



Minireview

Molecular and Cellular Basis of Neurodegeneration in Alzheimer's Disease

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The most common form of senile dementia is Alzheimer's disease (AD), which is characterized by the extracellular deposition of amyloid β -peptide ($A\beta$) plaques and the intracellular formation of neurofibrillary tangles (NFTs) in the cerebral cortex. Tau abnormalities are commonly observed in many neurodegenerative diseases including AD, Parkinson's disease, and Pick's disease. Interestingly, tau-mediated formation of NFTs in AD brains shows better correlation with cognitive impairment than $A\beta$ plaque accumulation; pathological tau alone is sufficient to elicit frontotemporal dementia, but it does not cause AD. A growing amount of evidence suggests that soluble $A\beta$ oligomers in concert with hyperphosphorylated tau (pTau) serve as the major pathogenic drivers of neurodegeneration in AD. Increased $A\beta$ oligomers trigger neuronal dysfunction and network alternations in learning and memory circuitry prior to clinical onset of AD, leading to cognitive decline. Furthermore, accumulated damage to mitochondria in the course of aging, which is the best-known nongenetic risk factor for AD, may collaborate with soluble $A\beta$ and pTau to induce synapse loss and cognitive impairment in AD. In this review, I summarize and discuss the current knowledge of the molecular and cellular biology of AD and also the mechanisms that underlie $A\beta$ -mediated neurodegeneration.

Keywords: Alzheimer's disease, amyloid β -peptide, APP, neurodegeneration, tau

INTRODUCTION

In 1906, Alois Alzheimer identified neuritic plaques and neurofibrillary tangles (NFTs) as prominent neuropathologic features in the brains of certain patients, and the pattern was eventually called Alzheimer's disease (AD; [Goedert and Spillantini, 2006](#)). In the 1980s, amyloid β -peptide ($A\beta$) and hyperphosphorylated tau (pTau) were recovered as major components of, respectively, neuritic plaques and NFTs of AD ([Grundke-Iqbal et al., 1986](#); [Ihara et al., 1986](#); [Kang et al., 1987](#); [Kosik et al., 1986](#); [Masters et al., 1985](#)). The amyloid hypothesis proposes that deposition of $A\beta$ plaques in the brain is the primary cause of AD ([Hardy and Higgins, 1992](#); [Hardy and Selkoe, 2002](#)). However, histologically determined numbers of insoluble $A\beta$ plaques in the brain do not correlate with dementia severity ([Hardy and Selkoe, 2002](#); [De Strooper and Karran, 2016](#)). Rather, the tau pathology observed in AD brains correlates better with the degree of cognitive decline ([Hardy and Selkoe, 2002](#); [Spires-Jones and Hyman, 2014](#)). Multiple studies strongly suggest that abnormal elevation in pTau is necessary but not sufficient to cause AD ([Huang and Mucke, 2012](#); [Hutton et al., 1998](#); [Nelson et al., 2012](#)), so what does cause it? This review provides the current understanding of the proteolytic processing of β -amyloid precursor protein (APP), the functional roles of APP-derived fragments, and AD-causing mutations, and it discusses the molecular and cellular mechanisms that underlie the pathogenesis of neurodegenerative AD.

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PROTEOLYTIC PROCESSING OF β -AMYLOID PRECURSOR PROTEIN

A β s, which largely consist of peptides that are 40 and 42 amino acids long (A β 40 and A β 42), are produced by sequential APP proteolytic processes by β -secretase (BACE) and γ -secretase (Figs. 1A and 1B; Esler and Wolfe, 2001; Goedert, 2015; Reinhard et al., 2005); A β 42 is more aggregation-prone and more neurotoxic than A β 40 (Jarrett et al., 1993; Klein et al., 1999). In the amyloidogenic pathway, human APP is first cleaved by β -secretase, generating a large soluble ectodomain (sAPP β) and the C-terminal C99 peptide (Fig. 1B), and proteolytic cleavages of the C99 peptide by γ -secretase release A β s and the APP intracellular domain (AICD; Figs. 1B and 2). Alternatively, in the non-amyloidogenic pathway, human APP is sequentially cleaved by α -secretase and γ -secretase, creating a soluble ectodomain (sAPP α), P3 peptide, and the AICD (Fig. 1B). P3 peptide corresponds to A β 17-40 and A β 17-42 and is non-amyloidogenic (Fig. 2; Selkoe, 1998). Therefore, α - and β -secretases have opposing effects on generating A β s due to their competitive cleavages of APP. In support of this, increased α -secretase activity through protein kinase C stimulation decreases A β generation (Hung et al., 1993; Lin et al., 1999; Skovronsky et al., 2000), whereas *BACE1* knockout mice lack brain A β s (Cai et al., 2001; Luo et al., 2001). γ -Secretase, a multi-protein complex that consists of at least four subunits—presenilin (PS), nicastrin, Aph-1, and Pen-2—functions as a transmembrane aspartyl protease that plays a critical role in not only generating A β s but also determining A β 42 to A β 40 ratios (Bai et al., 2015; De Strooper, 2003; Esler and Wolfe, 2001). Consistent with this notion, *PS1/PS2* double-null mutation resulted in the absence of A β production and complete inactivation of γ -secretase (Herreman et al., 2000; Zhang et al., 2000). The γ -secretase-mediated processing of APP is one of

the best-characterized examples for regulated intra-membrane proteolysis (RIP) that is an evolutionarily conserved mechanism from bacteria to humans (Brown et al., 2000). RIP of APP can be directly modulated by several γ -secretase associated proteins including TMP21, pigeon homologue protein, and proton myo-inositol cotransporter (Chen et al., 2006; He et al., 2010; Teranishi et al., 2015; Wakabayashi et al., 2009; Zhou et al., 2005). Because the known prerequisite for a γ -secretase substrate is the release of its bulky extracellular domain (Esler and Wolfe, 2001; Struhl and Adachi, 1998), another regulation is indirectly mediated by competitive α -secretase and β -secretase functions that are required for shedding the APP extracellular domain. Therefore, RIP of APP by these secretases is responsible for A β production, and it also plays a critical role in determining the ratio of A β 42 to A β 40. Understanding the regulatory mechanisms and alterations in RIP of APP in AD patients is necessary for identifying novel therapeutic targets for treating AD.

PROTEOLYTIC FRAGMENTS OF β -AMYLOID PRECURSOR PROTEIN

Emerging evidence suggests that soluble A β oligomers are the major neurotoxic species and are responsible for the progressive neurodegeneration in AD (Lacor et al., 2007; Li et al., 2009; Lue et al., 1999; McLean et al., 1999; Shankar et al., 2008). The soluble A β oligomers were shown to disrupt cognitive function when injected intracerebroventricularly in rats (Cleary et al., 2005; Shankar et al., 2008). Consistent with this, impaired learning and memory were observed in transgenic mice that overexpress full-length human APP751 with the familial Swedish mutation and the A β dimer-stabilizing mutation (AP679C), leading to the generation of highly soluble A β dimers (Müller-Schiffmann et al.,

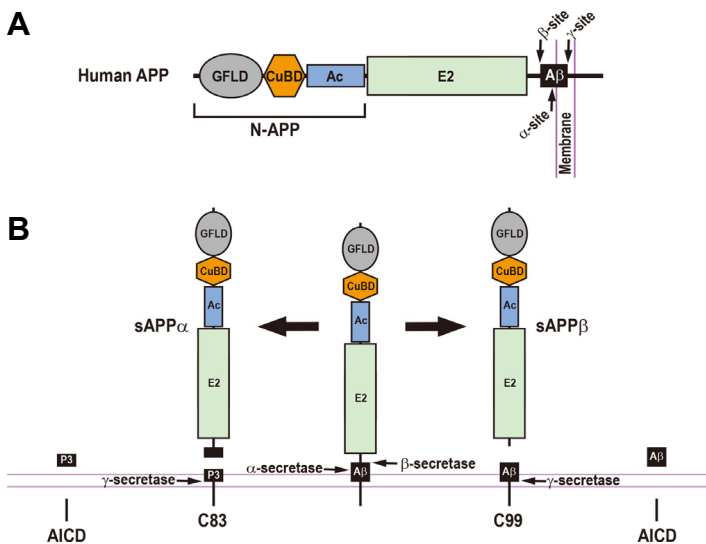


Fig. 1. The Regulated Proteolytic Processing of Human β -Amyloid Precursor Protein and the Resulting Cleavage Fragments.

(A) Schematic diagram of human β -amyloid precursor protein (APP). The arrows represent the cleavage sites by α -, β -, and γ -secretases. GFLD, growth factor-like domain; CuBD, copper-binding domain; Ac, acidic domain; E2, APP extracellular carbohydrate domain; A β , amyloid β -peptide; N-APP, a cleaved N-terminal fragment of APP. (B) Human APP can be processed through either amyloidogenic or non-amyloidogenic pathways. In the amyloidogenic pathway (right), the proteolytic cleavage of the APP by β -secretase produces a large soluble ectodomain of APP (sAPP β) and a membrane-associated C-terminal fragment (C99). The C99 is subsequently cleaved by γ -secretase, releasing an amyloid β -peptide (A β) and an APP intracellular domain (AICD). In a non-amyloidogenic pathway (left), α -secretase-mediated cleavage of the APP generates a soluble ectodomain of APP (sAPP α) and a membrane-tethered C-terminal fragment (C83). The subsequent cleavage of the C83 by γ -secretase gives rise to a P3 peptide and an AICD.

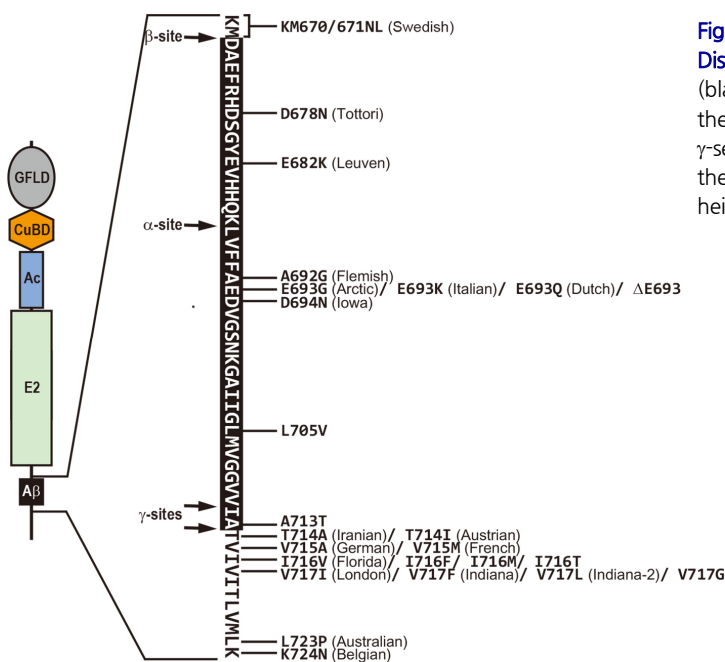


Fig. 2. Human APP Mutations that Cause Familial Alzheimer's Disease. The amino acid sequence of the amyloid β -peptide (black box) and flanking transmembrane regions is presented; the horizontal arrows indicate the cleavage sites by α -, β -, and γ -secretases. Many missense and deletion mutations within the APP were discovered to cause an inherited form of Alzheimer's disease.

2015). The soluble A β oligomers rapidly downregulate membrane expression of postsynaptic spine proteins including *N*-methyl-D-aspartate (NMDA) type glutamate and EphB2 receptors, leading to long-term potentiation (LTP) inhibition as well as enhancing long-term depression (LTD; Lacor et al., 2007; Shankar et al., 2008). Furthermore, the physiological functions of soluble A β 40 and A β 42 have been proposed to be involved in the control of cholesterol *de novo* synthesis and sphingomyelin levels, respectively (Grimm et al., 2005). Interestingly, proteolytic fragments of APP other than A β species were reported to have neuroprotective or neurotoxic activities (Chasseigneaux and Allinquant, 2012). Both sAPP α and sAPP β were shown to mediate neuroprotective function, but the neuroprotective effect of sAPP α was approximately 100 times more potent than sAPP β (Furukawa et al., 1996). The neuroprotective function of sAPP α is further supported by the finding that sAPP α knock-in mice showed almost complete restoration of the anatomical, behavioral, and electrophysiological abnormalities observed in APP knock-out mice (Ring et al., 2007). In contrast, neurotoxic sAPP β activity was also reported in mammals. Neurotrophic factor depletion increases sAPP β production and further induces proteolytic cleavage of sAPP β , releasing a cleaved N-terminal fragment, N-APP, which triggers axon degeneration and neuronal cell death through binding to death receptor 6 (Fig. 1A; Nikolaev et al., 2009). The AICD, which is produced from both amyloidogenic and non-amyloidogenic pathways (Fig. 1B), has been implicated in the pathological process of AD (Nhan et al., 2016). AICD overexpression in transgenic mice was shown to induce AD-like pathological features including GSK-3 β upregulation, tau hyperphosphorylation and its age-dependent aggregation, and hippocampal neurodegeneration (Ghosal et al., 2009; Ryan and Pimplikar, 2005). However, these AD-like

phenotypes were not reproduced in independently generated transgenic mice that overexpressed the same AICD (Giliberto et al., 2010), and the cause of this discrepancy remains unclear. In contrast, impaired calcium signaling observed in APP^{-/-} null-mutant cells can be restored by reintroducing an intact AICD, suggesting its functional role in calcium homeostasis (Hamid et al., 2007; Leissring et al., 2002). In addition, AICD overexpression in cultured cells resulted in cell death (Müller et al., 2008), and this apoptotic potential of AICD appears to be conserved between humans and *Drosophila* (Gunawardena and Goldstein, 2001; Hong et al., 2017; Wang et al., 2014). In summary, soluble A β oligomers are now considered to be the primary initiators of neurodegenerative AD processes. In addition, the neurotoxic activity of N-APP and AICD raises the possibility that soluble A β oligomers can collaborate with N-APP and AICD to accelerate neurodegeneration in AD patients (Fig. 3). Another possibility is that soluble A β oligomers antagonize the neuroprotective functions of sAPP α , sAPP β , and AICD. One intriguing question is which receptors and signaling components directly respond to soluble A β oligomers and result in neurodegeneration. Therefore, it will be important to identify the crucial genes that link soluble A β oligomers to synaptic impairment that correlates with dementia severity in AD.

GENETIC BASIS OF ALZHEIMER'S DISEASE

The two major types of AD are familial and sporadic (Tanzi, 2012). Early-onset familial Alzheimer's disease (EO-FAD), which accounts for less than 5% of AD, is a fully penetrant autosomal-dominant disorder resulting from rare mutations in APP, PS1 and PS2 (Tanzi, 2012). In contrast, late onset sporadic Alzheimer's disease (LO-SAD), which represents most cases of AD, is likely influenced by the combined action of

multiple genetic susceptibilities and environmental risk factors (Lambert and Amouyel, 2011). One major genetic risk factor for LO-SAD is the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE4*), which plays a crucial role in regulating cholesterol metabolism (Corder et al., 1993; Strittmatter et al., 1993). The contribution of *APOE4* to AD pathogenesis is associated with *APOE4*-mediated modulation of $A\beta$ aggregation and clearance (Bu, 2009). Many additional genes have been identified as genetic risk factors for LO-SAD (Bu, 2009; Lambert et al., 2013; Small and Petsko, 2015; Tanzi, 2012). Although there are differences in the genetic pathological causes between EO-FAD and LO-SAD, they show remarkable similarities in their pathophysiology and clinical symptoms (Bateman et al., 2011). First, similar patterns of senile $A\beta$ plaques, NFTs, and cerebral amyloid angiopathy are observed in both forms of AD. Second, structural and functional neuroimaging studies indicate that hippocampal and medial-temporal lobe atrophies are commonly found in both types of AD. Third, both AD forms share temporo-parietal hypometabolism and episodic memory and judgment impairment, which are responsible for cognitive deficits. In addition, myoclonus and seizures are also frequently observed. Finally, changes in biochemical markers including cerebrospinal fluid $A\beta_{42}$, tau, and pTau, during the neurodegeneration process are also very similar in both AD forms. These similarities in neuropathology strongly suggest the presence of common pathogenic biochemical processes underlying both EO-FAD and LO-SAD. Therefore, knowledge and disease-modifying drugs for AD obtained from studies on EO-FAD could be useful in providing preventive treatments for LO-SAD.

To date, a total of 25 pathogenic mutations (except for duplications) in APP associated with EO-FAD have been defined (<http://www.molgen.ua.ac.be/ADMutations/>) (Fig. 2). Most missense mutations in APP are clustered near the proteolytic cleavage sites that are responsible for $A\beta$ generation and clearance (Fig. 2), and they commonly increase the ratio of $A\beta_{42}$ to $A\beta_{40}$ (Tanzi, 2012). More than 200 mutations in PS1 and 16 in PS2 have been reported to cause EO-FAD (<http://www.molgen.ua.ac.be/ADMutations/>) (Tanzi, 2012). Pathogenic missense mutations in *PS1* and *PS2* shift the γ -secretase site from $\gamma 40$ to $\gamma 42$, resulting in an increase in the $A\beta_{42}$ to $A\beta_{40}$ ratio (De Strooper, 2007). Taken together, most missense mutations in *APP*, *PS1*, and *PS2* associated with EO-FAD appear to converge at a higher $A\beta_{42}$ to $A\beta_{40}$ ratio, leading to elevated levels of neurotoxic $A\beta$ oligomers, $A\beta$ plaque deposition, and the development of AD.

Although it is widely accepted that the elevated levels of aggregation-prone $A\beta$ including $A\beta_{42}$ and the longer forms are the primary pathogenic drivers, cognitive impairment in people with AD correlates better with tau pathology than $A\beta$ plaque deposition (Hardy and Selkoe, 2002; Spiros-Jones and Hyman, 2014). Tau is a microtubule-associated protein that regulates the stability of microtubules (MTs) located in axons, thereby contributing to axonal transport and outgrowth (Ballatore et al., 2007). In tauopathies including AD, fronto-temporal dementia (FTD), and Parkinsonism, tau is hyperphosphorylated, leading to its disengagement from the MTs and the formation of NFTs (Ballatore et al., 2007).

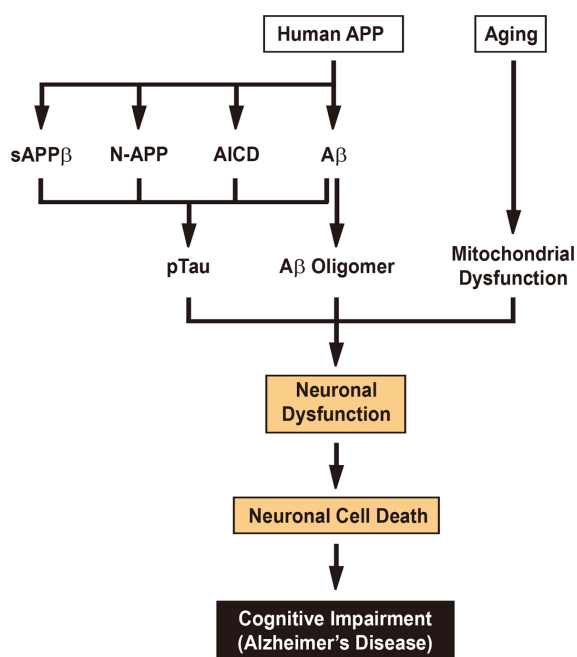


Fig. 3. The Main Drivers of Neurodegeneration in Alzheimer's Disease. Neuronal dysfunction and cell death are responsible for the development of Alzheimer's disease. Accumulating evidence suggests that abnormally elevated tau hyperphosphorylation, pathogenic $A\beta$ oligomers, and mitochondrial dysfunction cooperate to drive the neuronal dysfunction and cell death that underlie cognitive impairment. Although the amyloid hypothesis supports that neurotoxic $A\beta$ primarily induces tau pathology, other proteolytic fragments of the human APP including sAPP β , N-APP, and AICD, also appear to contribute to tau alterations. In addition, aging, which is tightly associated with mitochondrial dysfunction, can serve as the most significant nongenetic risk factor for Alzheimer's disease.

However, mutations in the human tau, *MAPT*, which cause *MAPT* hyperphosphorylation and aggregation with lack of $A\beta$ deposits, lead to FTD but not to AD (Hutton et al., 1998). In addition, neocortical NFTs, which are tightly associated with severe cognitive impairment, are consistently found in brains with AD, suggesting that $A\beta$ pathology acts upstream of tau pathology (Nelson et al., 2012; Huang and Mucke, 2012; Fig. 3). Furthermore, reduction in endogenous tau levels prevents behavioral abnormalities and premature mortality observed in the AD mouse model that overexpresses human APP with a familial AD mutation, with no alternation in $A\beta$ plaque deposition (Roberson et al., 2007). These observations demonstrate that $A\beta$ - and tau-induced neurotoxicity collaborates to cause progressive neurodegeneration and cognitive impairment in AD (Fig. 3).

SYNAPTIC DYSFUNCTION AND NEURONAL CELL DEATH IN ALZHEIMER'S DISEASE

Synapse loss in the neocortex and hippocampus, which play

a critical role in learning and memory (Kandel et al., 2014), is an early pathological hallmark of AD and correlates strongly with cognitive impairment (Arendt, 2009; DeKosky and Scheff, 1990; Terry et al., 1991). What are the cellular and molecular mechanisms underlying synapse loss? A great deal of evidence supports that soluble A β oligomers contribute to synapse dysfunction and loss by acting on multiple synaptic receptors including NMDA-type glutamate and α 7-nicotinic acetylcholine (α 7-nACh) receptors (Palop and Mucke, 2016; Spires-Jones and Hyman, 2014). NMDA receptors are required for generating both long-term potentiation and long-term depression but in distinct manners (Kandel et al., 2014). LTP is a synaptic plasticity mechanism that contributes to memory encoding in the hippocampus (Kandel et al., 2014); in contrast, LTD in the hippocampus is involved in memory decay (Kandel et al., 2014). NMDA receptor-induced large Ca²⁺ influx during LTP promotes the incorporation of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptors into synapses, leading to dendritic spine growth, whereas NMDA receptor-mediated reduced Ca²⁺ influx during LTD decreases the levels of AMPA receptors at the synapses and results in dendritic spine loss (Kandel et al., 2014). Several studies have shown that soluble A β oligomers inhibit LTP and induce progressive spine loss via downregulation of NMDA receptors, followed by synaptic removal of AMPA receptors (Chen et al., 2000; Cullen et al., 1997; Hsieh et al., 2006; Shankar et al., 2007; Walsh et al., 2002). In addition, soluble A β oligomers interfere with glutamate uptake at the synapses, resulting in enhanced LTD (Li et al., 2009). Consistent with this, NMDA receptor antagonists such as memantine and NitroMemantine can compromise A β -induced synaptic dysfunction and cognitive impairment (Figueiredo et al., 2013; Talantova et al., 2013; Zhu et al., 2013). Taken together, A β -mediated LTP inhibition, LTD enhancement, and synapse loss appear to underlie cognitive impairment in AD (Fig. 3; Palop and Mucke, 2010).

Soluble A β oligomers were shown to activate α 7-nACh receptors expressed in *Xenopus* oocytes (Dineley et al., 2002). Interestingly, α 7-nACh receptor blockade reduces the production of A β and A β -induced synapse loss, indicating the presence of positive feedback between α 7-nACh receptors and A β (Wei et al., 2010). Furthermore, substantial loss of cholinergic neurons in the nucleus basalis of Meynert was observed in AD brains, supporting the cholinergic hypothesis (Bartus et al., 1982; Whitehouse et al., 1981). Indeed, cholinesterase inhibitors including donepezil, galantamine, and rivastigmine, which inhibit acetylcholine degradation, are used to treat patients with early-stage AD (Canter et al., 2016; Zhu et al., 2013).

Progressive and substantial neuronal cell death in vulnerable brain regions including the hippocampus, nucleus basalis, and entorhinal cortex is another pathological hallmark of AD (Gómez-Isla et al., 1996; Simić et al., 1997; Whitehouse et al., 1981). Consistent with this, significant neuronal loss was observed in many different transgenic mouse models that commonly contain EO-FAD mutations in human full-length APP (Wirhth and Bayer, 2010). In addition, overexpression of N-terminally truncated A β _{PE3-42} peptide, which lacks two N-terminal amino acids and carries a pyrogluta-

mate at position 3, but not full-length A β 42 in transgenic mice induces robust neuronal loss (McGowan et al., 2005; Wirhth et al., 2009). Because tau abnormalities cause neuronal cell death (Gendron and Petrucelli, 2009), these findings suggest that neurotoxic A β and tau collaborate to mediate neuronal loss (Fig. 3). Neuronal cell death observed in AD is also associated with mitochondrial dysfunction (Knott et al., 2008; Reddy and Beal, 2008). Dynamin-related protein 1 was reported to mediate A β -related mitochondrial dysfunction and subsequent neuronal loss (Cho et al., 2009). In addition, a growing body of evidence suggests that mitochondrial dysfunction plays a critical role in the pathogenesis of AD (Reddy and Reddy, 2011; Swerdlow et al., 2010). Mitochondrial dysfunction in the brains of AD patients correlates with a wide range of mitochondrial abnormalities including mitochondrial DNA defects, decreased levels of mitochondrial enzyme activities, impaired mitochondrial trafficking, and increased oxidative stress (Reddy and Reddy, 2011; Swerdlow et al., 2010). Because mitochondria accumulate reactive oxygen species-induced damage with age, it seems that the most prominent nongenetic risk factor for AD, aging, in concert with soluble A β oligomers and pathological tau, contributes to AD pathogenesis through mitochondrial dysfunction (Fig. 3; Canter et al., 2016; Tu et al., 2014).

CONCLUSION

Tau pathology better correlates with cognitive decline in AD than does substantial A β plaque deposition, and the amyloid hypothesis suggests that the tau-mediated formation of NFTs observed in AD results from abnormally elevated A β . Recent evidence supports that soluble A β oligomers are the primary pathogenic drivers of neurodegeneration in AD and further proposes that soluble A β oligomers cooperate with pathological tau to progressively degenerate the learning and memory circuitry required for cognitive functions. In addition to neurotoxic A β and tau, the other critical risk factor for clinical onset of AD is aging; age-related mitochondrial damage appears to play an important role in A β /tau-induced neurodegeneration in AD. Even though great advances have been made in knowledge of the genetic and cellular mechanisms involved in the pathogenesis of AD, unfortunately, there is still no effective treatment that prevents, delays, and cures it. Therefore, better understanding of the pathological functions of neurotoxic A β oligomers and precise mechanisms of A β -mediated signaling cascades, in addition to defining the molecular link between A β /tau and aging, will help to guide therapeutic drug development for AD treatment.

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