegeneration in the late stages of AD and aging [7]. Current reports suggest that this tau form is an early toxic component in AD and is a crucial protagonist in neuronal dysfunction [10].

Tau is a substrate for caspases cleaving this protein's C-terminus or N-terminus regions [11–13]. These proteolytic processes generate tau fragments that induce aberrant neuronal functions, including synaptic impairment, cell death, neurodegeneration [14–16], and cognitive loss [17]. Interestingly, evidence has shown that caspase-3-cleaved tau contributes to neuronal damage [18–20]. More importantly, caspase-3-cleaved tau promotes mitochondrial injury, which is also considered an important event in the pathogenesis of AD [21–23]. Mitochondrial function plays an essential role in neuronal function [24–27], and several abnormalities in these organelles have been described in AD [28]. In this context, reports showed that truncated tau by caspase-3 induces defects in mitochondrial dynamics, transport, and bioenergetics [29, 30]. However, how cleavage of tau by caspases leads to mitochondrial dysfunction and consequently participates in the onset and progression of AD remains poorly understood. Therefore, in this review, we will discuss evidence supporting the toxic effects of truncated tau

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by caspases against mitochondrial and neuronal function and its role in the pathogenesis of AD.

The Physiological Role of Tau in Neurons

Tau has been studied for its role in tauopathies such as AD [23, 29, 31]. Tau is widely expressed in neurons, being more abundant in axons [32], although studies have shown their presence in synaptic zones [33]. During development, tau is distributed in neurons, while in the maturation process, tau is enriched in axons [34, 35]. The *MAPT* gene encodes tau on human chromosome 17q21 [34, 36]. Tau gene contains 16 exons producing six isoforms of tau where alternative mRNA splicing of exons 2 and 3 produces isoforms with no (0N with no exons 2 and 3), one (1N, with no exon 3) or two (2N, with exons 2 and 3) amino-terminals inserts in the central nervous system (CNS) [34, 37]. Instead, exons 10 form isoforms with three (3N, with no exons 10) or four (4N, with exons 10) microtubule-binding regions resulting in tau of 352 to 441 amino acids depending on the immature and mature brain [37].

Tau interacts with microtubules, specifically with tubulin (a central component of microtubules in the neuronal cytoskeletal) by the C-terminal domain [34], and this process is modulated through the phosphorylation state of tau [38]. In this context, the tau function is regulated by its phosphorylated and dephosphorylated states induced by several kinases and phosphatases, respectively [39]. Three categories of protein kinases phosphorylate tau: (a) second-messenger-activated kinases, including protein kinase C (PKC), protein kinase A (PKA), and Ca^{2+} /calmodulin-dependent protein kinase II (CAMKII); (b) Ser/Pro-directed kinases such as Mitogen-activated-protein-kinase (MAPK), Glycogen synthase kinase-3 beta (GSK-3 β), Cyclin-dependent kinase 2 (cdk2), and Cyclin-dependent kinase 5 (cdk5); and (c) other tau-directed kinases such as Ser-626, casein kinases, and DNA-dependent protein kinases [38, 39].

It is well understood that tau stabilizes and polymerizes microtubules which are vital for the axonal transport of organelles, proteins, and lipids by anterograde and retrograde movement through motor proteins such as kinesin (anterograde transport) and dynein (retrograde transport) [40, 41]. Axonal transport is pivotal to neuronal function, and abnormalities in this process induced by pathological forms of tau could trigger synaptic dysfunction and neuronal death [42].

Tau plays a vital role in synaptic function, being involved in the long terminal depression (LTD) process by its post-synaptic compartment localization in the hippocampus [43]. For example, Briner et al. described an interesting role of tau in N-methyl-D-aspartate (NMDA)-mediated synaptic function in hippocampal neurons [41]. This mechanism is related

to the interaction between tau, the Fyn protein, a non-receptor tyrosine-protein kinase member of the Src family, the post-synaptic density protein 95 (PSD95), and the NMDA receptors [44]. Here, microtubule stability and assembly are regulated by a proline-rich region of tau that contains PXXP motifs to promote interaction with Fyn [34, 37]. This interactive link promotes a complex formation composed of PSD95-NMDA receptor-Fyn-tau, where tau regulates this communication in post-synaptic zones, enhancing the synaptic process [45]. In pathological conditions, tau can be modified by promoting tau disassembly from microtubules reducing PSD95-NMDA receptor-Fyn-tau complex formation, and the latter affects post-synaptic NMDA localization and LTD activity [41–43, 45].

On the other hand, our previous work has suggested an exciting role of tau in regulating hippocampal mitochondrial function [44]. We showed that genetic ablation of tau reduced oxidative stress, improved mitochondrial function, and prevented cognitive decline in young and aged mice, indicating that tau plays an important role in regulating neuronal metabolism [46].

Tau undergoes post-translational modifications such as glycosylation, nitration, methylation, prolyl-isomerization, glycation, phosphorylation, and proteolytic cleavage [34]. Nevertheless, tau can be hyperphosphorylated and cleaved in the neurodegenerative context contributing to AD [8, 21, 23, 29]. Furthermore, several findings showed that tau is a substrate of several proteases, including caspases 2, 3, 6, and 9 [12, 13, 17, 47]. Interestingly, this evidence has shown that caspase induces cleavage of tau in the early stages of AD, which precedes NFT formation [7]. Complementary, several reports have demonstrated that proteolytic cleavage of tau contributes to its aggregation and, finally, to NFT formation [47–49], which is observed in the late stages of AD [50]. Therefore, in the following sections, we will discuss how tau could be proteolytically cleaved and how these toxic soluble forms may contribute to the pathogenesis of AD.

Soluble and Insoluble Tau Modifications

Deposits of misfolded proteins, including tau, are considered a hallmark in AD [51, 52]. The etiology of how soluble tau becomes insoluble has been primarily studied, highlighting the contribution of these forms in NFT formation [53]. As tau progresses to its final insoluble state (NFT), it first passes through a soluble state in which tau undergoes several conformational changes, including dimeric, oligomeric, and fibrillar states [54]. In this context, in vitro studies have shown that NFT formation consists of previous steps such as dimerization, multimerization, oligomerization, and finally, a fibrillar structure formation which fractions are insoluble in

detergents such as sarkosyl [55–57]. NFT (or insoluble state of tau) has been proposed as a protective or compensatory mechanism when soluble toxic tau forms are present [54, 58].

Additionally, studies have documented that N- and C-terminal truncation of tau is an early event in tau aggregation, inducing a soluble tau stage to sarkosyl, which later promotes tangle formation in transgenic rats expressing human truncated tau [59]. Concordantly, other studies suggested that neurons from the hippocampal Cornu ammonia (CA) 1 region of AD patients containing NFT can survive 15 to 25 years [60], indicating that the NFT presence is not related to neuronal loss in AD [60]. Importantly, Santa Cruz and collaborators have presented interesting evidence studying the role of NFT formation and the cognitive and neurodegenerative changes present during AD [61]. These studies showed that PHF-1 tau aggregates (hyperphosphorylated tau epitope of NFT) are not correlated with cognitive and memory impairment in AD murine model [61]. However, the presence of soluble tau induced neurotoxicity and cognitive decline, demonstrating the importance of pathological soluble forms of tau in the early stages of AD [61]. Complementary, other studies using P301L transgenic mice model

for frontotemporal dementia showed that the tangle-bearing neurons (confirmed by PHF-1 antibody) were Arc (reflect electrophysiological neuronal response) positive compared to soluble tau mice that presented a reduction in Arc levels and neuronal loss [15]. Therefore, this evidence strongly suggests that soluble tau can be the primary toxic agent against neuronal function and cognitive performance in the early stages of AD.

Interestingly, the study of soluble tau forms such as caspase-cleaved tau has caused great interest since its presence has been associated with several neuronal abnormalities observed in AD. The following section will discuss caspase's function and how its actions can negatively affect tau protein.

How Is Tau Cleaved?

Caspases are proteases with a well-identified role in programmed cell death, apoptosis, and inflammation [62, 63]. Several studies have explored the non-apoptotic role of caspases in the toxic proteolytic of different proteins, including tau, which contributes to AD onset [7, 64, 65]. This section

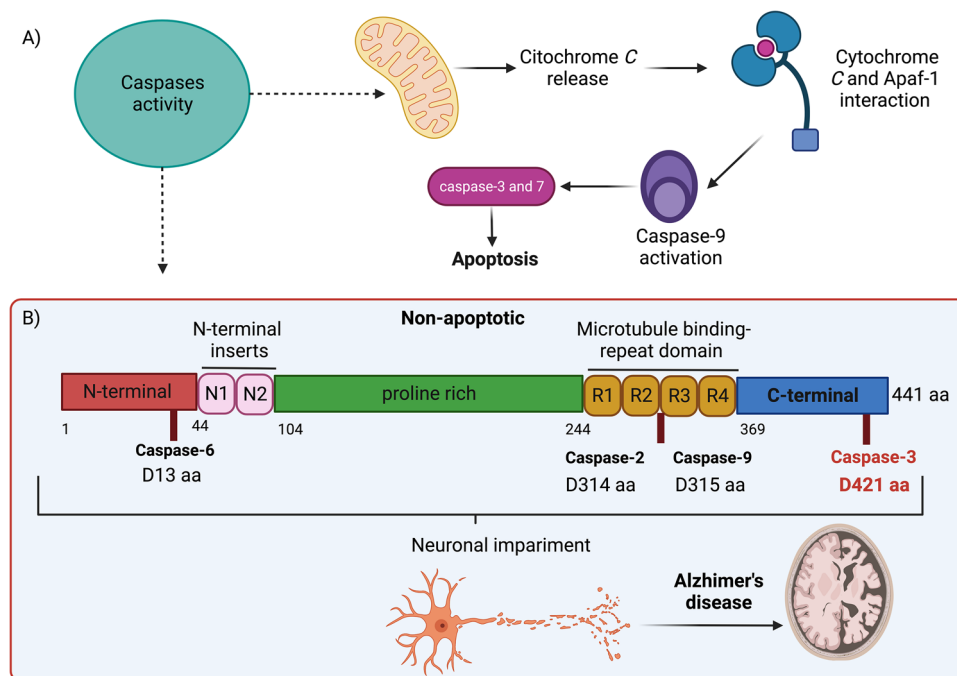


Fig. 1 Caspase activity modifies tau structure and induces neuronal damage in AD. (A) Caspases are involved in apoptotic activity. Here, cytochrome C is released from mitochondrial intermembrane space and binds to apoptosis protease-activating factor-1 (Apaf-1), which then promotes caspase-9 and caspase-3 activation leading to apoptosis. (B) Accumulative evidence has shown that caspases present a non-apoptotic activity, inducing cleave of tau protein. In this context, different caspases could cleave different tau regions; caspase-6

cleave N-terminal D13, and caspase-2, 9, and 3 cleave D314, D315, and AspD421, tau residues, respectively. More importantly, several studies have reported that cleaved tau by caspases induced neuronal impairment, whereas caspase-3-cleaved tau has been suggested to have an essential role in aging and the early stages of AD. Also, caspase-3-cleaved tau is accumulated in neurites zones, which could affect synaptic function

will briefly discuss caspases' contribution to the tau proteolytic process in the brain (Fig. 1).

Caspase Role

Caspases are a proteases family responsible for hydrolyzing cysteine-dependent peptide bond residues [66] and are defined by their different activities [67]. Furthermore, David and collaborators categorized the caspase family by its apoptotic role: caspases 3, 6, 7, 8, 9; and inflammation role: caspases 1, 4, 5, 12 [67]. Also, other studies grouped caspase family by caspase initiators: caspases 2, 8, 9, 10; effector caspases: caspases 3, 6, 7; and inflammatory caspases: caspases 1, 4, 5, 11, 12 [68]. Furthermore, caspases are activated by intrinsic cell pathways where mitochondria actively participate in the apoptotic process [69] by cytochrome *C* release [70]. This pathway is activated by oxidative stress [71], DNA damage [72], accumulation/aggregation of unfolded proteins [73], and hypoxia [74], among others. Briefly, cytochrome *C* is released from mitochondrial intermembrane space into the cytosol, which binds to the apoptosis protease-activating factor-1 adapter molecule (Apaf-1) [75]. Then, Apaf-1 will generate the caspase-9 activation, which promotes the activation of caspase-3 and 7 to induce apoptosis (Fig. 1) [75, 76].

Apoptotic cascade and consequent caspase-9 activation can be modulated by mitochondrial dysfunction [77–80]. Mitochondrial injury produced by ROS production is linked to several types of cellular damage, including hypoxia and unfolded protein aggregations [73, 74, 81, 82]. In addition, ROS-induced oxidative damage will affect mitochondrial permeability, realizing Cyt *C*, which starts an apoptotic cascade and caspase-9 activation [81, 82]. Interestingly, several reports have documented that soluble forms of tau-induced ROS overproduction lead to mitochondrial failure and, consequently, to neuronal damage induced by caspase activation [77, 81, 82]. This evidence indicates that mitochondrial dysfunction can be considered an upstream event in the caspase activation process.

Interestingly, caspases are also involved in non-apoptotic functions, specifically caspase-3, which participates in synaptic plasticity [78]. First, reports have demonstrated an increased caspase-3 expression in CNS [79, 80]. Also, Bravarenko and Cols showed by electrophysiological experiments that blockage of caspase-3 by z-DEVD-fmk prevented the long-term potential (LTPs) process suggesting a physiological role of caspase-3 in synaptic plasticity [83]. In addition, other studies presented that caspase-3 activity is observed in the post-synaptic zone of zebrafish's auditory forebrain, which is necessary for memory and learning performance [84]. However, additional research

has highlighted the contribution of proteolytical caspase-3 activity on tau modifications during aging and neurodegenerative diseases such as AD [10, 17, 47, 80, 85].

Tau as a Substrate for Caspase Activity

Nowadays, it is well documented that caspases exert apoptosis activity and can cleave different proteins in aspartate residues, including tau [86]. Importantly, Zhao et al. have identified that the proteolytic process of tau by caspases could be an event mediated by apoptosis (pro-apoptotic protein) [87]. An increase in apoptosis levels was correlated to an increase in caspase-3 activity and the cleavage of tau at D421, which is known as truncated tau by caspase-3 [87]. Additionally, apoptosis overexpression increased the cleavage of tau, affecting synaptic function, whereas apoptosis inhibition reduced caspase-3-cleaved tau production and synaptic failure [87]. Furthermore, several cleaved tau forms have been shown in five brain regions, including the AD brain's entorhinal cortex, prefrontal cortex, motor cortex, and hippocampus (Fig. 1) [88]. Interestingly, the most prominent cleaved tau forms found were truncated in the C-terminal in these AD patients [88]. Complementary, *in vitro* studies have demonstrated that the deletion in the first 150 aa and the last 50 aa of tau is involved in its pathologic activity promoting self-aggregation [89], which was an age-dependent effect [90].

Effector caspases depend on the cleavage at aspartate residues, where caspase-3 has an essential role in the proteolytic process in this tau region observed in AD [47, 68]. In this context, tau is an essential substrate for caspase-3, leading to the soluble monomeric state of tau and its aggregation in AD [91]. Also, several reports have indicated that tau is cleaved by caspase-3 at the carboxy-terminus residue aspartic acid (Asp421) [92, 93]. Furthermore, *in vitro* studies in SH-SY5Y cells subjected to UV-irradiation treatment showed an increase in caspase-3-cleaved tau levels and NFTs whose expression was inhibited by zVAD-fmk ((carbobenzyloxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone) pan-caspase inhibitor) treatment [47].

On the other hand, microtubule organization is essential to translate different cargoes in neurons maintaining their activity-dependent function [94, 95]. For example, a study demonstrated that truncated tau in Asp421 destabilizes microtubule activity in the mouse brain and HEK (human embryonic kidney) cells [96]. Here, studies using buffer PIPES (Piperazine-N, N'-bis(2-ethanesulfonic acid) and centrifugation showed that the interaction between truncated tau by caspase-3 and cytoskeleton reduced full-length tau/cytoskeleton binding inducing the disassembling of tau from microtubules [96].

Truncated Tau Impairs Neuronal Function

Synaptic plasticity is an active process linked to neurological modifications in the cytoskeleton involved in learning and memory [97]. Defects in cognitive and memory performance have been linked to AD [47, 98]. Studies have shown that soluble tau forms promote aggregation [57, 99], neuronal loss, and cognitive deficiencies [61]. More importantly, evidence proposes soluble tau as a toxic agent, while insoluble tau aggregates may protect neuronal cells [100]. In this context, it was thought that NFTs formed principally by aggregates of hyperphosphorylated tau at PHF-1 residues (Ser 396/Thr 404) causing synaptic and cognitive impairment in AD; however, current reports suggest that other actors, including caspase-3-cleaved tau, may contribute to this process (Fig. 2) [47].

Tau has been observed in synaptic compartments of the AD brain, playing a pivotal role in the defects of neuronal communication [101, 102]. Furthermore, several studies have demonstrated that truncated tau is detected in pre- and post-synaptic zones affecting neuronal function [16, 103]. Also, expression of human truncated tau at N- and C-terminals (encompassing three repeats (amino acid (aa) 151–391; line SHR24)) affected cytoskeletal proteins in the pre- and post-synaptic compartments in transgenic rats (heterozygous transgenic male rats expressing human N- and C-terminally truncated tau) [104]. Furthermore, truncated tau increased β -tubulin expression, reduced synaptophysin, slightly increased bassoon (synaptic vesicle clustering protein) expression levels, and significantly reduced the number of synaptic vesicles compared to wild-type rats [104].

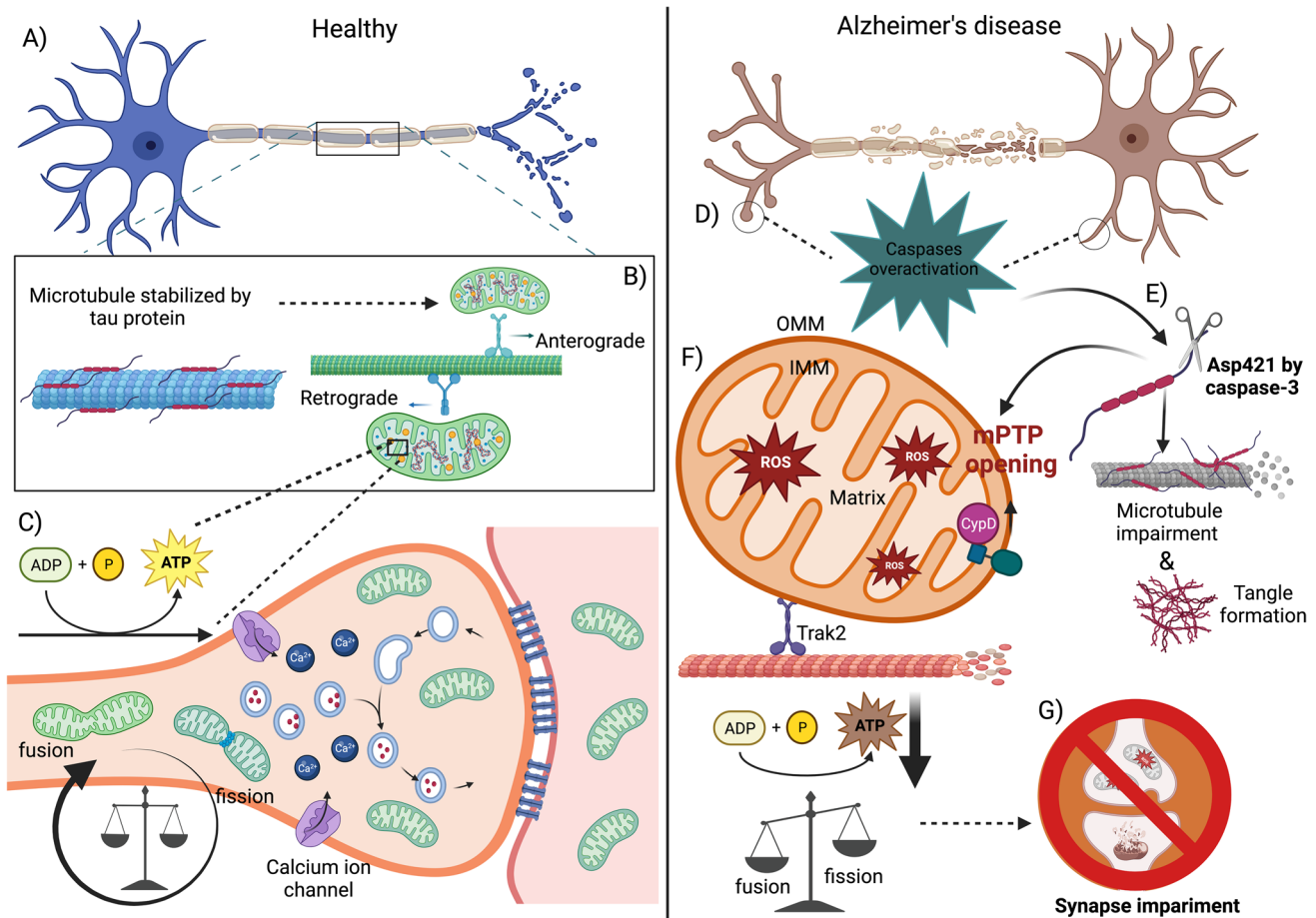


Fig. 2 Caspase-3-cleaved tau promotes mitochondrial dysfunction and synaptic injury. (A) In normal/physiological conditions, tau is enriched in axons (B), promoting microtubule stability and contributing to anterograde and retrograde transport of cargos such as mitochondria. (C) Mitochondria are essential organelles for neuronal activity by supplying ATP, regulating calcium levels, and recycling neurotransmitters. However, these processes are harmed in AD. (D) Additionally, caspase-3 activity has been involved in the onset and

progression of AD. (E) Caspase-3-cleaved tau induces microtubule destabilization leading to tangle formation, which is observed in the late stages of AD. (F) Caspase-3-cleaved tau promotes mitochondrial dysfunction, such as ROS increase, mitochondrial transport damage, ATP loss, and calcium deregulation, where mitochondrial permeability transition pore (mPTP) could play a pivotal role. (G) Mitochondrial injury induced by caspase-3-cleaved tau could lead to synaptic failure

Accordingly, using flow cytometry and immunofluorescence analyses, Sokolow and collaborators showed that truncated tau by caspase-3 was accumulated in synaptosomes from AD patients [16]. More importantly, these authors showed that caspase-3-cleaved tau was the most abundant in synaptic zones of AD patients [16].

On the other hand, using electrophysiology analysis, Loon et al. showed that overexpression of caspase-3-cleaved tau reduced long-term potentiation (LTP) in older C57BL/6 J mice compared to the age-matched control group without caspase-3-cleaved tau expression [105]. These effects also triggered a neuronal loss in the entorhinal cortex and hippocampus observed by NeuN immunoreactivity [105]. In the same context, synaptic impairment and neurodegeneration were studied in a murine model (embryos and positive F₀ mice) that expressed caspase-3-cleaved tau at developmental levels [106]. Immunohistochemical assays revealed that the expression of caspase-3-cleaved tau reduced synaptophysin (synaptic vesicle protein) levels in an age/dependent manner in the hippocampal CA3 region [106]. In addition, synaptic proteins such as PSD95, N-methyl-D-aspartic receptor 1 (NR1), and 2B (NR2B) were decreased in the hippocampus of 3- and 6-month-old mice expressing caspase-3-cleaved tau [106]. Complementary, these changes in synaptic density were associated with the impairment of spatial working memory observed in 1-month-old mice that expressed caspase-3-cleaved tau worsened age-dependently [106]. Interestingly, these observations were recently corroborated by our group in which caspase-3-cleaved tau expression reduced dendritic filopodia and synaptic vesicles number in hippocampal neurons from mice and rats [107].

As aforementioned, caspase-3 has been abundantly found in the post-mortem brain of AD patients in the frontal, temporal, parietal, and cerebellar cortex [108]. At the same time, caspase-3 has been observed in post-synaptic density, which is significantly increased in the cingulate cortex and hippocampus of the AD brain [109]. Although caspase-3 is vital to induce proper neuronal development, LTP, and consequent neuronal plasticity [110], its overactivation is critical to trigger neuronal injury [47]. For example, analysis of hippocampal tissue in C57BL/6 senescent mice (27 months old) showed high levels of caspase-3-cleaved tau compared to young mice (2 months old) [111]. These findings were associated with decreased interaction between this tau form and microtubules and reduced transport cargos promoting dendritic atrophy in hippocampal CA1 neurons [111].

Also, caspase-6 contributes to the tau-cleaved process, although its neurotoxic effect remains under discussion [112, 113]. Cleavage of tau by caspase-6 is produced at D13 N-terminal tau (Tau Δ casp6) [13]. Caspase-6-cleaved tau has been observed in shorted neurites and soma from neurons studied in post-mortem AD brains [114]. Interestingly, increasing levels of caspase-6-cleaved tau have been

found in hippocampal tissue from aging patients compared to young brains. Also, these changes were associated with reduced cognitive performance in aging patients [115]. Complementary, caspase-6-cleaved tau levels were observed in cerebrospinal fluid (CSF) of non-cognitively impaired (NCI), mild cognitive impairment (MCI), and AD patients, and they were correlated with neurocognitive and neuropathologic states being increased as cognitive performance and disease worsen [116].

Tau is also cleaved by caspase-2 at Asp314, generating Δ tau314 [117]. Furthermore, amino-terminal tau fragments cleaved by caspase-2 induce synaptic impairment and memory loss [112, 118]. For example, in hippocampal culture neurons, the expression of Δ tau314 promotes the spreading of tau into dendritic zones, while dendritic spines of wild-type neurons rarely showed the presence of tau [118], suggesting that caspase activity contributes to tau accumulation in post-synaptic zones. Concordantly, measurements of miniature excitatory post-synaptic currents (mEPSCs) in culture hippocampal neurons with Δ tau314 expression showed a significant reduction in mEPSCs amplitude and frequency [116]. Also, these studies showed a decrease in Glur1 (subunit of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor) expression [118], which was enough to induce neuronal and cognitive damage [118]. Finally, it was also observed that caspase-9 has proteolytic activity on tau at Asp315, where this overactivation is documented in AD brains [12]. In addition, several studies indicate that caspase-9 is involved in NFT formation, which was observed in both hippocampus and frontal cortex [12]. Notably, it has been reported that caspase-9 activity could trigger dystrophy neuronal, synaptic plasticity failure, and memory loss from FDD_{K1} mice (a mice model that develops synaptic and memory impairment by loss of BRI₂ protein, which regulates amyloid precursor protein (APP) processing) [12, 119].

Therefore, caspases-induced tau modifications result in neurotoxic effects associated with synaptic loss and severe cognitive impairment. More importantly, the analysis of caspase-3-cleaved tau has generated a significant impact since its presence is detrimental to neuronal function and the onset and progression of AD, which we will discuss in the next section.

Caspase-3-Cleaved Tau Is an Early Hallmark of AD

AD is a neurodegenerative disorder representing the most common form of dementia clinically characterized by cognitive deficits such as learning and memory impairment, spatial disorientation, and behavioral disabilities [120]. In addition, AD is characterized by synaptic loss [121], oxidative damage [122], and neuroinflammation [123], where tau

protein has been mainly postulated as a critical candidate to induce these effects [124, 125]. Accumulative evidence has suggested that NFTs are the main histopathologic hallmarks in AD [3, 126, 127]. However, it was demonstrated that the aggregation and insoluble tau state is not required to trigger the onset and memory impairment shown in AD [128]. In contrast, caspase-3-cleaved tau has raised interest in AD research since studies have demonstrated that this soluble tau form is considered an early event in tangle formation promoting neuronal injury [129]. For example, Kang and collaborators showed that PHF-1 tau is cleaved by caspase-3 during apoptosis-inducing neuronal damage in post-mortem tissue of AD patients and primary cortical neurons [19]. Here, cortical neurons were treated with staurosporine (100 nM) and calyculin A (10 nM) (apoptosis inducers), inducing cleavage of PHF-1 tau at 8 h by activation of caspase-3, which was inhibited by zDEVD (inhibitor of caspase-3) treatment [19]. More importantly, fragments of PHF-1 tau were observed from post-mortem brains of AD patients associated with increased caspase-3 and pro-caspase-3 levels accompanied by a 70% of colocalization between PHF-1 tau-positive neurons and caspase-3 [19]. These results suggest a crucial role of caspase-3 activity in the cleavage of hyperphosphorylated tau (Fig. 2) [64].

In the same context, the cleaved tau at C-terminal, specifically in AspD421 residue, by caspase-3 is considered an essential contributor to AD onset and progression [48, 130]. Evidence has shown a significative immunoreactivity of caspase-3-cleaved tau within the hippocampal CA1 region and entorhinal cortex in post-mortem brain from AD patients compared to control age-matched brain samples [64]. Also, Loon et al. demonstrated that 4- and 12-month-old mice (C57BL/6 J mice) expressing caspase-3-cleaved tau showed cognitive abnormalities such as spatial and recognition memory impairment, short-term work memory failure, and long-term potentiation (LTP) impairment in CA1 region by electrophysiologic analyses of field excitatory post-synaptic potentials (fEPSPs) [105]. Also, other studies reported that stable expression of caspase-3-cleaved tau in immortalized cortical neurons induced cell viability loss observed by an increase in lactate dehydrogenase (LDH) release compared to cells expressing full-length tau [20]. Furthermore, Conze and collaborators demonstrated that caspase-3-cleaved tau reduced axonal transport contributing to synaptic impairment [111]. First, they observed that 27-month-old mice (C57BL/6 J mice) showed increased caspase-3-cleaved tau levels compared to age-match mice [111]. In addition, PC12 cells (catecholamine cells positive for norepinephrine and dopamine) expressing caspase-3-cleaved tau showed a reduced number, velocity, and speed of axonal cargos mitochondria and synaptic vesicles, which also reduced dendritic length [111]. Therefore, the accumulation of caspase-3-cleaved tau negatively affects neuronal

transport and synaptic morphology, triggering cognitive damage and neurodegeneration (Fig. 2).

On the other hand, caspase-6-cleaved tau has also been proposed to promote AD progression [131]. Increased caspase-6 expression levels were observed in adult human neurons compared to the fetal brain [108, 132]. Active caspase-6 and caspase 6-cleaved tau are abundant in neurites plaques (NPS), neuropil threads (NPTs), NFT, and pre-tangles of AD brain [113], suggesting that caspase-6 is activated from early stages of tangle formation [111]. According to this, Albrecht and collaborators showed that active caspase-6 was observed in the hippocampus from MCI and AD brains [131]. However, caspase-6-cleaved-tau was significantly increased in severe AD post-mortem brains compared to age-match control and MCI brain samples [131]. Other studies have correlated increased caspase-6 activity with memory loss in the hippocampus and entorhinal cortex during aging [115, 133]. Importantly, caspase-6-cleaved tau has been observed in different hippocampal regions from AD cases, such as CA1, CA2, CA3, and CA4 [116]. In this context, LeBlanc and collaborators showed an increase in caspase-6 activity and caspase-6-cleaved tau levels in the CA1 region of the aged human brain, which was correlated with semantic and declarative memory impairment [134]. Although previous evidence has demonstrated a possible implication of caspase-6-cleaved tau in the pathogenesis of AD, nowadays has been discussed whether an increase in caspase-6 activity can be considered a key element to induced pathological modifications of tau in AD. For example, caspase-6 fails to induce tau hyperphosphorylation, aggregation, cognitive deficit, and neuroinflammation from transgenic mice expressing cleaved tau by caspase-6 [112]. Also, mice expressing CAMKII-Cre-dependent hTau and hCasp6 in the cortical region and hippocampal CA1 pyramidal did not show cognitive and locomotor decline accompanied by no changes in dendritic spines and inflammatory response [112].

Altogether, this evidence demonstrates that the cleavage of tau by caspase-6 could be associated with clinical signs of AD. However, more studies are necessary to understand its definitive role in this disease.

Caspase-2- and 9-cleaved tau have been found in AD brain patient samples [12, 135]. In this context, caspase-9 activation has been observed in the entorhinal cortex and hippocampus of AD cases and was colocalized with AT8 increased levels (indicates tau hyperphosphorylation in Ser202/Thr305 sites), and with oxidative damage observed by an increase in anti-8oxodG (8-Oxo-2'-deoxyguanosine) levels (oxidative damage indicator for either DNA or RNA) [12]. Also, caspase-2-cleaved tau levels were elevated in aged brain subjects with cognitive deficits [118]. In addition, the infusion of anti-caspase-2 morpholino oligonucleotides during 28 days in lateral ventricles of rTg4510 mice (mice model that expresses a form of tau

containing the P301L mutation linked to frontotemporal dementia) reduced caspase-2 cleavages of tau and, consequently, reverted cognitive impairment [118]. Accordingly, caspase-2 expression levels were increased in AD- and MCI-diagnosed brain samples [135].

Nevertheless, it was recently observed that caspase-2 mRNA levels are not elevated in both MCI and AD samples, which were not associated with a reduction in synaptosome-associated protein ((SNAP-25) protein complex responsible for pre-synaptic membrane fusion of synaptic vesicles) mRNA levels [136]. Therefore, the caspase-2 and 9-cleaved tau role in AD is still elusive.

Contribution of Caspase-3-Cleaved Tau to Mitochondrial Dysfunction in AD

Mitochondria are pivotal organelles to neuronal function, supplying energy and contributing to redox balance and calcium regulation, all essential for synaptic plasticity [137]. In addition, axonal mitochondrial transport is also crucial to neuronal function, which is regulated by motor proteins involved in mitochondrial attachment to microtubules and allows the arrival of these organelles to zones with high energy demands where synapses occur [137, 138].

Previously, we highlighted that the cleaved tau by caspases triggers neuronal dysfunction observed in AD cases and several murine models. However, to this date, how truncated tau is involved in mitochondrial impairment in AD has not been entirely understood. Therefore, we will discuss pivotal evidence demonstrating how caspase-3-cleaved tau at D421 is involved in mitochondrial and synaptic damage in AD (Fig. 2).

Mitochondrial Dysfunction Is a Critical Event in AD

Neuronal cells present a high energetic demand for synaptic function, regulating mitochondrial shape as a necessary process [139–142]. Mitochondrial shape (characterized by fusion and fission process) and its localization are regulated by a synaptic activity where its density and number increase in the dendritic compartment [139]. In this context, specialized GTPases proteins controlling the fusion of the outer mitochondrial membrane (OMM) are the mitofusins 1 and 2 (Mfn1/2), while optic atrophy protein 1 (Opa1) controls the fusion of the inner mitochondrial membrane (IMM) [143]. Also, Dynamin-related protein 1 (DRP1) is a cytosolic protein recruited into mitochondria by the Fis1 protein promoting mitochondrial fission [143]. Mitochondrial dynamics are negatively regulated during AD observing abnormal mitochondrial distribution and synaptic failure [144, 145]. For example, recent studies showed that mitochondrial genes involved in the regulation of mitochondrial morphology and

movement, such as Mfn2, DNML1, Opa1, and Fis1 genes (commanding mitochondrial morphology) and GAPDH (mitochondrial transport), are negatively modified in AD brains [144]. Also, complementary studies in primary neurons from APP AD mice showed a reduction of Drp1, Mfn2, Mfn1, and Opa-1 protein levels; however, Fis1 protein levels were significantly increased. These results were correlated with diminished mitochondrial density and dendritic spine numbers from primary culture neurons [145]. Additionally, Mankzak and collaborators showed adverse changes in mitochondrial dynamics genes in AD brain samples [146]. Here, Drp1 and Fis1 mRNA expression was upregulated, whereas Mfn1, Mfn2, and Opa1 mRNA expression was downregulated in early-stage AD patients [146]. Also, other studies demonstrated an abnormal regulation of mitochondrial dynamics and transport using primary neurons from transgenic mice Tg2576 (mouse model expressing human amyloid precursor protein) [147]. Notably, hippocampal neurons showed mitochondrial fragmentation produced by decreased Mfn1 and Opa1 levels and reduced mitochondrial number and anterograde transport [147].

During neuronal activity, ATP is generated by the action of electron transport chain (ETC) complexes, I–II and III (located at IMM), which pump protons into mitochondrial intermembrane space to activate ATP synthase (complex V) [140–142]. In addition, ROS are produced mainly by mitochondrial complexes I and III, which are balanced by antioxidant defenses produced by mitochondria [148–150]. On the other hand, mitochondria regulate cytosolic calcium levels by mitochondrial calcium uniporter (MCU), mitochondrial permeability transition pore (mPTP), and Na⁺/Ca⁺ and H⁺/Ca⁺ exchangers [151–154]. These mitochondrial events are essential to neuronal communication regulating dendritic spines and vesicle recycling [155, 156].

Mitochondrial dysfunction has been strongly associated with the onset and progression of AD, where ATP loss, ROS overproduction, and calcium deregulation were observed [157–160]. ETC activity, mitochondrial complexes protein expression, and consequently, ATP production were reduced in AD [161]. These results were accompanied by decreased glycolytic enzyme expression and decreased pyruvate dehydrogenase (PDH) activity [161]. Concordantly, other studies have reported a reduction in cerebral glucose utilization in AD patients by measuring 2[18F] fluoro-2-deoxy-D-glucose (18F-FDG) metabolism by positron emission tomography (PET) [162]. Furthermore, hippocampal tissue of 12-month-old 3xTg-AD mice, a mouse model that expresses three mutations associated with AD: APP, P301L, and presenilin 1, showed a reduction in PDH and complex IV proteins levels with a concomitant mitochondrial respiratory capacity impairment [160]. Also, studies using P301L mutant mice, a mouse model that showed accumulation of hyperphosphorylated tau, showed a decrease in complexes I and

V activities, mitochondrial respiratory capacity, and ATP production [163]. Furthermore, analysis of AD brain tissue shows a reduction in mRNA expression of glycolysis, tricarboxylic acid (TCA) cycle, and OXPHOS protein components [164]. Decreased mitochondrial membrane potential ($\Delta\Psi_m$) has also been considered a vital sign of mitochondrial injury observed in the brain cortex of APP mice [165]. ROS overproduction is also reported in different brain regions such as the cortex, hippocampus, striatum, and amygdala [166], triggering oxidative stress and, finally, synaptic failure in A β APP-Swedish mutation (A β PP_{sw}) mice [122]. These deleterious mitochondrial defects are shown in AD brains observing downregulation of complex I, III, and IV gene expression, affecting OXPHOS activity and consequently inducing $\Delta\Psi_m$ depolarization and ATP loss [167].

Mitochondrial calcium handling defects have been associated with neuronal dysfunction in AD [168, 169]. In this context, mPTP contributes to mitochondrial calcium uptake, whose activity is regulated by cyclophilin-D (CypD) [170]. Interestingly, hippocampal neurons treated with cyclosporin A (CsA), an inhibitor of mPTP opening, significantly prevent calcium overload, mitochondrial dysfunction, and excitotoxicity [171]. In addition, brain mitochondria have been observed to be sensible to mPTP opening in AD, leading to mitochondrial swelling, mitochondrial cristae disruption, $\Delta\Psi_m$ decay, and ATP loss [172]. Increased CypD levels have been observed in the AD brain and are associated with deregulating mitochondrial dynamics [146]. Furthermore, Du and collaborators showed that CypD contributes to mitochondrial bioenergetics defects (ROS, ATP, and calcium regulation) and, consequently, to synaptic injury and cognitive damage in AD mice model overexpressing a mutant human form of APP (mAPP, J-20 mice) [173]. Interestingly, CypD deletion rescue mitochondrial bioenergetic failure and neuronal function by regulating calcium concentration [173].

Mitochondrial dysfunction is an important event promoting the onset and progression of AD. Notably, solid reports suggest that proteolytic cleavage of tau by caspase-3, generating caspase-3-cleaved tau, induces mitochondrial defects, which will be discussed in the next section.

Mitochondrial Impairment Induced by Caspase-3-Cleaved Tau

Mitochondrial function impairment has been widely reported in AD pathology, where proteolytic cleavage of tau could be an important contributor to these abnormalities [19, 21, 29]. Interestingly, we showed that genetic suppression of tau improved mitochondrial bioenergetics and dynamics in tau knock-out ($-/-$) mice [46]. Also, we observed that homozygous tau knock-out (tau $-/-$) mice improved hippocampal memory performance, increased Mfn2 levels, and decreased Fis1 levels, reduced lipid

peroxidation, and nitrosylated protein levels, and increased ATP levels [46]. More importantly, tau ($-/-$) mice showed a reduction in mRNA and expression of CypD levels compared to age-matched mice (18 months old) [174], suggesting that CypD could play a key role in mitochondrial dysfunction induced by tau. Complementary studies of Lopes et al. demonstrated that tau ($-/-$) mice prevent dendritic dystrophy, improved vesicle recycling, and increased levels of ETC subunits such as complex I, III, IV, and V when tau ($-/-$) mice were subjected to stress [175].

Mitochondria are dynamic organelles that move, fusion, and divide and whose actions play a role in neuronal function through synapses [176]. In AD, mitochondrial dynamics are significantly altered, where reports showed that mitochondrial fragmentation is increased and the fusion process is reduced, leading to morphologic changes [159] and dynamic process imbalance [177, 178]. In this context, increased expression of Drp1 has been related to mitochondrial fragmentation and neurotoxicity promoted by tau pathology [179]. In this context, partial reduction of Drp1 has been proposed as a therapeutic target in AD since it improves cognitive performance and reverts neuronal plasticity injury in a transgenic tau mouse model [179]. Complementary, Fis1 levels have increased while Mfn1/2 and Opa1 expression is significantly reduced in hippocampal neurons from AD mice models [145]. Also, Opa1 deficiencies contribute to dendritic spines loss and reduced expression of synaptic proteins such as synaptophysin (pre-synaptic protein) and PSD95 (post-synaptic protein) in the hippocampus of Opa1 (+/-) mice which were associated with memory loss [180]. Previously, our group demonstrated that Opa1 and mitochondrial fusion is affected by the expression of caspase-3-cleaved tau in immortalized cortical neurons, rat hippocampal neurons, and wild-type and tau ($-/-$) mice cultured neurons [21, 181]. Also, the expression of caspase-3-cleaved tau enhances mitochondrial dynamics abnormalities (fragmentation) induced by A β treatment [181] (Fig. 2).

Mitochondrial transport and distribution are pivotal to the synaptic process, including vesicle recycling [182], exocytosis/endocytosis [155, 183], dendritic spines formation [184], and neuronal plasticity [185]. Mitochondrial transport is commanded by motor proteins such as kinesin (anterograde transport), dynein (retrograde transport) [186], and trafficking kinesin-binding (TRAK) 1/2, known as mitochondrial adaptor protein [187], which interacts with the heavy kinesin chains domain [188, 189]. Interestingly, aggregation of tau induced a decrease in mitochondrial velocity, reduced mitochondrial population in the neuronal process [190, 191], and decreased mitochondrial motor protein expression in rat neuroblastoma 2a (N2a) cells

[192]. Furthermore, mitochondrial transport was significantly affected by caspase-3-cleaved tau expression in hippocampal neurons from tau ($-/-$) knock-out mice and rats [30]. Likewise, rat/mice hippocampal neurons expressing cleaved tau by caspase-3 decrease the number of moving mitochondria in the axonal and dendritic processes without affecting mitochondrial velocity [193]. Concordantly, expression of caspase-3-cleaved tau significantly promoted mitochondrial accumulation in neuronal soma compared to hippocampal neurons transfected with full-length tau [30].

Interestingly, further studies showed that caspase-3-cleaved tau affects the function of mitochondrial adaptor protein TRAK2 affecting mitochondrial transport [30]. In this context, TRAK2 is pivotal to mitochondrial localization in synaptic terminals since its genetic deletion has shown a reduced mitochondrial location in the neuronal process [194]. Furthermore, our group showed that caspase-3-cleaved tau reduced the expression of TRAK2 in immortalized cortical neurons and hippocampal neurons, affecting its axonal distribution and inducing TRAK2 accumulation in neuronal soma [30]. Therefore, these findings strongly suggest that truncated tau at D421 by caspase-3 affects mitochondrial dynamics and transport, where abnormalities in Opa1 and TRAK2 could play a role in AD (Fig. 2).

Studies of our group determine that caspase-3-cleaved tau expression impairs mitochondrial bioenergetics, harming neuronal survival [20, 22, 81]. Also, the expression of caspase-3-cleaved tau enhanced mitochondrial membrane potential ($\Delta\Psi_m$) loss and increased superoxide production induced by A β treatment [181]. Surprisingly, the expression of phosphorylated tau (Ser396/404) did not show any summative effects against the $\Delta\Psi_m$ levels induced by A β treatment in hippocampal neuronal culture; however, caspase-3-cleaved tau reduced $\Delta\Psi_m$ and increased superoxide production compared to neurons expressing full-length tau and hyperphosphorylated tau (PHF-1) [193]. Likewise, expression of caspase-3-cleaved tau promoted a decrease in ATP levels compared to cortical neurons expressing full-length tau along with ROS overproduction and the impairment of the Nrf2-dependent antioxidant pathway [81]. Interestingly, sulforaphane treatment (activator of the Nrf2 pathway) reduced ROS levels and reversed mitochondrial damage increasing ATP levels and preventing $\Delta\Psi_m$ loss induced by caspase-3-cleaved tau [81] (Fig. 2).

Mitochondrial impairment induced by caspase-3-cleaved tau could be produced by activating mPTP [21, 107]. Caspase-3-cleaved tau expression reduces the influx of mitochondrial calcium, induces mitochondrial depolarization, and compromises mitochondrial membrane integrity [21]. Notably, the inhibition of mPTP opening by CsA prevented

mitochondrial calcium influx and rescued all mitochondrial abnormalities induced by truncated tau by caspase-3 [21]. In addition, CsA treatment reverted mitochondrial fragmentation and integrity and increased $\Delta\Psi_m$, which were affected by cleavage of tau at D421 [21]. Importantly, we recently showed that CsA prevented mitochondrial dysfunction, ROS increase, and ATP loss induced by caspase-3-cleaved tau [107]. Also, CsA treatment reduced dendritic spine loss and prevented synaptic vesicle impairment produced by caspase-3-cleaved tau in mice hippocampal neurons [107]. Altogether, these findings suggest a novel role of mPTP on mitochondrial injury induced by caspase-3-cleaved tau (Fig. 2).

However, further studies are needed to determine the mechanism involved in mitochondrial damage induced by caspase-3.

Tau Pathology in Other Diseases

AD onset correlates to chronic diseases such as diabetes mellitus [195]. Briefly, hyperglycemia is one of the main symptoms of diabetes that correlates with cognitive decline [196] observed in AD. Furthermore, accumulative evidence has shown that hyperglycemia and diabetes could also be risk factors for AD [197, 198]. In this context, hippocampal neurons exposed to hyperglycemia showed accumulation of A β , increased hyperphosphorylated tau levels, oxidative stress, and mitochondrial dysfunction [197, 199–202]. Additionally, increased lipid peroxidation was observed in the hippocampus of diabetic rats [203].

Furthermore, reports have suggested that diabetes and AD are associated with abnormal brain structure, mitochondrial dysfunction, and reduced energy metabolism by ATP loss, reduced $\Delta\Psi_m$, and oxidative stress [204]. More importantly, other studies showed that diabetic mice induced by streptozotocin contributed to the cleavage of tau by caspase-3 and tau hyperphosphorylation in the brain [205]. Also, caspase-3 activity was increased in primary cortical neuronal cultures treated with glucose [205]. Furthermore, other studies using the streptozotocin diabetic mice model showed increased caspase-3-cleaved tau and tau hyperphosphorylated levels in the cortex and hippocampus [206]. Additionally, Latina and collaborators showed that cleavage of tau (66–81 aa of N-terminal) observed in streptozotocin-diabetic mice model contributed to hippocampal recognition and spatial memory loss, oxidative stress, reduced complex IV activity, and decreased mitochondrial respiratory capacity [207].

Altogether, these findings suggested that diabetes could contribute to the onset and progression of AD. However, future research must elucidate how hyperglycemia or diabetic models could promote proteolytic cleavage of tau and mitochondrial dysfunction.

Conclusions

In this review, we discussed evidence showing an essential role of truncated tau by caspases in neuronal injury and mitochondrial dysfunction. Tau is a MAP that contributes to microtubule stability, transports cargo such as mitochondria, and influences neuronal activity. Tau presents different post-translational modifications where proteolytic cleavage by caspases has been involved in the pathogenesis of AD (Fig. 1). Importantly, accumulated evidence has demonstrated that caspase-3-cleaved tau promotes tau aggregation and induces NFT formation. Furthermore, caspase-3-cleaved tau appears in the early stages of AD, modifying mitochondrial dynamics, transport, and bioenergetic functions affecting neuronal communication. In this context, caspase-3-cleaved tau is observed in synaptic zones, and its presence has been associated with reduced vesicle release, dendritic spines loss, and synaptic failure. More importantly, current evidence suggests that caspase-3-cleaved tau can be associated with mPTP opening, increasing ROS production, inducing calcium overload, and promoting mitochondrial dysfunction (Fig. 2).

Finally, truncated tau could be essential to synaptic plasticity impairment through the harmful modifications of mitochondrial function and pathological tau aggregation observed in AD.

Abbreviations AA: Amino acids; AD: Alzheimer's disease; AMPA: α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Apaf-1: Apoptosis protease-activating factor-1 adapter molecule; Asp421: Asparagine 421; AT8: Marker of tau hyperphosphorylation in Ser202/Thr305 sites; ATP: Adenosine triphosphate; CA: Cornus ammonis; CAMKII: Ca^{2+} /calmodulin-dependent protein kinase II; Cdk2: Cyclin-dependent kinase 2; Cdk5: Cyclin-dependent kinase 5; CNS: Central nervous system; CsA: Cyclosporine A; DNA: Deoxyribonucleic acid; DRP1: Dynamin-related protein 1; fEPSPs: Field excitatory post-synaptic potentials; GSK-3 β : Glycogen synthase kinase-3 beta; HEK: Human embryonic kidney cells; IMM: Inner mitochondrial membrane; LDH: Lactate dehydrogenase; LTP: Long-term potentiation; LTD: Long terminal depression; MAP: Microtubule-associated protein; MAPK: Mitogen-activated protein kinase; MCI: Mild cognitive impairment; MCU: Mitochondrial calcium uniporter; mEPSCs: Miniature excitatory post-synaptic currents; MFN: Mitofusins; mPTP: Mitochondrial permeability transition pore; N2a: Neuroblastoma 2a; NCI: Non-cognitively impaired; NFTs: Neurofibrillary tangles; NMDA: N-Methyl-D-aspartate; NPS: Neurites plaques; NPTs: Neuropil threads; NRI: N-Methyl-D-aspartic receptor 1; NR2B: N-Methyl-D-aspartic receptor 2; Nr2f2: Nuclear factor (erythroid-derived 2)-like 2; OMM: Outer mitochondrial membrane; Opal: Optic atrophy protein 1; OXPHOS: Oxidative phosphorylation; PIPES: Piperazine-N,N'-bis(2-ethane sulfonic acid); PKA: Protein kinase A; PKC: Protein kinase C; PSD95: Post-synaptic density protein 95; ROS: Reactive oxygen species; SNAP-25: Synaptosome-associated protein; TRAK: Trafficking kinesin-binding; zVAD-fmk: Carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone; 8oxodG: 8-Oxo-2'-deoxyguanosine; $\Delta\Psi_m$: Mitochondrial membrane potential

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