

REVIEW

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# Advances in the pathogenesis of Alzheimer's disease: a re-evaluation of amyloid cascade hypothesis

Suzhen Dong<sup>1,2,3</sup>, Yale Duan<sup>3</sup>, Yinghe Hu<sup>1,2,3</sup> and Zheng Zhao<sup>3\*</sup>

## Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease characterized clinically by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of amyloid-beta (A-beta) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain. This review focused on the new developments of amyloid cascade hypothesis with details on the production, metabolism and clearance of A-beta, and the key roles of some important A-beta-related genes in the pathological processes of AD. The most recent research advances in genetics, neuropathology and pathogenesis of the disease were also discussed.

**Keywords:** Alzheimer's disease, A-beta, APP, BACE1, Presenilins, ApoE, Neprilysin/insulin-degrading enzyme

## Review

### Introduction

Alzheimer's disease (AD) was originally described by Alois Alzheimer in 1906 and was renamed several years later by Emil Kraepelin [1]. AD is characterized clinically by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of amyloid- $\beta$  ( $A\beta$ ) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain, which are commonly regarded as the hallmarks of the disease.

Epidemiological studies have shown that AD is the leading cause of dementia, accounting for about 50% of all cases worldwide [2]. Aging is the most obvious risk factor for developing AD. It was estimated that the age-associated prevalence rate of AD would be doubled every 5 years in the patients beyond 65 years of age [3]. In addition to aging, several other possible biological (such as genetic alterations and polymorphisms, and abnormal immune or inflammatory responses) and environmental factors (such as education, traumatic injury, oxidative

stress, drugs, and hormone replacement) and the interactions among these factors have been considered to be contributors to a common pathway leading to AD [4,5].

Despite the remarkable improvements in our understanding of the pathogenesis of the disease have been made over last several decades, the accurate mechanism of AD remains unclear. Several independent hypotheses have been proposed to address the pathological lesions and neuronal cytopathology in connection with apolipoprotein E (ApoE) genotyping, hyperphosphorylation of cytoskeletal proteins, oxidative stress, abnormal cell cycle re-entry, inflammation and  $A\beta$  metabolism. The amyloid metabolic cascade and the posttranslational modification of tau protein are considered to be the most important hypotheses in AD, although none of them or other theories alone is sufficient to explain the diversity of biochemical and pathological abnormalities of AD, which is believed to involve a multitude of cellular and biochemical changes [3]. According to amyloid cascade hypothesis [6,7], accumulation of extracellular senile plaques made primarily by deposits of  $A\beta$  peptide is thought to be one of the most prominent pathogenic mechanisms of AD. Although the direct causal link between  $A\beta$  and impaired neuronal function and memory is still under elucidation, it is undoubted that  $A\beta$  plays a critical role in the neuropathology of AD. This review focuses on the new

\* Correspondence: zzhao@brain.ecnu.edu.cn

<sup>3</sup>Key Laboratory of Brain Functional Genomics, Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, East China Normal University, 3663 Zhongshan Road (N), Shanghai 200062, China  
Full list of author information is available at the end of the article

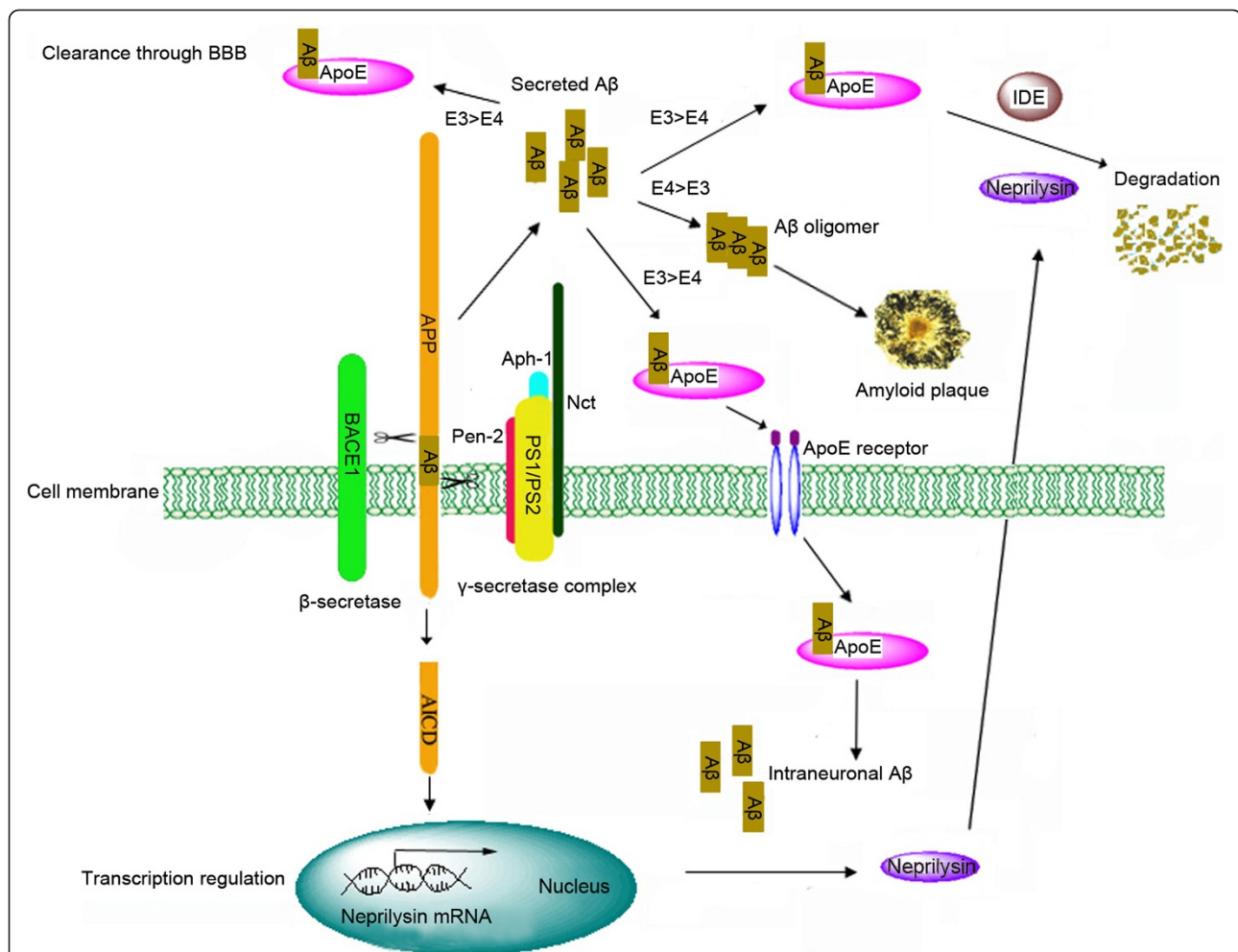
developments of amyloid cascade hypothesis and its relevance to the most recent research advances in the genetics, neuropathology and pathogenesis of AD. In the following sections, the recent progress of the studies on genes (see Figure 1) identified to be involved in the production, deposition and degradation of A $\beta$ , the possible contributions of different A $\beta$  assemblies to AD, and their pathological functions are reviewed.

## A $\beta$ -related genes

### Amyloid precursor protein (APP)

APP is an integral membrane glycoprotein expressed in the brain and central nervous system (CNS). It can undergo sequential proteolytic processing by two

pathways: the  $\alpha$  pathway and the  $\beta$  pathway. In most cases, APP is sequentially cleaved via  $\alpha$  pathway by  $\alpha$ -secretase and  $\gamma$ -secretase. The  $\alpha$ -secretase cleavage of APP is non-amyloidogenic, whereas the  $\beta$  pathway leads to A $\beta$  generation. In the  $\beta$  pathway APP is initially cleaved by  $\beta$ -secretase to release sAPP $\beta$  into extracellular space and leave the 99-amino-acids C-terminal fragment (C99) within the membrane. C99 is subsequently processed to 38-43 amino acids by  $\gamma$ -secretase to release A $\beta$  and APP intracellular C-terminal domain (AICD) [8]. In most cases, the  $\gamma$ -cleavage produces A $\beta$ 40, while it could also generate a more toxic variant, A $\beta$ 42. It has been recently found that  $\gamma$ -secretase activity for A $\beta$  production could be also negatively regulated by



**Figure 1 A $\beta$  and A $\beta$ -related genes in AD.** A $\beta$  is produced by sequential cleavage of APP by  $\beta$ -secretase (BACE1) and  $\gamma$ -secretase.  $\gamma$ -secretase is a multi-protein complex, of which PS1 or PS2 is the catalytic core. After being produced, A $\beta$  is secreted outside the cell and binds to various isoforms of ApoE. These A $\beta$ -binding ApoE isoforms will allow A $\beta$  to undergo metabolism in different pathways, e.g., clearance via BBB, degradation by A $\beta$ -degrading enzymes (IDE or neprilysin), deposition or trafficking into the cell. The affinity of ApoE4 to A $\beta$  is lower than that of ApoE2 or ApoE3. While ApoE2 and ApoE3 help A $\beta$  to be cleared by transport or degradation, ApoE4 mainly induce A $\beta$  to aggregation, implicating it to be a high risk factor for AD. There is a feedback existing in vivo to keep proper A $\beta$  levels. When A $\beta$  is generated, AICD is released, which is translocated into the nucleus and initiates the transcription of neprilysin. Increased neprilysin protein will degrade A $\beta$  and hereby reduces A $\beta$  to a proper level.

$\alpha$ -secretase, indicating a cross-talk between the  $\alpha$  pathway and the  $\beta$  pathway [9].

#### **Physiological functions**

Although APP has been implicated in the pathology of AD, much evidence shows that APP has its own physiological functions, especially in regulation of synaptic function and neuronal activity. Mice lacking APP and APP-like protein 2 show deficits in structure and function in neuromuscular synapses [10]. In cultured hippocampal neurons, lack of APP also affects synapse formation and transmission [11]. On the contrary, mice overexpressing APP exhibit enhanced synaptic plasticity and spatial memory [12]. Kamenetz *et al* found that APP processing could have a normal negative feed-back function in modulating A $\beta$  levels to maintain proper neuronal activity [13]. In addition, APP processing also regulates cholesterol metabolism. When A $\beta$  is produced, AICD is stabilized by Fe65, localized to the nucleus and binds to transcription factor Tip60. The protein-protein interaction initiates the transcription of the A $\beta$  degradation enzyme, neprilysin, thus reduces the A $\beta$  levels [14]. AICD-Fe65-Tip60 complex has been shown to suppress the transcription of lipoprotein receptor LRP1, which is known to regulate ApoE and cholesterol levels in CNS, suggesting a biological interaction between APP and ApoE/cholesterol metabolisms [15]. Furthermore, APP possesses the biological function in controlling cholesterol biosynthesis and sphingomyelin production via A $\beta$ -dependent modulation of neuronal levels of Hydroxymethylglutaryl-CoA reductase (HMGR) and sphingomyelinases (SMases), indicating a functional basis of APP processing for the link between lipids and AD [16]. Endogenous AICD in primary neurons is temporally up-regulated during neuronal differentiation, and such a physiological function is negatively mediated by neuron-specific c-Jun N-terminal kinase JNK3 via phosphorylation of APP [17]. APP and its mammalian paralogs, the amyloid precursor-like proteins 1 and 2, have been demonstrated to be capable of forming homo- and hetero-complexes that exhibit physiological function in promoting trans-cellular adhesion in vivo [18]. Han *et al* also characterized a neuroprotective function of APP in preventing tau hyperphosphorylation via suppressing overactivation of Cdk5 (Cyclin-dependent kinase 5) [19].

#### **Pathological functions**

It is well known that the pathological function of APP lies on its amyloidogenic processing. It has been recognized that many APP mutations cause autosomal dominant early-onset AD. Increasing of gene copy number including genomic duplication in the APP locus [20,21] may also lead to AD dementia in earlier life. Interestingly, a recently identified mutation adjacent to  $\beta$ -site

(A673T) of APP gene was shown to result in A $\beta$  reduction and protection against cognitive decline in the elderly without AD [22]. On the other hand, however, overexpression of FAD-linked mutant APP could lead to olfactory sensory neuron apoptosis in the absence of amyloid plaque, which might be the mechanism of deficits in odor detection, one of the earliest AD symptoms [23]. All these indicate that both APP genomic duplication and mutations can lead to changes in APP function and subsequent A $\beta$  metabolism, strongly implicating a central role of not only APP but also its  $\beta$ -cleavage in pathogenesis of AD. To identify the pathological functions of APP, many APP transgenic mice including wild-type human APP and FAD-linked APP mutations have been generated. FAD-linked APP mutation mice show an increase in the amount, length, and fibrillogenic generation of A $\beta$  species and have amyloid deposits at the age of 18 months [24] while, surprisingly, mice overexpressing APP do not develop AD pathologies or memory deficits but instead exhibit enhanced spatial memory, which depends on the function of AICD generated by  $\beta$ -secretase-mediated cleavage [12]. Studies on APP mutation transgenic mice have given us much information of AD pathogenesis, but the molecular mechanisms still need further investigation.

#### **Beta-site APP cleaving enzyme 1 (BACE1)**

BACE1 is known as the major  $\beta$ -secretase to cleave APP at  $\beta$ -site to produce  $\beta$ -CTF for A $\beta$  generation in neurons [25]. BACE1 and its homolog, BACE2, have different transcriptional regulations and functions. BACE1 knockout mice are almost normal without A $\beta$  generation [26], and BACE1 deficits can rescue the memory impairment and cholinergic dysfunction in mutant human APP transgenic mice [27]. Repetto *et al* demonstrated that overexpression of BACE1 in H4 human cells can regulate APP intracellular signaling by interaction with the ShcA adaptor protein [28]. BACE1-mediated  $\beta$ -cleavage has been showed to be physiologically modulated by different spliced transcripts [29] and the activation of protein kinase C [30]. Impaired intracellular calcium homeostasis may stimulate BACE1 gene expression via nuclear factor of activated T cells 1 (NFAT 1) signaling pathway, leading to accelerated production of A $\beta$  [31]. BACE1 could be modulated by A $\beta$ 42, but not A $\beta$ 40, via an NF $\kappa$ B-dependent signaling pathway [32], and A $\beta$ 42-positive plaques could increase BACE1 levels in surrounding neurons before neuron loss occurs [33]. A $\beta$ 42 could also induce expression of BACE1-antisense transcript, a natural regulator of BACE1 expression, which increased BACE1 mRNA stability [34]. Thus, increased BACE1 levels might be a positive feedback for A $\beta$ 42 to initiate the amyloidogenesis of AD. In addition, BACE1-dependent cleavage of low density lipoprotein receptor-

related protein (LRP) can mediate the endocytosis of APP and ApoE [35] and has been suggested to be involved in the pathology of AD.

### **Presenilin (PS) 1 and 2**

PS is an eight membrane-spanning protein with an N-terminus, a 'loop' domain between transmembrane (TM) domain six and seven, and a C-terminus that is oriented toward the cytoplasm. Aspartate residues at position D275 (in TM6) and D385 (in TM7) are critical for PS function [36]. There are two PS genes: PS1 and PS2. PS, nicastrin, aph-1, and pen-2 form the active  $\gamma$ -secretase complex while PS is the catalytic core of the complex [37].  $\gamma$ -secretase cleaves not only APP but many other type I transmembrane proteins (such as Notch, cadherins and LRP) as well [38], strongly implicating PS in both AD pathogenesis and many other neuronal physiological activities including development, calcium homeostasis and apoptosis.

### **PS gain of function**

PS1 mutations are the most common genetic cause for early-onset familial AD (FAD). PS genes harbor about 90% of identified FAD mutations. There have been more than 100 PS1 mutations being described. Some of them, such as L85P, P117L, P117S, insF1, and L166P, are associated with very early onset (usually before age of 30 years old) of cognitive decline [39]. Many of the PS1 mutations lead to an increase in relative production of more toxic A $\beta$ 42 peptides. The prevailing amyloid hypothesis posits that deposits of A $\beta$  peptides, especially the more hydrophobic and aggregation-prone A $\beta$ 42, initiates a pathogenic cascade, leading to neurodegeneration in AD [40]. This has been referred to as the toxic gains-of-function of PS in triggering neurodegeneration in AD. The amyloid cascade hypothesis is supported by the results from FAD-linked mutant transgenic mice. PS1 mutation significantly accelerates the rate of A $\beta$  deposition in mutant APP transgenic mice [24]. Expression of human mutant PS1 in PS1 null mice is sufficient to elevate A $\beta$ 1-42, supporting a gain-of-function activity of PS1 mutation [41].

### **PS loss of function**

However, the most recent evidence from several independent PS transgenic model-based studies emerged that supports the "PS loss of function" hypothesis as a potential pathogenic mechanism of AD. Firstly, mice lacking both PSs in the forebrain show AD-like progressive neurodegenerative phenotypes including forebrain degeneration, impaired synaptic plasticity and spatial memory without A $\beta$  production [42-46]. A number of PS1 mutations (L113P, G183V and insR352) have been found in patients with familial forms of frontotemporal

dementia (FTD), a common neurodegenerative dementia that lacks amyloidogenesis [47-49]. These observations suggest that neurodegeneration can take place in the absence of A $\beta$ .

PS genes have been identified to play an important role in many normal physiological activities. These physiological functions can be classified to  $\gamma$ -secretase-dependent and -independent functions. There are many identified  $\gamma$ -secretase substrates. By cleavage of these substrates, PSs mediate their multiple functions in development, calcium homeostasis, cell adhesion, transport, trafficking/localization, and apoptosis [36,38,50]. FAD-linked PS mutations might impair the  $\gamma$ -secretase-dependent proteolysis of some of the substrates, such as Notch, N-cadherin and tyrosinase, resulting in loss of the related functions of PS [51,52]. Meanwhile, FAD-linked PS mutations might also impair some  $\gamma$ -secretase-independent functions, such as the regulation of  $\beta$ -catenin-dependent signaling [53], modulation of phosphatidylinositol 4,5-bisphosphate metabolism [54], endoplasmic reticulum [Ca<sup>2+</sup>] leak function [55], PI3K/Akt signaling pathway-dependent neuroprotective roles [56], synaptic homeostasis [57] and fast axonal transport of APP [58]. In addition to involving in A $\beta$  generation, PS genes participate in the regulation of A $\beta$  degradation mediated by AICD-dependent transcriptional modulation of the degrading enzyme, neprilysin [14]. FAD-linked PS mutations may disrupt the physiological function of PSs in regulating A $\beta$  levels.

Surprisingly, many  $\gamma$ -secretase inhibitors at low concentration enhance A $\beta$ 42 production while reducing A $\beta$ 40 levels, similar to the effects of FAD-linked PS mutations [59-61], suggesting that PS mutation could result in a partial loss of its function. Furthermore, PS mutations are scattered throughout the protein's N-terminus, C-terminus and transmembrane domains, occurring at about 20% of the amino acid residues. As it is impossible for different PS mutations to gain the same toxic function, it is therefore most likely that the loss of normal PS function by 'random' changes of amino acid residues is the culprit for triggering AD pathogenesis. However, the "PS loss of function" hypothesis is still unable to explain the exact mechanism for FAD-linked APP mutations that cause AD. In this regard, it has been assumed that A $\beta$ 42 might act as an inhibitor of  $\gamma$ -secretase. APP mutations may interfere with the physiological roles of PS and hereby initiate the pathogenic cascades of AD [51]. Further investigations are required to confirm the hypothesis.

### **Apolipoprotein E (ApoE) and other apolipoproteins**

Apolipoproteins play important roles in regulating A $\beta$  pathology. ApoE is the predominant apolipoprotein in the CNS and is synthesized and secreted mainly by



astrocytes and microglia [62,63]. ApoE has critical roles in transporting lipids among CNS cells to keep lipid homeostasis, repairing injured neurons, maintaining synaptic connections, and scavenging toxins. ApoE gene encodes three alleles: ApoE2, ApoE3 and ApoE4. The alleles differ only in two residues at sites 112 and 158. ApoE3 has Cys-112 and Arg-158, ApoE4 has arginine and ApoE2 cysteine at both sites. The differences between the alleles determine their distinct functions. ApoE2 is neuroprotective while ApoE4 is related to a variety of diseases.

It has been recognized that ApoE4 is the major genetic risk factor for sporadic AD. ApoE4 is associated with cognitive deficits [64], and the effect of ApoE4 is moderated by cholesterol levels [65]. In contrast to ApoE2 and ApoE3, ApoE4 is more sensitive to stress or injury, which causes neuron-specific proteolysis with the formation of a bioactive toxic C-terminal fragment [66]. Transgenic mice expressing high levels of carboxyl terminal-cleaved product ApoE4 (272–299) in the brain die 2–4 months after birth. The cortex and hippocampus of the transgenic mice display AD-like neurodegenerative alterations [67].

ApoE acts as the A $\beta$  chaperone and binds to different forms of A $\beta$ , leading to changes in the structure, toxicity and deposition of A $\beta$  [68,69]. Pharmacological blocking ApoE-A $\beta$  interaction can significantly reduce the formation of amyloid plaques and attenuate the deficits of memory in the transgenic mice carrying a Swedish K670L/M671L APP mutation (APP<sub>SWE</sub>) or a K670L/M671L APP plus a PS1 M146L mutation (APP<sub>SWE</sub>/PS1) [70]. The effects of ApoE on A $\beta$  depositions are supported by the observation that intake of sugar-sweetened water induces amyloidosis and memory impairment and increases ApoE levels in the brain of a transgenic mouse model of AD [71]. Besides, it is recently demonstrated that increased expression of ApoE by the retinoid X receptors agonist results in enhanced clearance of soluble A $\beta$  and reduced A $\beta$  plaque, and leads to reversal of cognitive deficits and improvement of synaptic functions in an AD mouse model [72]. Nevertheless, increasing evidence suggests that the regulatory effect of ApoE on A $\beta$  deposition appears to be isoform-specific (ApoE4 > ApoE3 > ApoE2) and gene dosage-related [73]. ApoE promotes the proteolytic degradation of A $\beta$  by modulating the activity of A $\beta$  degrading enzyme, which depends on ApoE isoform structure and the lipidation status [69,74]. ApoE also participates in the regulation of A $\beta$  production through LRP pathway [75]. Given that APP processing is dependent on membrane cholesterol levels and that ApoE is the transporter of cholesterol [76], ApoE might therefore be an important player in A $\beta$  generation. In fact, it has been reported that activation of the amyloid cascade may isoform-specifically induce

lysosomal activation and neurodegeneration of hippocampal CA1, entorhinal and septal neurons, which are responsible for the marked cognitive deficits in apolipoprotein transgenic mice [77]. ApoE4-induced impairments of neuroplasticity following environmental stimulation are also found to be mediated by intraneuronal oligomerized A $\beta$  [78]. Furthermore, C-terminal fragment of ApoE could induce tau phosphorylation in neurons that represents another character in AD brain, depending on both the isoform and cellular source of ApoE [67,79].

In addition to ApoE, other apolipoproteins, such as ApoA-IV, were also found to regulate A $\beta$  metabolism. Genetic ablation of ApoA-IV in an AD mouse model accelerates A $\beta$  deposition, neuron loss and cognitive impairment [80].

#### **Neprilysin/insulin-degrading enzyme**

While familial early-onset AD is associated with increased A $\beta$  production, defective A $\beta$  degradation may be involved in late-onset AD (LOAD), which constitutes approximately 90% of all AD cases [81]. Many enzymes including, but not limited to, neprilysin (NEP) and insulin-degrading enzyme (IDE) have been implicated for a role in degrading A $\beta$  [82]. NEP and IDE are reduced in AD, and increasing evidence indicates an involvement of them in the imbalance of A $\beta$  production and clearance relating to AD pathology.

#### **Neprilysin (NEP)**

NEP is a 90 ~ 110 kDa plasma membrane glycoprotein of the neutral zinc metalloendopeptidase family that degrades enkephalins, endothelins, and A $\beta$  peptides [82]. Particularly, NEP is the major enzyme to degrade soluble extracellular A $\beta$  in the brain. Recent studies demonstrated that NEP levels decline in an age-dependent manner and inversely correlate with levels of insoluble A $\beta$  in the temporal and frontal cortex of AD and normal brain [83,84]. NEP expression or activities are decreased significantly in AD brain [85,86]. The finding that possession of ApoE4 was related to obvious reduction in NEP levels [85] suggests that down-regulation of NEP might be implicated in AD pathogenesis.

The transcription of NEP has been demonstrated to be regulated by AICD which is released during the A $\beta$  generation [14]. There is a physiological negative feedback in vivo that keeps A $\beta$  homeostasis, in which A $\beta$  production could lead to translocation of AICD to nucleus and transactivation of NEP. NEP therefore has a role in governing the balance between A $\beta$  production and degradation. If such a balance is disrupted, A $\beta$  would come to be oligomerized and lead to formation of the fibrillar A $\beta$  protein (fA $\beta$ ). The resulting fA $\beta$  can inhibit the proteolytic activities of the proteases by binding to NEP and

IDE [87], leading to the formation of a positive feedback that accelerates amyloid deposition. Indeed, studies on transgenic mice of AD have shown that NEP-mediated degradation of A $\beta$  plays a key role in AD neurodegeneration and serves as a novel therapeutic approach to AD [88]. These findings also suggest that AD pathogenesis might result from deficits in A $\beta$  clearance. On the other hand, however, recent observations in drosophila demonstrated that NEP overexpression could result in the inhibition of CREB-mediated transcription, age-dependent axon degeneration and shortened lifespan [89]. Studies on crossing hAPP transgenic mice and NEP transgenic mice also showed that, although NEP overexpression inhibits plaque formation, it fails to reduce pathogenic A $\beta$  oligomers and improve the impaired learning and memory function [90].

#### **Insulin-degrading enzyme (IDE)**

IDE is an 110 kDa zinc metalloendopeptidase that highly expresses in the liver, testis, muscle and brain [82]. The enzyme has been implicated in the pathogenesis of AD and type II diabetes due to its capabilities in degrading A $\beta$ , AICD [91,92], amylin, insulin and insulin-like growth factors [82]. IDE gene is located in chromosome 10 that is highly associated with later-onset AD (LOAD) [93]. Some genetic variants of IDE have also been strongly implicated in LOAD [94,95]. IDE mRNA and protein levels are markedly decreased in hippocampus of AD patients with ApoE  $\epsilon$ 4 allele, the genotyping known as a high risk factor for LOAD [96]. Membrane-bound IDE levels and its activity are significantly decreased in subjects with mild cognitive impairment (MCI) and appear to decrease continuously during the conversion from MCI to AD [97]. IDE activity is reduced in affected versus unaffected subjects of three chromosome 10-linked AD pedigrees, although no significant difference of IDE expression has been observed [98]. However, recent studies on transgenic AD mouse models showed that cortical IDE mRNA and protein levels are elevated in parallel with A $\beta$ 40 and A $\beta$ 42 generation [99]. In transgenic tg2576 mice, IDE expression is increased with age and is located around amyloid plaque as a result of A $\beta$ -induced inflammation [100]. This phenomena is similar to the observation that IDE is immunopositive in senile plaques in human AD brain [101]. Studies on triple-transgenic mice (hAPP<sup>swe</sup>/PS1 M146V/hTau P301L) showed that the expression of IDE was regulated by 17 $\beta$ -estradiol via an ER $\beta$ /PI3K pathway [102]. Unlike NEP that hydrolyzes both monomeric and oligomeric A $\beta$ , IDE is found to degrade only soluble monomeric A $\beta$  [103]. A recent study by Llovera *et al* demonstrated that the catalytic domain of IDE could form a stable complex with A $\beta$ , which might disrupt A $\beta$  clearance and facilitate AD neurodegeneration [104].

There have been also studies showing that IDE can cleave C-terminal domain of human acetylcholinesterase (hAChE) and trigger its conformational conversion from  $\alpha$  to  $\beta$ -structure, which acts as the seed of A $\beta$  fibrils and enhances the rate of amyloid elongation [105]. This suggests an important role of IDE digestion of C-terminal domain of hAChE in amyloidogenic pathogenesis of AD.

IDE plays essential role in insulin homeostasis, implicating a close relationship between AD and type II diabetes (DM2). A large body of evidence has indicated that cognitive capacity is often impaired in patients with diabetes [106] while insulin resistance is a high risk factor of AD [107]. IDE knockout mice exhibit hallmarks of both AD and DM2 [92]. Diet-induced insulin resistance leads to increased  $\gamma$ -secretase activity and decreased IDE activity, resulting in elevated A $\beta$ 40 and A $\beta$ 42 levels in the brain of Tg2576 mice [108]. Further exploration of the underlying mechanism has shown that defective insulin receptor signaling may lead to up-regulation of A $\beta$  generation. Insulin resistance induced by intake of sucrose-sweetened water or a safflower oil-enriched diet exacerbates the AD pathology in transgenic AD animal models [71,109].

#### **A $\beta$ and neurodegeneration**

Although it has been widely accepted that A $\beta$  plays a central role in the onset and progression of AD pathology, it remains unclear whether soluble or insoluble A $\beta$  located in extracellular or intracellular is the culprit to impaired neuronal function and memory. Meanwhile, much progress based on neurotoxic lesion, pharmacological, genetic, and neurophysiological studies in recent years has led to identification of many new physiological and biological alterations, such as mitochondrial dysfunction, oxidative stress, synaptic transmission, axonal trafficking and membrane disruption, that are responsible for the functions of A $\beta$  with significant implications in developing AD [110,111]. In the following sub-sections, we selectively review the present research status in characterization of neurotoxic form of A $\beta$ , and in the pathological functions of A $\beta$  in synaptic dysfunction and neuronal inflammation.

#### **A $\beta$ : soluble or insoluble, extracellular or intracellular, which one is neurotoxic form to AD?**

In the last two decades, A $\beta$  hypothesis has been the focus of AD researches. According to the hypothesis, deposition of A $\beta$  peptide is the primary cause of driving AD degeneration and all of the other pathological features including intracellular neurofibrillary tangles (NFT) and neuron loss are the downstream events of the amyloid cascade [40]. The hypothesis, however, has been challenged in recent years [112]. Appearance of large "cotton wool" plaques resulting from PS1

mutations has been demonstrated to be associated with some special symptoms such as spastic paraparesis rather than early-onset AD [113]. Decreased dendritic spine density, impaired synaptic plasticity, and cognitive dysfunction occur long before amyloid depositions that appear at 18 months in Tg2576 mice [114]. Hippocampal neuron loss in AD mouse models has been observed both at the site of amyloid aggregation and in areas distant from plaques [115].

The classical view is that A $\beta$  is deposited extracellularly, however, emerging evidence from transgenic mice and human patients has indicated that this peptide can also be accumulated intraneuronally that contributes to AD pathogenesis [116]. A PS1 mutated transgenic mouse model with intracellular A $\beta$  accumulation but without amyloid plaques exhibits AD-like neurodegeneration [117]. Results from the triple-transgenic AD mouse model (hAPP<sup>swe</sup>/PS1 M146V/hTau P301L) showed that impaired synaptic plasticity and cognitive dysfunction occur prior to the apparent plaques, and are correlated with the accumulation of intraneuronal A $\beta$  in hippocampus and amygdala [118,119]. Intracellular A $\beta$  has been found to accumulate before the generation of amyloid plaques in many other AD mouse models [120-124] and in human AD [20,21,125]. As mentioned above, overexpression of FAD-linked mutant APP alone could induce the apoptosis of olfactory sensory neuron and this neurodegeneration is reversible, suggesting that amyloid plaques are not necessary for AD neurodegeneration [23].

Evidence has also emerged that the soluble A $\beta$ , but not amyloid plaques, initiates pathological cascade. A $\beta$  dimers derived from untreated human cerebrospinal fluid (CSF) suppress hippocampal synaptic plasticity in vivo [126]. Neuron exposure to prefibrillar A $\beta$  can cause tau-dependent microtubule disassembly [127]. A $\beta$  oligomers have been observed to disrupt calcium signaling [128], affect the function of NMDA receptor [129,130], and induce oxidative stress [131] and mitochondrial dysfunction [132]. Furthermore, in vitro studies have demonstrated that  $\beta$ -sheet intermediate (I $\beta$ ) of A $\beta$  prior to fibril formation is more toxic than the fibrils [133]. It has also been shown that soluble A $\beta$  oligomers induce reduction in postsynaptic receptors and disruptions of synaptic morphology in cultured hippocampal neurons [134,135]. Notably, intracerebroventricular injection of AD brain-derived extracts containing soluble A $\beta$  could lead to obvious inhibition of hippocampal LTP in rats, supporting the role of SDS-stable A $\beta$  dimer in mediating synaptic plasticity disruption [136].

Pyroglutamate-amyloid- $\beta$  (pE3-A $\beta$ ), an N-terminal truncated A $\beta$  species, has recently been found in A $\beta$  deposits specific to AD brain but absent in normal aging. Transgenic mice expressing this kind of truncated

A $\beta$  showed progressive neurodegeneration including neuron loss, impaired LTP, microglia activation and astrocytosis [137]. A signal transduction pathway of soluble A $\beta$  oligomer has recently been delineated, in which oligomeric A $\beta$  activates Fyn kinase by binding to cellular prion protein (PrP<sup>c</sup>) and results in the phosphorylation of NR2B subunit of NMDA receptor, and eventually leads to dendritic spine loss and altered synaptic function [138].

In contrast to the observations mentioned above, Lesne *et al* identified the extracellular accumulation of a soluble 56-kDa A $\beta$  assembly (termed A $\beta$ \*56) composed of 12 A $\beta$  peptides that contributes to the memory impairment in Tg2576 mice [139]. This finding has been supported by others using transgenic mice with increased formation of amyloid plaques but reduced A $\beta$ \*56 levels [140]. Taken together, although increasing data have been accumulated that strongly suggest the soluble A $\beta$  and intracellular A $\beta$  to be more suspicious in underlying AD pathogenesis, the involvement of extracellular A $\beta$  in pathologies of the disease is still not neglectable.

#### **Other pathological functions of A $\beta$**

##### **A $\beta$ and synaptic dysfunction**

A $\beta$  has long been shown to affect excitatory synaptic neurotransmission [13] and hippocampal synaptic plasticity [110,126,141]. A $\beta$  oligomers are able to bind specifically to excitatory pyramidal neurons and affect their synaptic structure, composition and density and the membrane expression of NMDA receptor [135]. Similar observations on rat hippocampal slices have also shown that A $\beta$  oligomers induce loss of hippocampal synapses and spines in a NMDA receptor-dependent manner [130]. A $\beta$  exhibits a specific inhibitory role in a pre-synaptic P/Q calcium current, which is required for synaptic plasticity [128]. A $\beta$  also plays an important role in activity-dependent presynaptic vesicle release [142]. Moreover, A $\beta$  can induce neuronal network dysfunction including abnormal induction of excitatory neuronal activity and compensatory inhibitory circuits [143]. The abnormalities of synapse and neuronal network resulting from A $\beta$  might be the physiological basis of cognitive decline in AD animal models and patients.

##### **A $\beta$ and inflammation**

Microglia is rapidly recruited around amyloid plaques after its appearance [144]. A $\beta$  can trigger the translocation of microglia from bone marrow to the sites around amyloid plaques [145]. A $\beta$  up-regulates P38 MAPK or p44/42 MAPK signaling, which may lead to microglia activation with release of cytokines including tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin-1  $\beta$  (IL1- $\beta$ ) [146]. The microglia around plaques maintains the

stability of the plaques [147]. Both pharmacological blockade and genetic knock-out of TNF- $\alpha$  or iNOS down-regulate A $\beta$ -induced cognitive dysfunction in AD mouse model, revealing that TNF- $\alpha$  and iNOS are key mediator of A $\beta$  neurotoxicity [148]. Genetic disruption of transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling mitigates A $\beta$  levels and amyloid plaques, and partially rescues the cognitive abnormality in Tg2576 mice [149]. However, the roles of TGF- $\beta$  signaling are in a debate. Tesseur *I et al* showed that deficiency in TGF- $\beta$  signaling promotes A $\beta$  accumulation and neuronal degeneration [150]. Accumulating evidence also suggests that functional loss of TGF- $\beta$  signaling may contribute to A $\beta$ -induced neurodegeneration and tau pathology, indicating a neuroprotective role of this pathway [151].

## Conclusion

AD is a complex neurodegenerative disease involving the interactions among various potential biological and environmental factors. Among them, abnormal processes of A $\beta$  production, degradation and deposition have been strongly implicated in the underlying neuropathology and neuropathogenesis of familial earlier-onset and sporadic later-onset forms of AD. Genes involved in these processes, including APP, BACE1, PS1/2, ApoE, NEP, IDE and so on, play important roles in AD initiation and progression. Further dissection with depth and breadth of genetic influences may help defining the precise mechanisms involved in the disease pathogenesis, and eventually leading to development of new arrays of therapeutics with symptomatic effects or disease-modifying potential.

## Abbreviations

AD: Alzheimer's disease; A $\beta$ : Amyloid- $\beta$ ; SP: Senile plaques; NFT: Neurofibrillary tangles; ApoE: Apolipoprotein E; CNS: Central nervous system; APP: Amyloid precursor protein; C99: C-terminal fragment; AICD: APP intracellular C-terminal domain; LRP1: Lipoprotein receptor-related protein; HMGR: Hydroxymethylglutaryl-CoA reductase; SMases: Sphingomyelinases; JNK: c-Jun N-terminal kinase; Cdk5: Cyclin-dependent kinase 5; FAD: Familial Alzheimer's disease; BACE1: Beta-site APP cleaving enzyme 1;  $\beta$ -CTF:  $\beta$ -C-terminal fragment; BACE2: Beta-site APP cleaving enzyme 2; NFAT 1: Nuclear factor of activated T cells 1; NRG1: Neuregulin 1; PS: Presenilin; TM: Transmembrane; aph-1: Anterior pharynx-defective 1; pen-2: Presenilin enhancer 2; FTD: Frontotemporal dementia; PI3K: Phosphoinositide\_3-kinase; Akt: Protein kinase B; NEP: Nephilysin; IDE: Insulin-degrading enzyme; ECEs: Endothelin-converting enzymes; ACE: Angiotensin-converting enzyme; MMPs: Plasmin and matrix metalloproteinases; LOAD: Later-onset AD; MCI: Mild cognitive impairment; ERbeta: Estrogen receptor beta; hAChE: Human acetylcholinesterase; DM2: Type II diabetes; PrPc: Cellular prion protein; MAPK: Mitogen-activated protein kinase; TNF- $\alpha$ : Tumor necrosis factor  $\alpha$ ; IL-1 $\beta$ : Interleukin-1  $\beta$ ; GSK3: Glycogen synthase kinase 3.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

SZ Dong and YL Duan collected the reference materials and drafted the manuscript. YH Hu and Z Zhao conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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## Author details

<sup>1</sup>Shanghai Engineering Research Center for Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China. <sup>2</sup>Institute of Chemical and Translational Genomics, East China Normal University, Shanghai 200062, China. <sup>3</sup>Key Laboratory of Brain Functional Genomics, Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, East China Normal University, 3663 Zhongshan Road (N), Shanghai 200062, China.

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