The most common form of senile dementia is Alzheimer’s disease (AD), which is characterized by the extracellular deposition of amyloid β-peptide (Aβ) 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 Aβ 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 Aβ oligomers in concert with hyperphosphorylated tau (pTau) serve as the major pathogenic drivers of neurodegeneration in AD. Increased Aβ 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 Aβ 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 Aβ-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 (Aβ) 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 Aβ plaques in the brain is the primary cause of AD (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). However, histologically determined numbers of insoluble Aβ plaques in the brain do not correlate with dementia severity (Hardy and Higgins, 1992; 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.
PROTEOLYTIC PROCESSING OF β-AMYLOID PRECURSOR PROTEIN

Aβs, which largely consist of peptides that are 40 and 42 amino acids long (Aβ40 and Aβ42), 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): Aβ42 is more aggregation-prone and more neurotoxic than Aβ40 (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 (sAPPβ) and the C-terminal C99 peptide (Fig. 1B), and proteolytic cleavages of the C99 peptide by γ-secretase release Aβs 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 (sAPPα), P3 peptide, and the AICD (Fig. 1B). P3 peptide corresponds to Aβ17-40 and Aβ17-42 and is non-amyloidogenic (Fig. 2; Selkoe, 1998). Therefore, α- and β-secretases have opposing effects on generating Aβs due to their competitive cleavages of APP. In support of this, increased α-secretase activity through protein kinase C stimulation decreases Aβ generation (Hung et al., 1993; Lin et al., 1999; Skovronsky et al., 2000), whereas BACE1 knockout mice lack brain Aβs (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 Aβs but also determining Aβ42 to Aβ40 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 Aβ 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, pig 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 Aβ production, and it also plays a critical role in determining the ratio of Aβ42 to Aβ40. 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 Aβ 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 Aβ 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 Aβ dimer-stabilizing mutation (APPS679C), leading to the generation of highly soluble Aβ dimers (Müller-Schiffmann et al., 2000).
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.

The soluble Aβ oligomers rapidly downregulate membrane expression of postsynaptic spine proteins including α-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 Aβ40 and Aβ42 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 Aβ species were reported to have neuroprotective or neurotoxic activities (Chasseigneaux and Allinquant, 2012). Both sAPPα and sAPPβ were shown to mediate neuroprotective function, but the neuroprotective effect of sAPPα was approximately 100 times more potent than sAPPβ (Furukawa et al., 1996). The neuroprotective function of sAPPα is further supported by the finding that sAPPα 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 sAPPβ activity was also reported in mammals. Neurrotoxic factor depletion increases sAPPβ production and further induces proteolytic cleavage of sAPPβ, 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-3β 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 (Gliberto 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 Aβ 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 Aβ oligomers can collaborate with N-APP and AICD to accelerate neurodegeneration in AD patients (Fig. 3). Another possibility is that soluble Aβ oligomers antagonize the neuroprotective functions of sAPPα, sAPPβ, and AICD. One intriguing question is which receptors and signaling components directly respond to soluble Aβ oligomers and result in neurodegeneration. Therefore, it will be important to identify the crucial genes that link soluble Aβ 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
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multiple genetic susceptibilities and environmental risk factors (Lambert and Amouyel, 2011). One major genetic risk factor for LO-SAD is the ε4 allele of the apolipoprotein E gene (APOE-ε4), 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 Aβ 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 Aβ 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 temporal-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 Aβ levels prevent behavioral abnormalities and premature mortality observed in the AD mouse model that overexpresses Aβ 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 Aβ plaque deposition (Roberson et al., 2007). These observations demonstrate that Aβ- 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

Synapses are lost 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 Schelt, 1990; Terry et al., 1991). What are the cellular and molecular mechanisms underlying synapse loss? A great deal of evidence supports that soluble Aβ oligomers contribute to synapse dysfunction and loss by acting on multiple synaptic receptors including NMDA-type glutamate and α7-nicotinic acetylcholine (α7-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 Aβ 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 Aβ 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 Aβ-induced synaptic dysfunction and cognitive impairment (Figureiredo et al., 2013; Talantova et al., 2013; Zhu et al., 2013). Taken together, Aβ-mediated LTD inhibition, LTD enhancement, and synapse loss appear to underlie cognitive impairment in AD (Fig. 3; Palop and Mucke, 2010).

Soluble Aβ oligomers were shown to activate α7-nACh receptors expressed in Xenopus oocytes (Dineley et al., 2002). Interestingly, α7-nACh receptor blockade reduces the production of Aβ and Aβ-induced synapse loss, indicating the presence of positive feedback between α7-nACh receptors and Aβ (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 (Wirths and Bayer, 2010). In addition, overexpression of N-terminally truncated Aβ1-42 Peptide, which lacks two N-terminal amino acids and carries a pyrogluta-
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